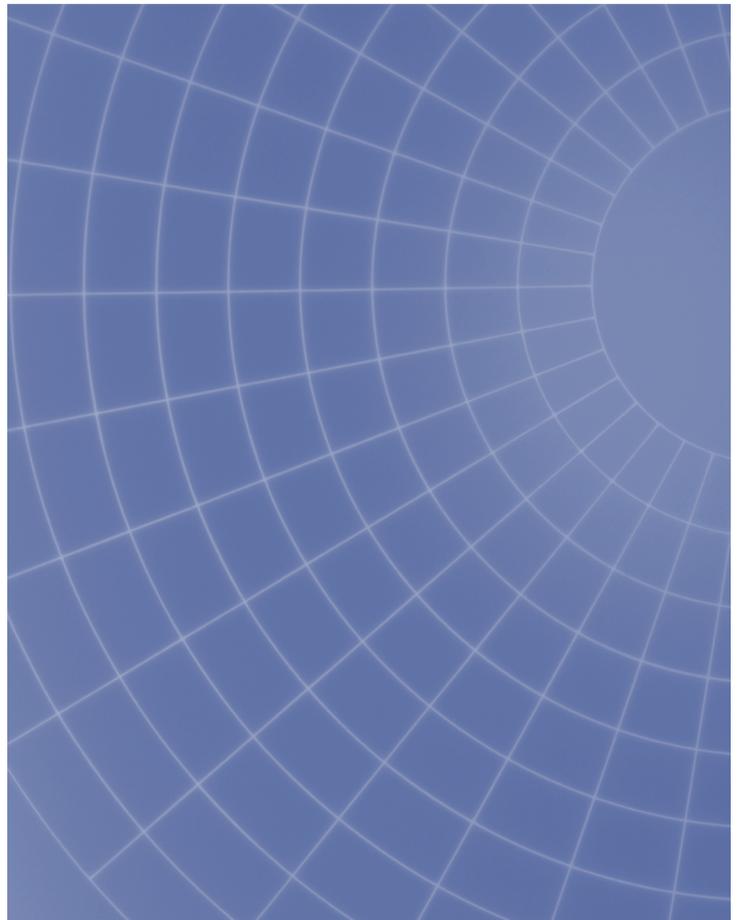


Understanding EU Drug Safety Reporting



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Understanding EU Drug Safety Reporting

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Introduction

In 2014 European regulators began inspecting drugmakers for compliance with new post-market reporting and surveillance requirements for drugmakers. They also have raised the bar for winning a drug approval at the European Medicines Agency, which now requires drugmakers to design and implement a substantial safety plan for each drug. While drugs have always had to meet safety regulations, the new rules demand much stronger and thoroughly prepared pharmacovigilance activities on the part of drugmakers.

This report will help drugmakers understand the pharmacovigilance rules and what their obligations are under them by exploring the following five requirements of the law:

- Companies must deal with a new regulatory body, the Pharmacovigilance Risk Assessment Committee (PRAC). This new body prepares recommendations on all pharmacovigilance activities and risk management systems for drugs sold in Europe.
- Drugmakers face new definitions and requirements regarding risk management plans, pharmacovigilance systems and pharmacovigilance master files as well as the need to appoint a qualified person for pharmacovigilance (QP) to be the contact person for EU authorities.
- Drugmakers must submit periodic safety update reports (PSURs) including results of any studies with potential impact on the marketing authorization that approved the drug.
- Drugmakers must adjust to a broader definition of adverse drug reactions (ADRs) that requires them to report ADRs caused by their products in all uses, including off-label use or misuse.
- Companies must incorporate into their product labeling the black triangle now used to designate drugs that are subject to additional monitoring.

The report will also look at other regulatory developments that are in early stages, such as EU member states establishing public web portals that contain summary of product characteristics (SmPC) and patient information leaflet (PIL) information for drugs and international regulators increasingly sharing safety data so that regulators in one country will quickly learn of safety problems in other countries.

This report is based on a webinar presented by Elisabethann Wright, a partner in Hogan Lovells' office in Brussels. She focuses on European Union law relating to life sciences, with particular emphasis on pharmaceutical law, medical devices, food law and the environment. Wright has been with Hogan Lovells since 2006 and previously worked in private practice and with international institutions.

The Creation, Roles and Responsibilities of the PRAC

The Pharmacovigilance Risk Assessment Committee (PRAC) was created under the new pharmacovigilance rules to be the arbiter of issues involving the safety of medications before, during and after approval. Understanding the PRAC and its role is essential to understanding how the new pharmacovigilance rules work.

The PRAC is composed of one expert member from each EU member state; six pharmacology and pharmacoepidemiology experts; a representative healthcare professional; and a patient representative. It has no representatives from the pharmaceutical industry. Appendix A contains a listing of the PRAC's members.

The specific roles of the PRAC are:

- To investigate drug safety issues identified by the EMA or member states.
- To review safety-related submissions needed to win a drug approval.
- To routinely review periodic safety update reports (PSURs) submitted by drugmakers to identify signals of new or changing drug risks.
- To approve protocols and amendments for noninterventional post-authorization studies of drugs.
- To provide recommendations regarding the organization and functioning of EU-wide pharmacovigilance databases.

For existing drugs, the PRAC's main function is to step in when problems with a drug's safety are detected. The PRAC makes recommendations on the need and scope of "for cause" pharmacovigilance inspections, which are used to investigate cases where the EMA believes a drugmaker is not complying with its pharmacovigilance requirements.

The PRAC also reviews the outcome of routine inspections of a company's pharmacovigilance system and assesses drugmaker corrective and preventive action plan submissions related to their pharmacovigilance systems.

In cases where routine inspections find that patient welfare has been put at risk, investigators can refer the case directly to the PRAC for a scientific assessment of the specific drug. When issues are identified during inspection that potentially impact a drug's benefit-risk profile, the lead investigators will contact the pharmacovigilance assessors in their member state to discuss next steps. If the safety implications are deemed broader than the national market, the issue will be brought to the PRAC's attention as well. Findings that will be referred to the PRAC for review include:

- Failure to provide pharmacovigilance data to national regulatory authorities or the EMA;
- Failure to evaluate safety signals, which may affect the benefit-risk profile of a drug;

- Failure to take action when a signal assessment demonstrates a new risk; and
- Failure or significant delays in implementing risk-minimization measures.

When the PRAC becomes involved in one of these issues, the PRAC representative will suggest proposed corrective actions and determine whether the issues require a complete review of the drug's safety data and risk communications.

In addition, the PRAC will advise both EU-wide and nation-specific bodies on how to best monitor risk management activities of drugmakers.

The PRAC's Role in Preapproval Activities

For preapproval issues, the PRAC was set up to work hand-in-hand with two already-established regulatory bodies — the Committee for Medical Products for Human Use (CHMP), which it advises on centrally authorized medicines; and the Coordination Group for Mutual Recognition and Decentralized Procedures — Human (CMDh), which it advises on the use of medicines in member states.

Under the new rules, the CHMP rapporteur must cooperate closely with the PRAC rapporteur. The CHMP is responsible for including safety requirements in all recommendations for a drug's approval, and it's recommendation must cover:

- Recommendation on the frequency of submission of PSURs;
- Details of any measures for the safe use of the drug contained in the risk management system to be imposed as conditions of the marketing authorization;
- If appropriate, the written requirement to conduct post-authorization safety studies or to comply with requirements on suspected adverse reaction recording or reporting stricter than those provided for in the EU law.

To make these recommendations, the CHMP will rely on the PRAC to conduct a review of the product's application. The PRAC may also conduct a premarketing pharmacovigilance inspection to verify the drug applicant's capacity to carry out its proposed pharmacovigilance measures.

The PRAC determines whether it will make its inspections based upon the safety profile of the drug under consideration and how important the risk management activities are to protecting patients.

Conditional Marketing Authorization

The PRAC may recommend that the EMA apply conditions to a marketing authorization, such as making the drug's approval subject to:

- Specific safety measures contained in a risk management plan;
- Conduct of post-authorization studies;
- Adverse events reporting requirements that are stricter than normal and customized specifically for the drug; and

- The existence of an amended pharmacovigilance plan to address defects it finds in a submitted plan.

There is also a catch-all phrase in the regulations that allows the PRAC to set any other conditions or restrictions with regard to the safe and effective use of the drug that it determines are required.

Renewing Authorization

Once approved, a marketing authorization is valid for five years and drugmakers must submit a renewal application that addresses safety issues, which the PRAC will again review.

Renewal applications should include evaluation of data contained in suspected adverse reaction reports and periodic safety update reports involving both on- and off-label uses.

Once renewed, the marketing authorization will be valid for an unlimited period, unless the regulatory authority decides, on grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

The exposure of an insufficient number of patients to the drug may result in the authorities imposing an additional five-year renewal of the marketing authorization. But the term “insufficient number of patients” is not defined in the law, Wright notes. What number is deemed sufficient is expected to be assessed on a case-by-case basis, she said, based on whether the product is an orphan drug, the kind of condition being treated, the number of similar products on the market, and the risk-benefit analysis.

For products that are taking some time to get a foothold in the market, insufficient exposure is an issue drugmakers should be mindful of. In addition to safety concerns, it can affect reimbursement approvals because EU member states may not approve paying for a drug unless the product has been used, while physicians may not prescribe the product without available reimbursement, creating a vicious cycle. It can take two years or more to get this sort of situation straightened out, so drugmakers need to be aware that these types of delays may lead to a conditional renewal and force them to go before the PRAC a third time.

One final element of the PRAC’s operations is being created now. The EMA is planning a process under which the PRAC can hold public hearings. Once the rules are in place, the PRAC will be able to hold public hearings as part of safety reviews of drugs, and seek public input on a drugmaker’s proposed risk management plans. Public hearings will be held on a case-by-case basis, and it’s not yet clear how the PRAC will decide when to invite public input on a drug.

Given the limited time the PRAC has been operational, not a lot is known about how it will conduct itself. In July 2014, the EMA released its first Pharmacovigilance System Manual (see Appendix B), which lays out the roles and interactions of the PRAC, the CHMP and the CMDh in overseeing drug safety and describes how the EMA will measure performance of the system.

The manual is a useful reference for drugmakers because it clarifies how the law is designed to function, said Wright. “As things move along, and as the new PRAC becomes more active, it becomes increasingly important to companies to understand what their obligations are under the new pharmacovigilance legislation,” she said.

Changes in Marketing Authorization Applications

Drugmakers should keep in mind the pharmacovigilance rules from the earliest days of the drug approval process, as the rules spell out what drugmakers must submit as part of their marketing authorization application. And these, in turn, are the commitments the company must honor after approval. The new submission requirements call for risk management plans, which include the details of the proposed pharmacovigilance systems and pharmacovigilance system master files. Drugmakers now must also appoint a qualified person for pharmacovigilance (QP) to oversee postmarket safety activities of a drug.

Risk Management Plan (RMP)

The risk management plan (RMP) that drugmakers must now create must detail a set of pharmacovigilance activities to identify and minimize risks, and assess the effectiveness of the RMP. Broadly, the risk management plan contains the following elements:

- The safety profile of the drug that identifies its known risks and the steps the drugmaker is taking to mitigate them;
- A listing of any post-authorization obligations that have been imposed as a condition of the drug's approval along with a timeframe for meeting those obligations; and
- If the plan refers to post-authorization studies, the plan must spell out who will conduct them — the drugmaker or another party, such as a government body.

The risk management plan should also contain a product overview that provides the administrative information about the plan and an overview of the product(s) covered within it. The information should include:

- Active substance information
 - Active substances;
 - Pharmacotherapeutic groups (ATC code);
 - Name of drugmaker;
 - Date and country of first authorization worldwide (if applicable);
 - Date and country of first launch worldwide (if applicable);
 - Number of drugs to which the plan refers;
- Administrative information on the plan
 - Cutoff date for data to be included in the plan;
 - Date submitted and the version number;
 - List of all parts and modules of the plan with date and version of the plan;

- For each drug included in the plan
 - Authorization procedure (central, mutual recognition, decentralized, national);
 - Product name in the European Economic Area (EEA);
 - Brief description of the product including
 - Chemical class;
 - Summary of mode of action;
 - Important information about its composition, such as origin of active substance of biologics, relevant adjuvants or residues for vaccines;
 - Indications — Both current and proposed
 - Dosage — Both current and proposed
 - Pharmaceutical forms and strengths — Both current and proposed
 - Whether the product is the subject of additional monitoring in the EU.

In the safety profile, the RMP should outline the important documented risks — and potential risks — associated with use of the drug, including adverse events/reactions and interactions with other drugs and foods. In addition, the plan needs to address missing information, such as gaps in knowledge about a drug about risks it might pose to a particular patient population. It should also identify the populations potentially at risk where the product is likely to be used, in both labeled and off-label use, and outstanding safety questions which warrant further investigation after approval to better understand the drug's risks.

In the RMP, the safety profile will form the basis of the pharmacovigilance plan, and the risk minimization steps it will include.

The RMP should discuss the epidemiology of the indications for the drug including incidence, prevalence, mortality and co-morbidity, and should whenever possible be broken down by age, sex and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible, (because the epidemiology of the indications may vary across regions), but the emphasis should be on the epidemiology in the EU of the proposed indication.

The RMP should also present a summary of the important nonclinical safety findings, such as toxicity, general pharmacology and drug interactions. What constitutes an important safety finding will depend on the drug, the target population and experience with similar compounds or therapies in the same class.

Quality aspects relevant to safety, such as important information on the active substance or its impurities, should also be noted. If a product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity should be explicitly addressed and the implications for use in this population discussed.

Data on the patients studied in clinical trials also should be provided in the RMP, as well as data on which sub-populations within the expected target population have not been studied or have only been studied to a limited degree.

Over the life of a drug, the RMP needs to be regularly updated and it should provide the number of patients exposed to the drug post-authorization; how the drug has been used in approved and off-label situations; and the number of patients included in any completed safety and use studies. Details of significant actions taken to update information on the safety of the drug should also be provided.

Pharmacovigilance System

With the risks identified, drugmakers next need to develop a pharmacovigilance system, which includes the pharmacovigilance system master file, and incorporate it into the RMP.

The pharmacovigilance system simply lays out the steps a company plans to take to monitor the safety of a drug, identify any changes in the drugs' risk-benefit balance and take action if needed to protect patients.

As part of the approval process, drugmakers may also have to provide a copy of their pharmacovigilance system master file, which documents the pharmacovigilance system. Each company must also appoint a qualified person for pharmacovigilance (QP) to be responsible for the pharmacovigilance system.

Reviewers will look to see that six specific topics are covered in the pharmacovigilance system.

- Ongoing review of safety. The system must provide for continuous safety profile monitoring and benefit-risk evaluation of pharmacovigilance data.
- Effectiveness. The drugmaker needs to create a system that will credibly prevent or minimize drug risk.
- The system must demonstrate how it will facilitate the drugmakers submitting accurate and verifiable data on adverse reactions to regulators. The rules make clear that drugmakers must be proactive in soliciting feedback about a drug through well-publicized websites, reporting hotlines and reporting forms.
- The system must provide for effective communication with regulators, including communication on periodic safety update reports (PSURs), individual case safety reports (ICSRs) and post-authorization safety studies (PASS);
- The system must spell out how product information will be updated as new scientific knowledge comes to light.
- The system must call for adequate communication of safety information to healthcare professionals and patients.

Drugmakers should also establish processes to monitor the performance and effectiveness of their pharmacovigilance system that includes regular management reviews, audits and ongoing compli-

ance monitoring. Reviews of the system should include the review of standard operating procedures and work instructions, deviations from the established system, and audit and inspections reports.

Pharmacovigilance System Master File

The pharmacovigilance system master file itself is the detailed document that describes how the pharmacovigilance system for a drug will operate. It includes detailed information about the processes, data handling, records and personnel for all the drugmaker's pharmacovigilance activities for each drug. It should cover all the following aspects of pharmacovigilance:

- How the company conducts continuous monitoring of the drug's risk-benefit profile and what it does with the results of that monitoring;
- The description of policies related to the drug's risk management system and how the drugmaker monitors the effectiveness of risk minimization measures;
- How the drugmaker collects individual case safety reports and what it does with them;
- The drugmaker's schedule for producing and submitting periodic safety update reports, if applicable;
- How the drugmaker communicates safety issues to consumers, healthcare professionals and regulators;
- How the drugmaker makes updates to the summary of product characteristics (SmPC) and patient information leaflets (PIL);
- How the drugmaker responds to regulators' requests for information;
- How the drugmaker searches literature for safety information on its product;
- Controls on its database that contains safety information, including change controls, safety data exchange agreements and safety data archiving; and
- How the company audits its pharmacovigilance system, trains employees and imposes quality control over the system.

The master file needs to make clear which elements of the pharmacovigilance system the drugmaker handles itself and which ones it outsources.

The master file is the central document inspectors will ask to review when they inspect a company's pharmacovigilance system.

In addition to the elements of the system itself, the master file also needs to have a detailed section about the QP, spelling out his qualifications for the position and demonstrating that he has the authority to carry out his responsibilities.

Qualified Person for Pharmacovigilance (QP)

The duties of the QP — which are extensive — must be defined in a job description and the hierarchical relationship of the QP must be shown on each company's organizational chart.

The responsibilities of the QP include:

- Reviewing drug safety profiles and any emerging safety concerns;
- Ensuring that the company is satisfying all any postmarket safety requirements that are a condition of a drug's approval;
- Creating and updating drug safety risk management plans;
- Reviewing and signing-off on protocols for post-authorization safety studies and monitoring the studies and their results;
- Ensuring submission of all pharmacovigilance-related documents, such as PSURs and adverse events reports;
- Ensuring that regulators get the information they need for benefit-risk evaluation;
- Providing input into the preparation of regulatory action in response to emerging safety concerns, such as urgent safety restrictions and communication to patients and health-care professionals; and
- Acting as a single pharmacovigilance contact point for regulators in member states and the EMA and also as a contact for pharmacovigilance inspections.

The QP may delegate specific tasks to qualified and trained individuals — for example, acting as safety experts for certain products — provided that the QP maintains system oversight and overview of the safety profiles of all products. Such delegation should also be documented.

Information on the QP must be included in the pharmacovigilance system master file. Each pharmacovigilance system can have only one QP. However, a QP may be employed by more than one drugmaker for shared or separate pharmacovigilance systems, or may fulfill the role of QP for more than one pharmacovigilance system of the same drugmaker.

In addition to the QP, regulators in EU member states can require that companies have a pharmacovigilance contact person in their country to be their liaison to the QP if the QP is not based there.

Drugmakers must ensure that the QP has sufficient authority to carry out his or her duties. Drugmakers must also ensure that the QP has access to the pharmacovigilance system master file as well all related information on:

- Safety concerns and any other information relating to benefit-risk evaluation;
- Clinical trials and other studies that may be relevant to the safety of the drugs;
- Data from contractors; and
- Pharmacovigilance procedures at all levels to ensure consistency and compliance.

Management should inform the QP about the outcomes of the regular reviews of the quality system, as well as any changes the reviews prompt. Management should also inform the QP of

scheduled pharmacovigilance audits. The QP should also be able to trigger a pharmacovigilance audit independently. Management should provide the QP with a copy of the corrective and preventive action plan after each audit relevant to the pharmacovigilance system so that the QP can assure that appropriate corrective actions are implemented.

In particular with regard to drugmakers' adverse reaction database (or other systems to collate adverse reaction reports), drugmakers should implement procedures to ensure that the QP is able to quickly and easily obtain information from the database to respond to urgent requests for information from regulators at any time.

When a drugmaker intends to expand its product portfolio, by acquisition of another company or by purchasing products from another drugmaker, the QP should be notified as early as possible so the potential impact on the pharmacovigilance system can be assessed and the system adapted accordingly.

Drugmakers must also ensure that the QP has the knowledge and the skills for the performance of pharmacovigilance activities. Where the QP has not completed basic medical training, the drugmaker must ensure that the QP is assisted by a medically trained person.

The drugmaker should provide the QP with documented training in its pharmacovigilance system prior to the QP taking the position. Consideration should be given to additional training, as needed, of the QP in the drugs covered by the pharmacovigilance system.

The QP must reside and operate in the EU or one of the non-EEA countries Norway, Iceland or Liechtenstein. Back-up procedures in the case of absence of the QP must be in place and should be accessible through the QP's contact details. The QP should ensure that the back-up person has all necessary information to fulfill the role.

New Postmarket Safety Study Definition and Requirements

One bright spot for drugmakers under the updated EU pharmacovigilance rules is the standardized definition of a post-authorization study. Under the new definition, these studies are only conducted to identify safety hazards, confirm the safety profile, or measure the effectiveness of risk management measures. They can be voluntary, but most will be mandated by the EMA to satisfy specific weaknesses the EMA has identified in the drug's application.

Previous legislation did not clearly define what a post-authorization study was, and there was inconsistency in the way member states defined the term. While mandatory postmarketing studies will probably be more common under the pharmacovigilance rules, a consistent, EU-wide expectation of what post-authorization safety studies cover should make them easier for drugmakers to design, implement and manage.

When a study is required, a draft protocol must be submitted to the PRAC or to an EU member state authority (if requested) for endorsement before initiation of the study or modification of the protocol. The PASS format is laid down in Annex III of the Commission Implementing Regulation.

The drugmaker may be required to submit the protocol and progress reports directly to regulators in the EU member states in which the study is conducted.

One broad requirement that drugmakers must be aware of is the studies are prohibited from being promotional in nature. Drugmakers are allowed to compensate healthcare professionals who participate in the study, but only for time and expenses incurred. The PRAC will reject studies it deems promotional.

Results of the study must be communicated to the authorities via periodic safety update reports and the final report should be sent to the PRAC and, if required, the authorities of the EU member state where the study took place.

Drugmakers will be required to conduct post-authorization efficacy studies as a condition of approval in the following circumstances:

- When an initial efficacy assessment requires confirmation;
- When further efficacy data is necessary for drugs that are used in combination with other drugs, to clarify uncertainties that had not been addressed when the drugs were authorized;
- When there are uncertainties with respect to the efficacy of a drug in certain sub-populations that could not be resolved prior to marketing authorization;
- When there is a potential lack of efficacy in the long term that raises concerns about the maintenance of a positive benefit-risk balance of the drug;

- When benefits of a drug demonstrated in clinical trials are significantly affected by the use of the drug under real-life conditions, or, in the case of vaccines, protective efficacy studies have not been feasible;
- When a change in the understanding of the standard of care for a disease or the pharmacology of a drug requires additional evidence on its efficacy; or
- Where new scientific evidence is published suggesting that previous efficacy evaluations might have to be revised significantly.

Wright said one of the potential causes of a safety study — the need to better understand the safety effects of a combination of drugs — is likely to be complicated in the EU, where combination drugs are not common.

Where these products do require a safety study, the EMA expects them to be covered by a protocol developed jointly by both drugmakers whose products are used in the combination. This level of cooperation may be difficult to obtain, especially when it involves off-label uses of a drug combination.

Redefining Adverse Event Reporting with Off-label Uses

A significant new challenge in satisfying the EU pharmacovigilance rules is tracking and reporting off-label uses of a drug without appearing to promote those uses.

Before these rules, when drug companies conducted pharmacovigilance studies they had to report only on adverse events that related to the use of a product for its intended, authorized purpose. But, under the new rules, companies have to look for risks beyond the authorized purpose, said Wright.

The rules also call for drugmakers to provide an estimate of the size and characteristics of the population exposed to the product. This includes people using the product for its approved indications as well as people who might use it for unapproved, off-label uses.

“All of the guidance that we’ve given our clients for many years is to be careful not to follow too closely off-label use of your product, because if you do, you’re going to be perceived to be potentially promoting it. Suddenly, that’s no longer correct because you’re required to,” she said.

With the advent of the new rules, drugmakers must tailor their adverse events monitoring systems so that they capture events unrelated to the approved uses.

In addition to altering their data gathering systems to look for and accept these off-label adverse events reports, drugmakers must build systems for maintaining these records. The covered records include all reports of suspected adverse reactions from anywhere in the world, whether reported by healthcare professionals or consumers or events identified during a post-authorization study. Drugmakers also must make sure that subsidiaries or resellers outside the EU report adverse reactions related to any drugs that are also sold in the EU. The rules also require that reports must be stored and accessible at a location within the EU.

Drugmakers must also document their responses to adverse events. All pharmacovigilance data and documents in adverse reaction reports must be retained for at least 10 years after the product is off the market in the EU.

New Drug Safety Warning Symbol

A final key part of the new pharmacovigilance legislation is that it requires medicinal products that are being monitored particularly closely by regulatory authorities to carry a special symbol: an inverted black triangle.

Any drug regulator in the EU can order this additional monitoring, generally because the drug is new to the market or because there is limited data on its long-term use.

To comply with the new legislation, the black triangle must be included in both the summary of product characteristics and the patient information leaflet.

Far more important than the symbol's design is the message that accompanies it. The black triangle must be accompanied by a text encouraging patients and healthcare professionals to report any unexpected adverse events experienced in the treatment with these products.

Healthcare professionals have an ethical obligation to report. What will be new for drug-makers, Wright said, is they now must provide a detailed explanation for patients and others about how to report by mail, electronically and by other means, such as the telephone.

She said U.S.-based pharmaceutical companies may find fulfilling this obligation less of a challenge than European-based companies because such reporting is encouraged in the U.S. already, whereas it is a newer concept in the EU.

Coming Developments in Pharmacovigilance

As the pharmacovigilance rules have been put in place, there are several pieces yet to fall into place. For example, member states are required to establish public web portals that contain summaries of product characteristics and patient information leaflets for medicinal products authorized in EU member states.

These portals will also include:

- Public assessment reports;
- Summaries of risk management plans;
- Lists of medicinal products subject of additional monitoring; and
- Ways to report suspected adverse events in relation to medicinal products.

At this point, the websites are in their infancy, as member states budget for and design the portals, which must be interoperable with the central EudraPharm database, which will provide comprehensive information on all medical products authorized in the EU by the EC and the EU member states.

EudraPharm ultimately will connect with the European Clinical Trials Database (EudraCT). It marks the final step of a process through which summary clinical trial results will be made publicly available through the EU Clinical Trials Register (EU CTR).

The goal of the web portals is to make risk information about drugs more widely available in people's native language and increase reporting of adverse reactions. EudraPharm "still has got a long way to go before it's going to provide any kind of meaningful information about medicinal products," Wright said. For now, she said, the EMA's website is the best source of information about drugs in Europe, but she expects the EudraPharm network will eventually surpass it.

"In EudraPharm's defense, it has faced a lot of obstacles in getting as far as it has. And they are not only because a lot of marketing authorization holders objected to having their information — the risk management, for example — made publicly available," she said.

Drugmakers should be prepared for the day when the network of sites is up and running because they will want to make sure their product information is accurate and up-to-date in all the locations where it appears.

Another change that's in the works involves possible changes to the SmPC and PIL formats. The EC was expected to present a report on the shortcomings of the current formats in 2012, but the report is still being developed. It may eventually lead to changes in these forms.

At the heart of the whole pharmacovigilance network is the EMA's EudraVigilance database, which houses all data on side-effect reports and adverse reactions/events. As the pharmacovigilance systems generate more and more data, the EMA expects the database will help it with signal-detection of safety problems that will drive new rapid-alert and incident-management systems for responding to the signals.

As it has been building out its database, it's also updating the access policy for the Eudra-Vigilance database. The new policy changes will allow much greater access to the database to international regulators, the World Health Organization, and individual researchers who want to make use of the data. The changes mean more people will be reviewing pharmacovigilance data looking for drug safety problems.

Another element of pharmacovigilance planning that drugmakers should be aware of is the increased sharing of information between the EU and other countries. While it has been slow to develop, such sharing is in the offing.

In February 2014, EMA and the FDA set up a new working group on pharmacovigilance topics, which will meet on a regular basis via videoconference to share data about drug safety issues. The goal of the group is to more quickly identify safety issues in one country that may affect another country. Canadian and Japanese regulatory authorities also will participate in the meetings as observers.

Appendices

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- G. Pharmacovigilance Inspections
- H. Pharmacovigilance Audits
- I. Risk Management Systems
- J. Management and Reporting of Adverse Reactions to Medicinal Products
- K. Periodic Safety Update Report
- L. Post-Authorisation Safety Studies
- M. Member States' Requirements for Transmission of Information on Non-interventional Post-authorisation Safety Studies
- N. Signal Management
- O. Additional Monitoring
- P. Safety Communication
- Q. Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators

Appendix A: PRAC Members

PRAC Members

The following list contains the current members and alternates of the Pharmacovigilance Risk Assessment Committee (PRAC).

Chair

June Munro Raine

Director of Vigilance and Risk Management

Medicines and Healthcare products Regulatory Agency, (United Kingdom)

Vice-Chair

Almath Spooner

Pharmacovigilance and Risk Management Lead

Irish Medicines Board, (Ireland)

Members Nominated by Member States

Austria

Harald Herkner

Associate Professor and Consultant

Department of Emergency Medicine/Medical University Vienna, (Austria)

Alternate

Jan Neuhauser

Deputy Head of Department Clinical Assessment of Safety and Efficacy Medical Assessor

AGES, (Austria)

Belgium

Jean-Michel Dogné

Full Professor (Drug Development, Pharmacovigilance, Pharmacology)

University of Namur, (Belgium)

Alternate

Veerle Verlinden

File Manager and Evaluator (Pharmacovigilance)

Federal Agency for Medicines and Health Products, (Belgium)

Bulgaria

Maria Popova-Kiradjieva

Head of Drug Information and Pharmacovigilance Department in Medicines Use Control

Department

Bulgarian Drug Agency, (Bulgaria)

Alternate

Yuliyana Eftimova

Chief Expert — Pharmacovigilance Division

Bulgarian Drug Agency, (Bulgaria)

Croatia

Viola Macolić Šarinić

Head of Agency

Agency for Medicinal Products and Medical Devices (HALMED), (Croatia)

Alternate

Marin Banovac

National Expert on Signal Management

European Medicines Agency, (United Kingdom)

Cyprus

Nectaroula Cooper

Head of the Pharmacovigilance Department

Pharmaceutical Services, Ministry of Health, (Cyprus)

Alternate

Zena Gunther

Pharmacist

Pharmaceutical Services, Ministry of Health, (Cyprus)

Czech Republic

Jana Mladá

Head of Marketing Authorization Branch

State Institute for Drug Control, (Czech Republic)

Alternate

Eva Jirsová

Head of Pharmacovigilance Unit

State Institute for Drug Control, (Czech Republic)

Denmark

Doris Stenver

Chief Medical Officer

Danish Health and Medicines Authority, (Denmark)

Alternate

Torbjorn Callreus

Chief Medical Officer

Danish Health and Medicines Authority, (Denmark)

Estonia

Maia Uusküla

Head of the Bureau of Pharmacovigilance

State Agency of Medicines, (Estonia)

Alternate

Katrin Kiisk

Deputy Director General

State Agency of Medicines, (Estonia)

Finland

Kirsti Villikka

Senior Medical Officer

Finnish Medicines Agency, (Finland)

Alternate

Terhi Lehtinen

Senior Medical Officer

Finnish Medicines Agency, (Finland)

France

Arnaud Batz

Pharmacovigilance Assessor

ANSM — French Health Authority, (France)

Alternate

Patrick Maison

Director

ANSM, (France)

Germany

Martin Huber

Head of Department “PRAC and other Committees”

Federal Institute for Drugs and Medical Devices (BfArM), (Germany)

Alternate

Valerie Strassmann

Head of Department “Post-Authorisation Safety Studies, Pharmacovigilance Centres, Pharmacoepidemiology”

Federal Institute for Drugs and Medical Devices (BfArM), (Germany)

Greece

Leonidas Klironomos

Pharmacovigilance Officer

Ministry of Health, National Organization for Medicines, (Greece)

Alternate

Agni Kapou

Pharmacovigilance Officer in the Adverse Drug Reaction Department

Ministry of Health — National Organization for Medicines (EOF), (Greece)

Hungary

Julia Pallos

Head of Biomedical Division and Pharmacovigilance

GYEMSZI — National Institute of Pharmacy, (Hungary)

Alternate

Melinda Palfi

Assessor

National Institute for Quality and Organizational Development in Healthcare and Medicine

GYEMSZI — National Institute of Pharmacy, (Hungary)

Iceland

Guðrún Kristín Steingrimsdóttir

Clinical Assessor

Icelandic Medicines Agency, (Iceland)

Alternate

Hrefna Gudmundsdóttir

Clinical Expert — Scientific Advice and Pharmacovigilance
Icelandic Medicines Agency, (Iceland)

Ireland

Almath Spooner
Pharmacovigilance and Risk Management Lead
Irish Medicines Board, (Ireland)

Alternate

Ruchika Sharma
Vigilance Assessor
Irish Medicines Board, (Ireland)

Italy

Carmela Macchiarulo
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Italian Medicines Agency, (Italy)

Alternate

Jelena Ivanovic
Physician (M.D., Ph.D.) — AIFA Expert on Issues Concerning Antiretroviral Medicines Use
in Pregnancy (PK/PD, efficacy and safety)
Italian Medicines Agency, (Italy)

Latvia

Andis Lacis
Assistant Professor of Pediatric Oncology
Riga Stradins University, (Latvia)

Alternate

Inguna Adoviča
Director
State Agency of Medicines of the Republic of Latvia, (Latvia)

Liechtenstein

It was mutually agreed that Austria will take over Liechtenstein's tasks in the PRAC.

Lithuania

Jolanta Gulbinovic

Chief expert

State Medicines Control Agency, (Lithuania)

Alternate

Rita Dzetaveckiene

Pharmacovigilance Assessor

State Medicines Control Agency, (Lithuania)

Luxembourg

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Division of Pharmacy and Medicines, Ministry of Health, (Luxembourg)

Alternate

Nadine Petitpain

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University Hospital of Nancy, (France)

Malta

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Pharmacovigilance Pharmacist

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Netherlands

Sabine Straus

Staff Member

Medicines Evaluation Board, (Netherlands)

Alternate

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Pharmacovigilance Expert

Medicines Evaluation Board, (Netherlands)

Norway

Ingebjørg Buajordet

Scientific Director

Norwegian Medicines Agency, (Norway)

Alternate

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Norwegian Medicines Agency, (Norway)

Poland

Adam Przybylkowski
External Expert, Pharmacovigilance Department
The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products,
(Poland)

Alternate

Magdalena Budny
Top Specialist in Assessment of Clinical Safety Variations, PSURs and RMPs
The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products,
(Poland)

Portugal

Margarida Guimarães
Pharmacovigilance and Project Manager/Assessor
INFARMED — National Authority of Medicines and Health Products, (Portugal)

Alternate

Magda Pedro
Quality Auditor of the Internal Audit Body of INFARMED
INFARMED — National Authority of Medicines and Health Products, (Portugal)

Romania

Nicolae Fotin
Head of the Logistics, Informatics and Data Management Department
National Agency for Medicines and Medical Devices, (Romania)

Alternate

Roxana Stefania Stroe
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National Agency for Medicines and Medical Devices, (Romania)

Slovakia

Tatiana Magalova
Senior Pharmacovigilance Assessor
State Institute for Drug Control, (Slovakia)

Alternate

Anna Mareková
Pharmacovigilance Assessor
State Institute for Drug Control, (Slovakia)

Slovenia

Milena Radoha-Bergoč
Head of Pharmacovigilance Department
Agency for Medicinal Products and Medical Devices of the Republic of Slovenia, (Slovenia)

Alternate

Gabriela Jazbec
Pharmacovigilance Assessor
Agency for Medicinal Products and Medical Devices of the Republic of Slovenia, (Slovenia)

Spain

Dolores Montero Corominas
Head of the Division of Pharmacoepidemiology and Pharmacovigilance
Agencia Española de Medicamentos y Productos Sanitarios, (Spain)

Alternate

Miguel-Angel Macia
Head Risk Assessment Unit-Pharmacoepidemiology and Pharmacovigilance Division
Spanish Agency of Medicines and Medical Devices (AEMPS), (Spain)

Sweden

Qun-Ying Yue
Senior Expert in Pharmacovigilance
Medical Products Agency, (Sweden)

Alternate

Ulla Wändel Liminga
Scientific Director Pharmacology/Toxicology
Medical Products Agency, (Sweden)

United Kingdom

Julie Williams
Expert Assessor in Pharmacovigilance and Risk Management Planning
Medicines and Healthcare products Regulatory Agency, (United Kingdom)

Alternate

Rafe Suvarna
Alternate Committee for Medicinal Products for Human Use (CHMP) member
Medicines and Healthcare products Regulatory Agency, (United Kingdom)

Independent Scientific Experts Nominated by the European Commission

Jane Ahlqvist Rastad
Clinical Assessor, Senior Expert
Medical Products Agency, (Sweden)

Marie Louise (Marieke) De Bruin
Pharmacovigilance Expert
Medicines Evaluation Board, (Netherlands)

Stephen J. W. Evans
Professor of Pharmacoepidemiology
London School of Hygiene and Tropical Medicine, (United Kingdom)

Brigitte Keller-Stanislawski
Head of the Department Safety of Medicinal Products and Medicinal Devices
Paul-Ehrlich-Institut, (Germany)

Herve Le Louet
Head of the Pharmacovigilance and Risk Management Department
University Hospital Henri Mondor, (France)

Lennart Waldenlind
Clinical Assessor
Medical Products Agency, (Sweden)

Representative of Healthcare Professionals Nominated by the European Commission

Filip Babylon
Pharmacist/Pharmacy Owner
Apotheek Babylon BVBA, (Belgium)

Alternate

Kirsten Myhr
Special Adviser on Medicines Information to Health Professionals and Consumers, Handling Adverse Drug Reactions Reports from Health Professionals on Behalf of the Norwegian Medicines Agency
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Representative of Patients Organizations Nominated by the European Commission

Albert van der Zeijden
Patient Advocate
International Alliance of Patients' Organizations (IAPO), (Netherlands)

Alternate

Marco Greco
Chairman
European Federation of Crohn's & Ulcerative Colitis Associations (volunteer), (Italy)

Appendix B: Pharmacovigilance System Manual



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 June 2014
EMA/623550/2013
Inspections and Human Medicines Pharmacovigilance Division

EMA pharmacovigilance system manual

Version 1.1



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20/01/2014	F. Diafouka	Adoption	- Insertion of comments received from all 4 Human Medicines divisions.	Adopted by Human Medicines Leadership Team on 20/01/2014
28/01/2014	F. Diafouka	Sign off prior to internal publication	- Sign off of EMA Pharmacovigilance System Manual for internal use	Signed off by the EMA Executive Director on 28/01/2014
12/06/2014	F. Diafouka	Update for sign off prior to publication on EMA website	- Insertion of updated organisational chart - Harmonised description of Divisions' responsibilities - Updated description of EU Telematics programme - Deletion of 3 annexes	Signed off by the EMA Executive Director on 30/06/2014

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1. Legal background

Legal requirements related to the European Medicines Agency (EMA) pharmacovigilance system for human medicines are laid down in [Regulation \(EC\) No 726/2004](#), [Directive 2001/83/EC](#) and [Commission Implementing Regulation \(EU\) No 520/2012](#).

Article 28e of Regulation (EC) No 726/2004 specifies that "the Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available in the Union." The establishment of a functioning EMA pharmacovigilance system is to be the subject of regular audits and regular publication of a report by the European Commission, as outlined in Articles 28f and 29 of Regulation (EC) No 726/2004. Article 28f states that "the Agency shall perform regular independent audits of its [pharmacovigilance tasks](#) and report the results to its Management Board on a 2-yearly basis", while Article 29 emphasises that "the Commission shall make public a report on the performance of the [pharmacovigilance tasks](#) by the Agency on 2 January 2014 at the latest and subsequently every 3 years thereafter."

Article 87a(b) of Regulation (EC) No 726/2004 links in the more detailed Commission Implementing Regulation by stating that "in order to harmonise the performance of the pharmacovigilance activities provided for in this Regulation, the Commission shall adopt implementing measures as provided for in Art. 108 of Directive 2001/83/EC covering the following areas:

(b) The minimum requirements for the quality system for the performance of pharmacovigilance activities by the Agency."

Three paragraphs in Article 8 of the Commission Implementing Regulation set out the specific characteristics of the EMA pharmacovigilance system. Those characteristics are described further in the non-legally binding good pharmacovigilance practice (GVP) modules I and II, relating respectively to the description of the [pharmacovigilance systems and their quality systems](#) for competent authorities and for marketing-authorisation holders and the [pharmacovigilance system master file](#) for marketing-authorisation holders.

Article 8 of the Commission Implementing Regulation (EC) No 520/2012 makes reference in particular to the following points:

- (1) Marketing authorisation holders, the national competent authorities and the Agency shall establish and use a quality system that is adequate and effective for the performance of their pharmacovigilance activities.
- (2) The quality system shall cover organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.
- (5) All persons involved in the procedures and processes of the quality systems established by the national competent authorities and the Agency for the performance of pharmacovigilance activities shall be responsible for the good functioning of those quality systems and shall ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system.

2. EMA mission and principal activities

In accordance with the provisions of European Union (EU) legislation relating to medicinal products, the European Medicines Agency is the EU body responsible for coordinating the existing scientific

resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

The EMA is responsible, in particular, for:

- providing independent, science-based recommendations on the quality, safety and efficacy of medicines, and on more general issues relevant to the promotion and protection of public health that involve medicines;
- implementing measures for continuously supervising the quality, safety and efficacy of authorised medicines to ensure that their benefits outweigh their risks;
- publishing impartial and comprehensible information about medicines and their use;
- developing best practice for medicines evaluation and supervision in Europe, and contributes alongside the Member States and the European Commission to the harmonisation of regulatory standards at the international level.

The [mission statement](#) of the EMA can be found on its public website.

The scientific resources and experts dedicated to the performance of pharmacovigilance activities defined by the EU legislation include, in particular, the Pharmacovigilance Risk Assessment Committee (PRAC) and the Committee for Medicinal Products for Human Use (CHMP).

The mandate of the PRAC covers all aspects of the risk management, including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit. The CHMP is responsible for preparing the Agency's opinions on all questions concerning medicines for human use and plays a key role in the monitoring of the change in the benefit-risk balance for medicinal products, making, when necessary recommendations to the European Commission regarding changes to a medicine's marketing authorisation, or its suspension/withdrawal from the market. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD-h) is responsible for examining any questions relating to marketing authorisations and variations of the terms of the marketing authorisation for medicinal products authorised through the mutual recognition or the decentralised procedure.

In order to comply with its legal obligations related to the promotion and protection of public health through the safety monitoring of authorised medicinal products and to detect and confirm any change to their risk-benefit balance, the Agency operates a quality assured pharmacovigilance system. The EMA has a coordinating role in the functioning of the EU pharmacovigilance system in collaboration with the Member States and the European Commission.

3. EMA pharmacovigilance system

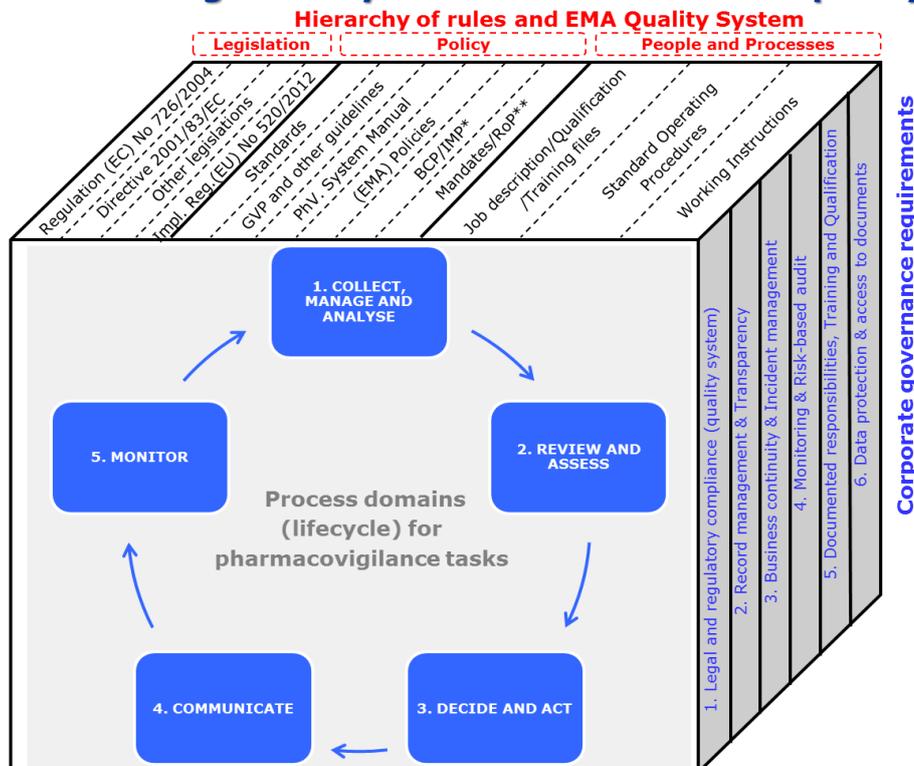
The EMA pharmacovigilance system is described in this manual, which covers the EMA organisational structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management. This manual does not cover pharmacovigilance aspects related to veterinary medicines.

The detailed operational requirements of all EMA pharmacovigilance tasks that constitute the EMA pharmacovigilance system are set out in the Agency's policies, standard operating procedures (SOPs) and work instructions (WINs), which are part of the EMA's integrated quality management system and can be found on the [Agency's website](#).

The EMA pharmacovigilance system is embedded in the Agency's overall quality system, and takes account of key corporate governance structure requirements outlined in the Agency's mission and policies, such as transparency and data protection (see Figure 1.).

Figure 1. The EMA pharmacovigilance system in the context of the EMA quality system

EMA Pharmacovigilance system in context of EMA quality system



* IMP = incident management plan. ** RoP = rules of procedure.

The pharmacovigilance system manual sets out the key principles for monitoring the performance of the EMA pharmacovigilance system and reporting on the EMA pharmacovigilance tasks, as laid down in the legislation.

3.1. Documentation

The EMA pharmacovigilance system is documented in this pharmacovigilance system manual, which is reviewed at least once a year by the Human Medicines Leadership Team, which provides recommendations to the EMA Strategy Board. Updates of the manual take account of:

- ongoing implementation of the pharmacovigilance legislation leading to the adoption of new pieces of guidance (e.g. GVP) as well as the development and operation of new pharmacovigilance tasks or re-engineering of existing pharmacovigilance tasks;
- ongoing development and implementation of other legislation, as applicable;
- relevant EMA organisational changes leading to changes of accountability or responsibility.

The pharmacovigilance system manual and any change to it are authorised by the Executive Director of the EMA.

It is the responsibility of the Inspections and Human Medicines Pharmacovigilance Division (P-Division) to maintain the pharmacovigilance system manual for which the signed copy is published. The pharmacovigilance system manual is modified by P-Division staff appointed by the Head of P-Division.

For any request for amendment of the EMA pharmacovigilance system manual, the Head of P-Division or the lead author can be contacted.

If the change request is authorised by the EMA Executive Director further to its agreement by the Human Medicines Leadership Team and endorsement by the EMA Strategy Board, the electronic version (master copy) of the pharmacovigilance system manual will be updated and a change notification will be published on the Agency's intranet and sent both to the initial requester and the Human Medicines Leadership Team. If the change request is not approved, the initial requester as well as the Human Medicines Leadership Team will receive a notification, together with a justification for not accepting the change.

3.2. Definition and characteristics

The EMA pharmacovigilance system is the system used to fulfil the Agency's legal tasks and responsibilities in relation to pharmacovigilance, and is designed to monitor the safety of authorised medicinal products within the Agency's scope and detect and confirm any change to their risk-benefit balance. The EMA pharmacovigilance system is characterised by its structures, resources, processes, tools, outputs and outcomes.

The cycle of the quality system is based on the four following activities:

- Quality planning: establishing structures and planning integrated and consistent processes.
- Quality adherence: carrying out tasks and responsibilities in accordance with quality requirements.
- Quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out.
- Quality improvements: correcting and improving the structures and processes where necessary.

3.3. EMA data and record management

All data, documents and records related to the EMA pharmacovigilance system are physically and electronically stored in designated folders and databases, and retained in accordance with the relevant legislation and requirements of the EMA integrated quality management system on data and record management.

3.4. Subcontracting of EMA pharmacovigilance tasks

The subcontracting of EMA pharmacovigilance tasks belonging to the EMA pharmacovigilance system is done in accordance with the requirements of the EMA integrated quality management system.

The EMA retains responsibility for the pharmacovigilance tasks that have been subcontracted and performs regular audits of subcontractors.

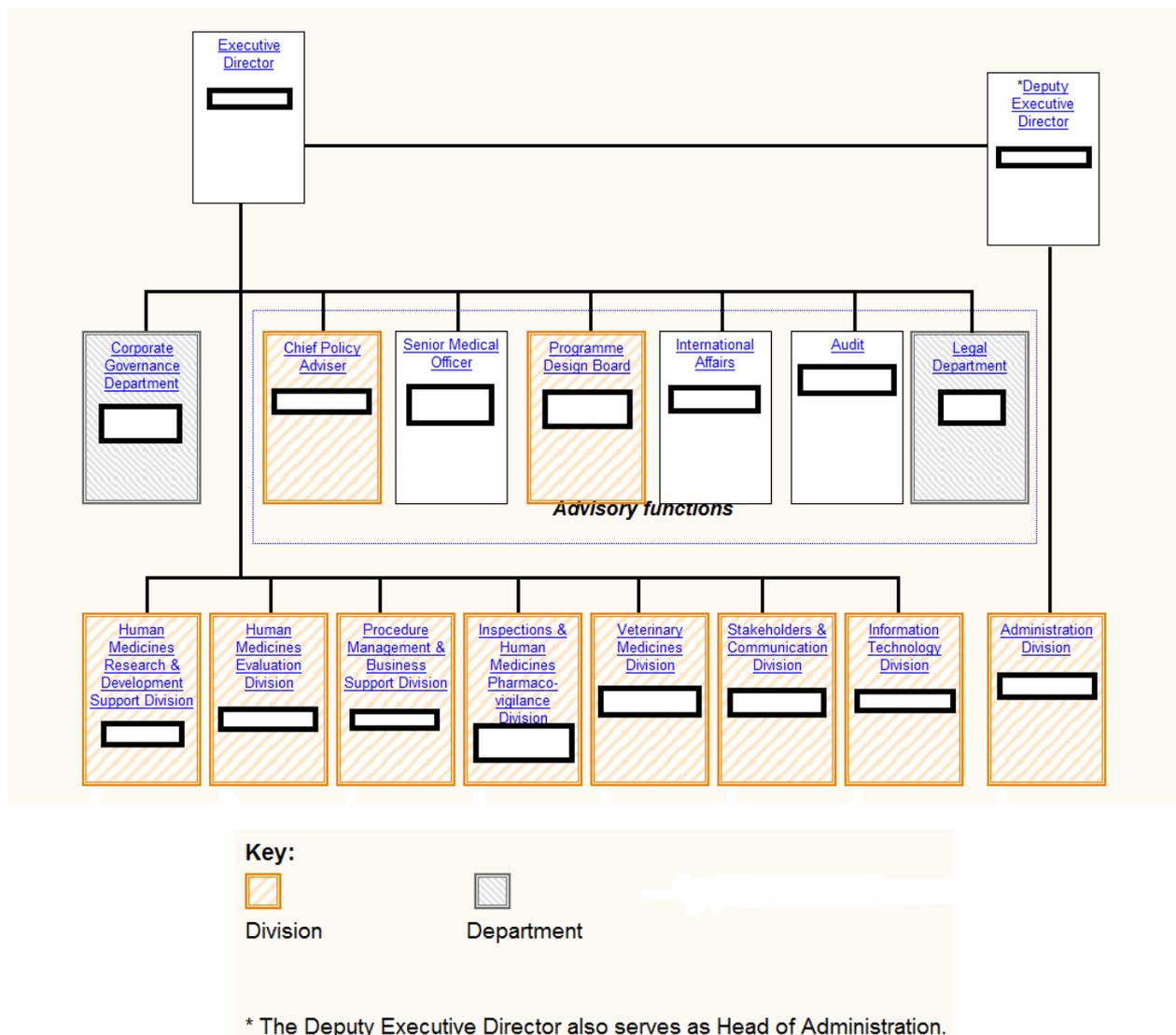
A list of subcontractors involved in EMA pharmacovigilance tasks is maintained by the Agency.

4. Overall responsibilities

4.1. EMA organisational structure

The EMA organisational chart (see Figure 2.) displays the overall matrix approach, the hierarchical relationship within divisions and the relationships between all EMA divisions.

Figure 2. EMA organisation chart (as of 1st February 2014)



4.2. EMA responsibilities

4.2.1. Executive director

The EMA executive director is the legal representative of the European Medicines Agency and has overall responsibility for:

- the day-to-day administration and operations, including the EMA pharmacovigilance system (for which he authorises the pharmacovigilance system manual and any change to it);
- the management of all Agency resources;

- the compliance with legal timelines;
- the appropriate coordination between committees and the coordination group;
- all budget and staff-related matters;
- the provision of the secretariat for the EMA Management Board.

The Management Board is the EMA supervisory body to which the executive director submits for approval each year a draft report covering the activities of the EMA in the previous year and a draft work programme for the coming year.

The Management Board is the European Medicines Agency’s integral governance body. It has a supervisory role with general responsibility for budgetary and planning matters, the appointment of the EMA executive director and the monitoring of the Agency’s performance.

4.2.2. Heads of division

The heads of division are responsible for the daily operation of the EMA pharmacovigilance tasks within their divisions and for monitoring the quality of the outputs generated under their responsibility.

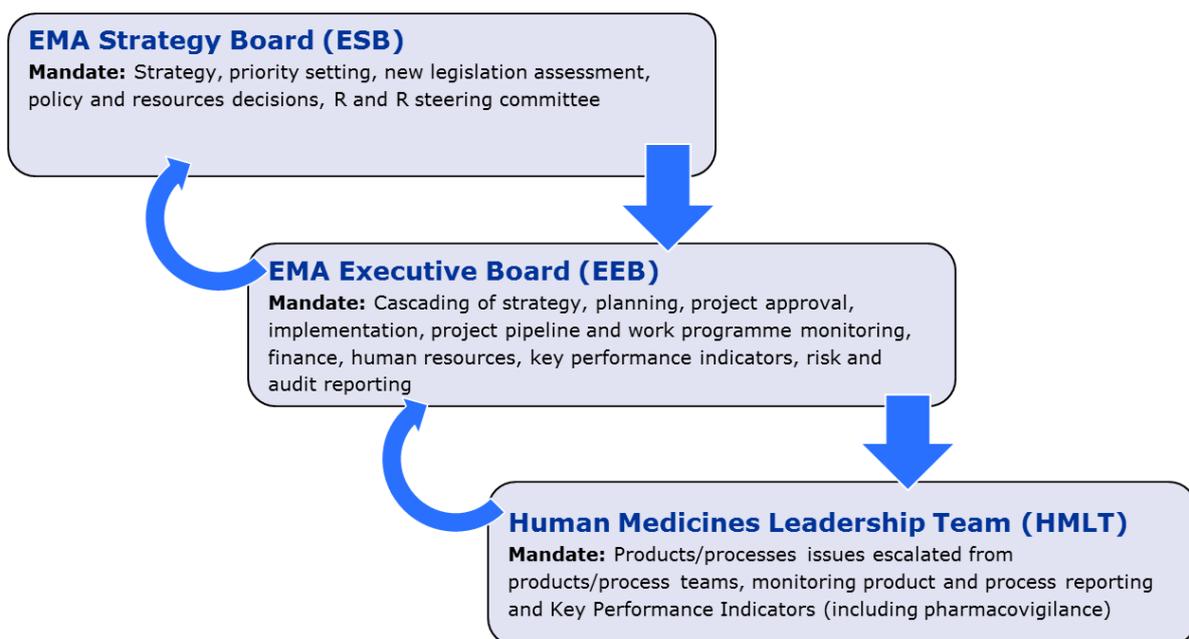
The heads of division — particularly Divisions D, B, E and P (for full names of the corresponding divisions see Section **4.2.4 Divisions supporting the functioning of the EMA pharmacovigilance system**), who form the core of the Human Medicines Leadership Team — are responsible for the overall organisation, effective running and monitoring of their EMA pharmacovigilance tasks.

On the basis of the data and information provided by the other heads of division, the head of P-Division is responsible for coordinating the monitoring of the EMA pharmacovigilance system.

4.2.3. Governance of EMA management

Figure 3. outlines the EMA governance for human medicines, including pharmacovigilance-related aspects.

Figure 3. EMA governance for human medicines



4.2.4. Divisions supporting the functioning of the EMA pharmacovigilance system

4.2.4.1. Inspections and Human Medicines Pharmacovigilance (P-Division)

The Division is responsible for pharmacovigilance, including signal detection and management and monitoring of products on the market, and provides leadership for the Agency's pharmacovigilance system.

It ensures the coordination of inspections and good practice standards. It deals with incident management in the area of safety and quality of human medicines, in liaison with the European medicines regulatory network. The Division maintains close contact with international partners in the areas of inspection and pharmacovigilance in conjunction with the Agency's International Affairs function.

4.2.4.2. Procedure Management and Business Support (B-Division)

The Division ensures operational excellence in the management of the Agency's product-related procedures (e.g. Risk Management Plans (RMPs), Periodic Safety Update Reports (PSURs)), associated regulatory support and validation of applications. It provides organisational, regulatory and procedural management for the operation of the committees, including the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD-h).

It is responsible for product, application and information support to the Agency's operations, management of product databases (e.g. SIAMED, EudraVigilance, PSUR repository) and data quality, data analysis to support the Agency's decision-making, and provision of access to documents and information.

4.2.4.3. Human Medicines Evaluation (E-Division)

The Division is responsible for the planning and reporting of the activities related to human medicines evaluation (e.g. RMPs, PSURs), in particular ensuring that the evaluation of all submissions is performed in a timely manner, and with the highest possible quality.

It manages the establishment of competencies in the therapeutic areas related to the medicinal products being evaluated, as well as those specialist scientific disciplines that are necessary to ensure a comprehensive assessment, to support and complement the competencies available in the network.

4.2.4.4. Human Medicines Research and Development Support (D-Division)

The Division is in charge of providing scientific advice on all products and issues related to medicine development, and of proposing measures specifically aimed at fostering development of new medicines in orphan diseases and paediatric populations.

It is responsible for provision of regulatory intelligence to Agency staff, scientific bodies and interested parties throughout the medicinal-product lifecycle, and for coordinating the development of best evidence to support regulatory decision-making, managing research projects and scientific procurement, and liaising with research funding bodies.

4.2.4.5. Stakeholders and Communication (S-Division)

The Division is responsible for ensuring that the Agency has a coherent, coordinated and consistent approach to stakeholder and partner relations management and communication.

It manages relations with and information to patients and healthcare professionals, and coordinates medicines information in the European medicines regulatory network. The Division manages the Agency's online presence, external communication and press relations, as well as the information centre.

The Division manages relations with the pharmaceutical industry, and provides support to micro, small and medium-sized enterprises (SMEs) through its SME Office.

4.2.4.6. Administration (A-Division)

The European Medicines Agency's Administration Division is responsible for managing revenue, expenditure and accounts according to existing rules and regulations, for recruiting, managing and administering staff and seconded personnel, and for providing and running the necessary infrastructure services for the effective functioning of the Agency.

It cooperates closely with the European Parliament and the Council of the European Union (Budgetary Authority), as well as the European Commission, European Court of Auditors and other European agencies on matters relating to administration, the budget, personnel and rules and regulations on finances, audit and accounting.

4.2.4.7. Information Technology (I-Division)

The Division enables the Agency, its staff, members of its committees, working parties and advisory groups, and other stakeholders, to make efficient and effective use of information technology in order to achieve its organisational and policy objectives.

It provides high-quality and advanced information-technology-infrastructure solutions and e-services, support services, and unified telecommunications facilities including solutions for physical and virtual meetings, in addition to the information systems required to support Agency corporate business processes.

It delivers the systems defined in the European Union telematics strategy for use by the European regulatory network, the pharmaceutical industry, healthcare professionals and the general public.

4.2.5. Audit function

The Audit function is responsible for providing to the executive director independent, objective assurance and consulting services designed to add value and improve the organisation's operations. The function provides independent and professional audit services, founded on sound values and ethics, to support informed decision-making and accountability across the Agency. The Audit activity helps the Agency to accomplish its objectives by bringing a systematic, disciplined approach to evaluating and improving the effectiveness of risk management, control and governance processes.

The head of the Audit function has overall responsibility for pharmacovigilance audits of EMA pharmacovigilance tasks.

4.2.6. Corporate Governance Department

The Corporate Governance Department reports directly to the EMA executive director and provides support to the Management Board and Agency management, through coordination of planning, monitoring, risk management, quality management (including all EMA policies, standard operating procedures and work instructions supporting EMA pharmacovigilance tasks) and internal communication activities.

It also ensures a permanent link between the EMA executive director and the EU Member State national competent authorities.

4.2.7. Human Resources Department

The head of the Human Resources Department has the responsibility to support all heads of division in relation to all aspects related to human resources management, such as coordination of recruitment of adequately qualified and experienced EMA staff, and oversight of the development and maintenance of training plans and records supporting EMA pharmacovigilance tasks.

4.2.8. Chief Policy Adviser

The Chief Policy Adviser focuses on the strategic alignment of the Agency to European Union (EU) legislation, liaison with EU institutions, development of new policies and crisis management.

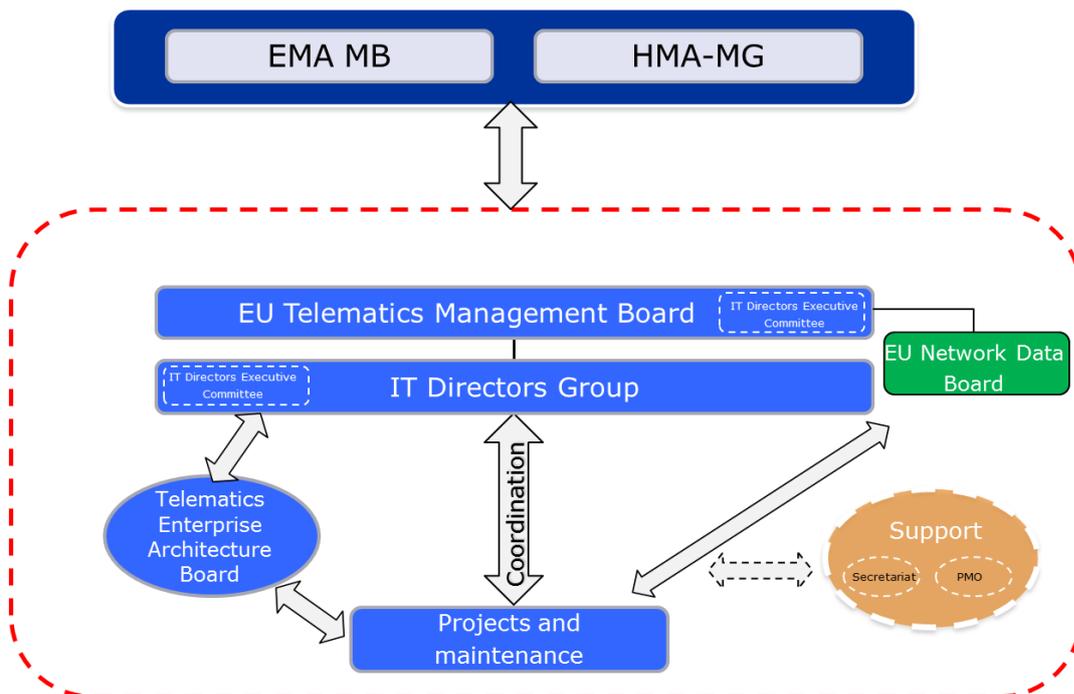
4.2.9. EU Telematics programme

EU Telematics is the collective name for a joint endeavour in the context of the regulation of medicines for human and veterinary use between the European Commission, the European Medicines Agency and national competent authorities (medicines regulatory authorities in Member States). Together, these make up the EU regulatory network which has shared responsibility for implementing the EU Telematics Strategy.

The EU Telematics Strategy aims to put in place and maintain common information-technology (IT) services to implement European pharmaceutical policy and legislation. These services should be effective, add value and help to optimise support to the EU regulatory network in the regulation of medicines for the protection of human and animal health.

Figure 4. Joint EU Telematics governance model

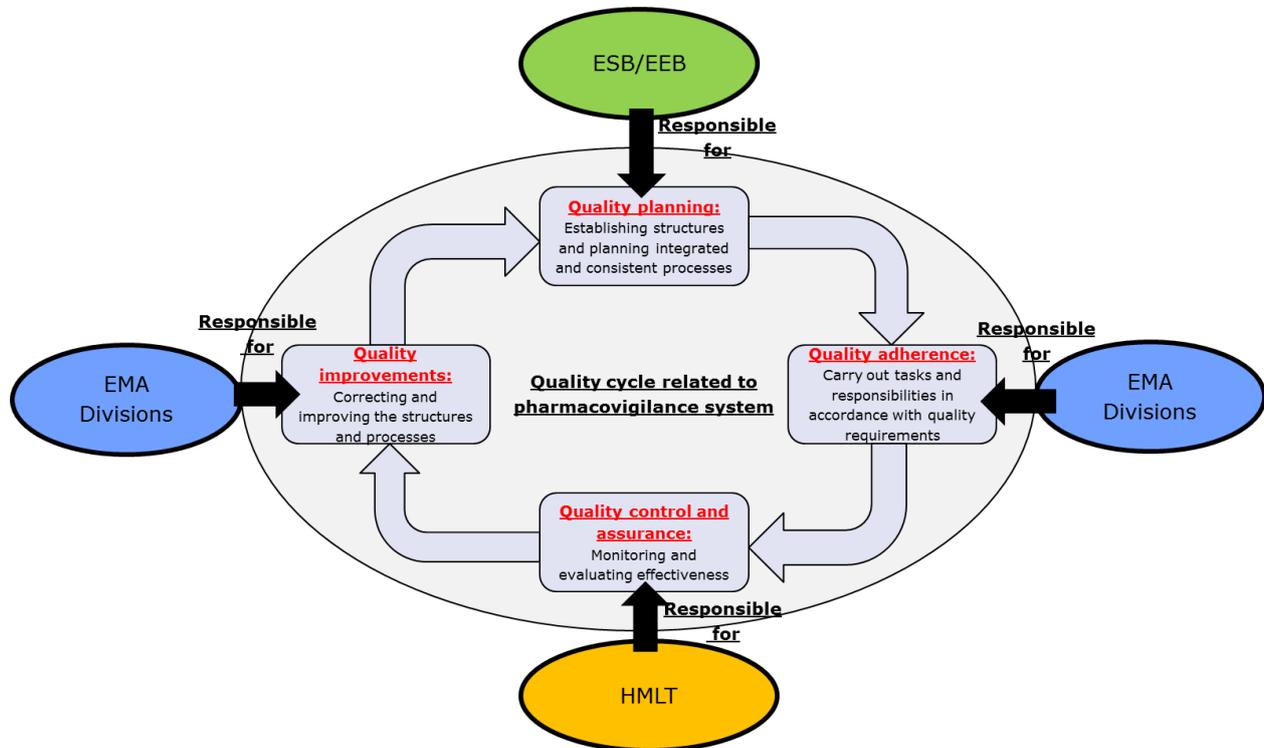
The joint EU Telematics governance model



4.3. EMA management responsibility in the quality cycle of the pharmacovigilance system

Figure 5 displays EMA leadership responsibility in the quality cycle related to the pharmacovigilance system. All steps forming part of the quality cycle are described in Article 8 of the Implementing Regulation.

Figure 5. EMA leadership responsibility in the quality cycle (pharmacovigilance system)



4.4. Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (PRAC) is the committee at the European Medicines Agency that is responsible for assessing and monitoring safety issues for human medicines.

The PRAC's recommendations are considered by the Committee for Medicinal Products for Human Use (CHMP) when it adopts opinions for centrally authorised medicines and referral procedures and by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) when it provides a recommendation on the use of a medicine in Member States.

4.5. Committee for Medicinal Products for Human Use (CHMP)

The Committee for Medicinal Products for Human Use is responsible for evaluating applications and formulating opinions serving as a basis for granting, varying, suspending or withdrawing marketing authorisations for centrally authorised products. The CHMP also prepares opinions on post-authorisation emerging safety concerns, procedures for the assessment of periodic safety update reports (PSURs) and procedures for post-authorisation safety studies for centrally authorised products, as well as for nationally authorised products (including those through the mutual recognition or the decentralised procedure), in the framework of regulatory procedures at EU level in which at least one centrally authorised product is involved. For questions related to pharmacovigilance activities and risk-management systems, the CHMP relies on the recommendations of the PRAC.

4.6. Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) is responsible for examining any questions relating to marketing authorisations and variations of the terms of the marketing authorisation for medicinal products authorised through the mutual recognition or the decentralised procedure, as well as questions concerning nationally authorised products arising from assessments of periodic safety update reports, non-interventional post-authorisation safety studies and regulatory procedures at EU level. For questions in relation to pharmacovigilance, the CMDh reaches a position, based on a PRAC recommendation, on regulatory procedures at EU level when only nationally authorised products are concerned.

5. EMA pharmacovigilance tasks

The following EMA pharmacovigilance tasks for centrally authorised products and nationally authorised products, where applicable (see also Figure 6), are based both on the EU pharmacovigilance legislation and the good pharmacovigilance practice (GVP) modules:

1. EMA pharmacovigilance system delivering the requirements of the quality system (based on GVP Module I).
2. Pharmacovigilance inspections (based on GVP Module III).
3. Risk-management systems (based on GVP Module V).
4. ADR management (based on GVP Module VI), including ADR collection and management as well as provision of data support and analysis.
5. Periodic safety update reports (based on GVP Module VII), including management of EURD list.
6. Post-authorisation studies (based on GVP Module VIII).
7. Signal management (based on GVP Module IX).
8. Emerging safety issues (based on GVP Module IX) and incident management (see Section 12 of this manual).
9. Management of the list of products, including products under additional monitoring (GVP Module X), as well as the list of withdrawn products.
10. Safety communications (based on GVP Module XV).
11. Pharmacovigilance referrals.
12. Guidance coordination (including GVP development) and standards for the system.
13. Training and capacity building, including ENCePP.
14. Monitoring the compliance of marketing-authorisation holders.
15. Coordination of pharmacovigilance enquiries.
16. Coordination of development of best evidence to support regulatory decision-making.

5.1. Groups of processes covering pharmacovigilance throughout the product lifecycle

In order to build a responsibility assignment matrix (see Figure 6), the EMA pharmacovigilance tasks are set out in five process groups covering pharmacovigilance throughout the product lifecycle:

1. **Collect, manage and analyse.** This process group describes the collection, overall management and analysis, where applicable, of data, information and documents in relation to product safety.
2. **Review and assess.** This process group describes the overall review and analysis (e.g. by rapporteurs) of data, information and documents in relation to product safety.
3. **Decide and act.** This process group describes the overall coordination of decision-making through committees (e.g. PRAC, CHMP) and other relevant group (e.g. CMDh).
4. **Communicate.** This process group describes the overall coordination of safety communication.
5. **Monitor.** This process group describes the overall monitoring of implementation and impact of proposed regulatory actions.

6. Responsibility assignment matrix for pharmacovigilance tasks

6.1. Definitions

A responsibility assignment matrix (based on the RACI model, 'responsible, accountable, consulted, informed') describes the cross-functional roles and responsibilities and participation by various EMA divisions in completing pharmacovigilance tasks belonging to the overall EMA pharmacovigilance system.

Although the RACI approach is followed and will be enriched as the organisational structure of the Agency evolves, Figure 6, for simplicity, only displays the EMA divisions accountable for pharmacovigilance tasks embedded within the relevant process domains.

Responsible EMA divisions are those which do the work to achieve the pharmacovigilance task. Accountable EMA divisions (sometimes also referred to as approver or final approving authority) are those divisions ultimately answerable for the correct and thorough completion of the pharmacovigilance tasks. Accountable EMA divisions must sign off on (approve) work that responsible EMA divisions provide.

In the RACI model, 'consulted' refers to those whose opinions are sought by means of a two-way communication, while 'informed' relates to those who are kept up to date on progress, often only on completion of the pharmacovigilance task, by means of a one-way communication.

6.2. EMA responsibility assignment matrix for pharmacovigilance tasks

The responsibility assignment matrix (see Figure 6) is agreed and adopted by the Human Medicines Leadership Team and endorsed by the EMA Strategy board. It puts emphasis on the groups of processes that support the performance of pharmacovigilance tasks. I-Division is, however, accountable for ensuring appropriate functioning of all IT systems supporting the groups of processes and therefore the pharmacovigilance tasks. A-Division plays a key role in human resources management.

In line with the responsibility assignment matrix, specific responsibilities are described in accordance with the requirements of the EMA integrated quality management system.

Figure 6. Responsibility assignment matrix

Process domains for pharmacovigilance (throughout the product lifecycle)						
Accountability for EMA pharmacovigilance tasks		1. COLLECT/ MANAGE/ ANALYSE	2. REVIEW/ ASSESS	3. DECIDE/ ACT*	4. COMMU- NICATE	5. MONITOR
Accountable division per task		Responsibility per process domains				
EMA pharmacovigilance tasks						
P	1. EMA PhV system (GVP M. I)	P	P	P	S	P
P	2. Pharmacovigilance inspections (GVP M. III)	P	P	P	S	P
E	3. Risk-management systems (GVP M. V)	B	E	E	S	E
B	4. ADR management (GVP M. VI)	B	B	-	-	-
E	5. Periodic safety update reports (GVP M. VII)	B	E	E	S	E
E	6. Post-authorisation studies (GVP M. VIII)	B	E	E	S	E
P	7. Signal detection and management (GVP M. IX)	P	P	P	S	P
P	8. Emerging safety issues and incident management	P	P	P	S	P
B & P**	9. Management of lists of products (incl. GVP M. X)	B	B	B & P**	S	B
S	10. Safety communications (GVP M. XV)	S	S	S	S	S
B	11. Pharmacovigilance referrals	B	B	B	S	B
D & B	12. Guidance coordination and standards	D	D	D & B	S	D

Process domains for pharmacovigilance (throughout the product lifecycle)

Accountability for EMA pharmacovigilance tasks		1. COLLECT/ MANAGE/ ANALYSE					2. REVIEW/ ASSESS	3. DECIDE/ ACT*	4. COMMU- NICATE	5. MONITOR	
		Responsibility per process domains									
Accountable division per task	EMA pharmacovigilance tasks										
D	13. Training and capacity building, including ENCePP	D	D	D	S	D					
B	14. Monitoring of MAHs compliance	B	B	B	S	P					
D	15. Coordination of pharmacovigilance enquiries	D	D	D	D	D					
D	16. Coordination of development of best evidence to support regulatory decision-making	D	D	D	S	D					

* B-Division is accountable for the functioning of the decision-making through the committees and the CMDh. The divisions highlighted in the table are accountable for appropriately providing the committees with the data, information and documents required to support the overall decision-making process.

** P-Division is accountable for the maintenance of the list of products under additional monitoring.

7. Human resources management

7.1. Recruitment and training of EMA personnel

In line with relevant EU legislation and the requirements of the EMA integrated quality management system, all EMA staff are recruited on the basis of their adequate qualifications and experience. All incoming and existing EMA personnel receive initial and continued training in relation to their roles and responsibilities.

In liaison with D-Division, P-Division carries out at least once a year an assessment of training needs related to the performance of EMA pharmacovigilance tasks, taking account of scientific progress and development of new pharmacovigilance concepts. The proposed training needs are presented to the Human Medicines Leadership Team, which then provides recommendation to the EMA Strategy Board.

It is every line manager's responsibility to ensure through the establishment of a job profile that EMA personnel have adequate qualifications, experience and training to undertake their assigned EMA pharmacovigilance tasks (e.g. training needs and plans are reviewed in the biannual performance evaluation report (PER)).

Training is recorded and can be viewed through SAP HR, which is an IT system covering learning solutions for every EMA staff member and line manager, including training (See Annex 1). Training plans are established and monitored regularly to ensure that training needs to ensure adequate performance of the EMA pharmacovigilance tasks are met.

7.2. Job descriptions

Individual roles and responsibilities are documented within job descriptions that are kept up to date in accordance with relevant EMA Policies that relate to the updating of job profiles and job descriptions.

7.3. Declaration of interests

For all EMA personnel and Member State experts, declarations of interests are managed in accordance with the requirements of the EMA integrated quality management system.

8. Computerised systems and databases supporting the EMA pharmacovigilance system

A wide range of computerised systems and databases are used to support efficient functioning of the EMA pharmacovigilance system.

These computerised systems and databases are developed and maintained through both a dedicated EMA and EU IT governance structure (see section **4.2.9 EU Telematics programme**) and established working methodologies described in accordance with the requirements of the EMA integrated quality management system.

A list of functionality, together with a short description of computerised systems and databases used to support the functioning of the EMA pharmacovigilance system (receipt, collation, recording and exchange of safety information), is displayed in Annex 1.

9. Monitoring the EMA pharmacovigilance system

The EMA is legally required to monitor the performance of its pharmacovigilance system, its structures, processes, outputs and outcomes.

Outputs and outcomes are mainly distinguished by time and measurability. Outputs relate to tangible objects resulting directly from a process or task (e.g. safety communication on the EMA website). Outcomes, on the other hand, relate to the benefits received by stakeholders targeted by the outputs (e.g. changes in prescribing or dispensing behaviours as a result of DHCP letters).

9.1. Definitions of performance measures aligned with quality objectives of the pharmacovigilance system

Performance measures should be aligned with the following overall quality objectives for pharmacovigilance, as set by the EMA Strategy Board and laid down in GVP Module I:

- complying with the legal requirements for pharmacovigilance tasks and responsibilities;
- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure;
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public;

- contributing to the protection of patients' and public health.

Performance indicators (PIs) can be defined as quantifiable measures that reflect performance in the context of achieving wider goals and objectives of the Agency.

Key performance indicators (KPIs) are indicators most important to a strategic understanding of the Agency's functioning. An appropriate selection of KPIs mitigates the need for several reports on a wide range of measures that may be less relevant.

It is the responsibility of P-Division, which oversees the monitoring of the EMA pharmacovigilance system, to review at least annually the pertinence of all PIs/KPIs and propose some adjustments for alignment with the wider goals and objectives of the Agency.

It is the overall responsibility of responsible and accountable EMA divisions to monitor the quality of their outputs and to provide P-Division with the data on the KPIs and PIs related to their pharmacovigilance tasks, in accordance with the agreed reporting cycle.

9.2. Characteristics of performance measures

Objectives and performance measures (i.e. PIs and KPIs) are selected and agreed beforehand by the Human Medicines Leadership Team and adopted by the EMA Strategy Board for pharmacovigilance tasks related solely to the EMA and at EMA Management Board level for tasks related to the EU pharmacovigilance system.

Objectives and performance measures must be aligned and take into account SMART elements ('Specific Measurable Achievable Realistic objectives to be achieved within Timelines').

As opposed to performance indicators, key performance indicators relate to key processes where a deviation from target is likely to impact the functioning of the EMA pharmacovigilance system.

The European Medicines Agency maintains a list of key performance indicators, performance indicators, descriptive statistics providing an indication on workload, and impact indicators (to be further developed).

9.3. Reporting cycle

The reporting frequency is defined at Human Medicines Leadership Team level.

At least on a quarterly basis, the relevant heads of division accountable for a specific set of EMA pharmacovigilance tasks report their KPIs to P-Division.

At least on a quarterly basis, the relevant heads of division accountable for a specific set of EMA pharmacovigilance tasks report their PIs to P-Division.

9.4. Monitoring tools and mechanisms

The monitoring of all EMA pharmacovigilance tasks is an ongoing and continuous activity that is built into the EMA pharmacovigilance system.

Heads of division are accountable for setting up effective tools supporting the identification of results of performance measures that could lead to deviations from objectives. In line with agreed frequency, those results of performance measures are reported to P-Division and reviewed by the Human Medicines Leadership Team meeting. This management review also takes account, where relevant, of both results from internal controls (e.g. ex-post controls) performed according to the requirements of

the EMA integrated quality management system and quantitative and qualitative review of queries coming through the EMA pharmacovigilance helpdesk.

Any deviation from an objective, together with appropriate action taken, is discussed at Human Medicines Leadership Team level and escalated to the EMA Strategy Board when needed, in accordance with the set escalation criteria.

Further to their agreement at least at Human Medicines Leadership Team level, the relevant corrective actions and timelines are assigned to the heads of division.

Heads of division are then accountable for undertaking the assigned corrective actions and reporting on their status to P-Division within the Human Medicines Leadership Team meeting at least on a quarterly basis.

9.5. Pharmacovigilance audits

In accordance with Article 28f of Regulation (EC) No 726/2004, the Agency shall perform regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis.

The schedule of the pharmacovigilance audits is to be found in Annex 2.

The specificities of the risk-based audits of the Agency's quality system (for pharmacovigilance activities) are as described in the Implementing Measures Articles 8,14,15,16,17(1) and GVP Module IV – Pharmacovigilance audits. This GVP Module provides guidance on planning and conduct of the legally required audits, and in respect of the operation of the EU regulatory network, the role, context and management of pharmacovigilance audit activity. This Module is intended to facilitate the performance of pharmacovigilance audits, especially to promote harmonisation, and encourage consistency and simplification of the audit process through collaboration with the Pharmacovigilance Audit Facilitation Group composed of representatives from the PRAC, Member States and the EMA.

The EMA has an independent internal Audit (AF-AUD) function, which reports directly to the EMA executive director. AF-AUD is responsible for the planning and conduct of an effective pharmacovigilance audit programme designed to test the EMA pharmacovigilance tasks within the EMA pharmacovigilance system, as well as the provision of reports to the EMA Management Board every two years.

In line with relevant EMA policies, standard operating procedures and work instructions, it is the responsibility of the Head of AF-AUD to plan and ensure appropriate execution of the pharmacovigilance audit programme and to assess its efficacy, as well as ensuring that pharmacovigilance audits and subsequent improvement action plans are adequately documented and implemented, and to report directly to the EMA executive director.

It is the responsibility of the head of P-Division to report on at least a quarterly basis to the Human Medicines Leadership Team on the progress related to the implementation of corrective actions, particularly if there are corrective actions linked to critical findings.

10. Business continuity arrangements

The EMA pharmacovigilance system is operated in accordance with the requirements of the EMA integrated quality management system, as well as plans related to business continuity arrangements.

11. Incident management plans

An incident management plan for human medicines has been in operation within the EU regulatory network since September 2009.

The [EU regulatory network incident management plan for medicines for human use](#) aims to ensure that the most appropriate actions are taken across the EU whenever incidents (new events or information) arise concerning human medicines. It covers medicines authorised centrally, nationally and through the decentralised and mutual-recognition procedures.

The plan's execution involves representatives from the European Medicines Agency, the European Commission and medicines regulatory authorities in the EU Member States.

12. Annexes

Annex 1 — (Non-exhaustive) list of computerised systems supporting the functioning of the EMA pharmacovigilance system

EudraVigilance

EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA).

EudraVigilance supports the following:

- the electronic exchange of suspected adverse reaction reports (known as individual case safety reports) between the European Medicines Agency, national competent authorities, marketing-authorisation holders, and sponsors of clinical trials in the EEA;
- the early detection of possible safety signals associated with medicinal products for human use;
- the continual monitoring and evaluation of potential safety issues in relation to reported adverse reactions;
- the decision-making process, especially in the form of risk management, based on a broader knowledge of the adverse reaction profile of medicinal products, based on information collected through the EudraVigilance Medicinal Products Dictionary (XEVMPPD).

SAS

SAS is a set of informatics tools used by B-Division to support any activities related to data management, data analytics and business intelligence.

EPITT

EPITT (European Pharmacovigilance Issues tracking Tool) is a database developed by the EMA to promote the rapid communication of pharmacovigilance and risk-management issues between the EMA, all national competent authorities (NCAs) of the European Economic Area (EEA), the CHMP, the PhVWP/PRAC and the CMDh. EPITT provides access to documents related to the safety of medicinal products/substances authorised in the EEA. It is also an easy query tool accessible to the scientific colleagues of all the NCAs and all EMA staff members.

SIAMED II

SIAMED II is the Agency's product information and application tracking system. It is used for managing:

- pre-submission activities;
- applications within the centralised procedure;
- fee calculation;
- managing product data;
- maximum residue limits;

- post-authorisation measures and PSURs.

The information it stores is also used to generate most of the Agency's procedural documents, such as scientific opinions or template letters, as well as a growing number of statistics. It also supports other business applications such as SAP and EudraPharm.

DREAM

The DREAM (Document Records Electronic Archive Management) system combines two older systems:

- EDMS (Electronic Document Management system), since 2004;
- MMD (Managing Meeting Documents), since 2006/2007.

DREAM is a single, web-based system with added functionality, including search, the ability to set retention periods and a simplified tabling feature in MMD. The DREAM system has been available since 9 August 2010.

EudraCT

EudraCT is the EU's electronic database of clinical trials. It contains information submitted by sponsors and informs users about ongoing clinical trials in all EU Member States and EEA countries, enabling an overview of multi-state trials.

- From here, users can create a clinical-trial application (CTA) for a trial to be conducted within the EEA. Once completed, it is ready for submission to a national competent authority or an independent ethics committee.
- Registered users can log in to the system to perform tasks relating to their roles.
- XML documents of the CTA or third-country clinical-trial information can be uploaded using the Load button.
- Allows users to create, update, validate and post result data sets, and load summary attachments to the EudraCT database.

EudraGMP

EudraGMDP is the name for the EU database referred to in Article 111(6) of Directive 2001/83/EC and Article 80(6) of Directive 2001/82/EC. It contains the following information:

- manufacturing and import authorisations;
- good manufacturing practice (GMP) certificates;
- statements of non-compliance with GMP;
- Good Manufacturing Practice (GMP) inspection planning in third countries.

In addition, the following new information is required in the database for the first time in 2013 (as data transfers from national systems can be complex, it will take several months for all the national competent authorities to complete the uploading of this data):

- wholesale distribution authorisations;
- Good Distribution Practice (GDP) certificates;
- statements of non-compliance with GDP;

- registration of manufacturers, importers and distributors of active substances for human use located in the EEA.

Almost all information uploaded into the database is available to the public. National competent authorities are able to exclude some information from public view. This includes information of a commercially sensitive or personal nature, inspection planning and information that may need to be restricted in the interests of security.

IMS dataset

The EMA has procured access to over 30 million electronic medical records of patients in Germany, the UK and France by means of a licence through IMS Health Ltd. The data are used for in-house pharmacoepidemiology studies.

THIN dataset

THIN is a medical research database of anonymised UK patient records from information entered by general practices. The EMA has access to it by means of a procured licence. It is used for in-house pharmacoepidemiology studies.

ENCePP databases

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was established in 2006 by the European Medicines Agency in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. The network is comprised of research centres, existing networks and data sources. Its goal is to further strengthen the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorisation studies focusing on safety and on benefit:risk, using available expertise and research experience across Europe.

Studies database

The E-Register of Studies (EU Post-Authorisation Studies (PAS) register) aims to provide a publicly accessible resource for the registration of pharmacoepidemiological and pharmacovigilance studies. Its purpose is to:

- increase transparency;
- reduce publication bias;
- facilitate exchange of pharmacovigilance information between the Agency, Member States and marketing-authorisation holders and the public;
- promote information exchange;
- facilitate collaboration within the scientific community;
- facilitate optimal use of pharmacoepidemiology and pharmacovigilance expertise in Europe by preventing unnecessary duplication of research;
- act as the publicly available EU electronic register of post-authorisation studies (EU PAS Register) referred to in the good pharmacovigilance practices (GVP) Module VIII on post-authorisation safety studies (PASS);

- For non-interventional PASS conducted voluntarily or pursuant to an obligation, GVP VIII requires the marketing-authorisation holder to make study information (including for studies conducted outside the EU) available in the EU PAS Register.

Pharmacoepidemiological or pharmacovigilance studies applying for the ENCePP Seal must be registered in the ENCePP E-Register of Studies before the study commences, but also any other non-interventional study not formally applying for the ENCePP Seal should be registered voluntarily, to ensure transparency.

ENCePP resources database

The ENCePP Database of Research Resources is an electronic index of available EU research organisations and data sources in the field of pharmacoepidemiology and pharmacovigilance. It is publicly available through the ENCePP web portal.

The database serves as a central resource for both researchers and study sponsors seeking to identify organisations and data sets for conducting specific pharmacoepidemiology and pharmacovigilance studies in Europe.

It comprises two indices: the *Inventory of ENCePP research centres* and the *Registry of EU data sources*. Both the Inventory and the Registry are fully searchable and allow the identification of centres and data sets by country, type and many more relevant keywords.

SAP HR

SAP HR is an IT system that includes for every EMA staff member and line manager learning solutions (training and IQM manual), travel and expense management (missions and training missions) and appraisals management (workflow for contract renewals). SAP HR also allows recording of each staff member's working hours, requesting absence electronically and managing posts in line with the establishment plan.

JIRA application (Ask EMA)

JIRA is the request management software used by Ask EMA, which builds upon the web form already available on the Agency's website. It is also able to capture requests sent by email to the Info@ functional e-mail address and supports manual request creation. It is essential for addressing stakeholder queries.

vFire (EV 1st line support)

The vFire application is a service management workflow tool for logging and tracking queries from internal users and external requesters. It is managed by EudraVigilance First Line Support (Information Technology Division) and is essential for addressing stakeholder queries.

TrackWise

TrackWise is the EMA's electronic audit management system. This software is used for tracking the Agency's processes and the creation and archiving of related records and associated document.

Appendix C: Directive 2010/84/EU

DIRECTIVES

DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 December 2010

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee ⁽¹⁾,

Having regard to the opinion of the Committee of the Regions ⁽²⁾,

Having regard to the opinion of the European Data Protection Supervisor ⁽³⁾,

Acting in accordance with the ordinary legislative procedure ⁽⁴⁾,

Whereas:

(1) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use ⁽⁵⁾ lays down harmonised rules for the authorisation, supervision and pharmacovigilance of medicinal products for human use within the Union.

(2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess

adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

(3) In the light of the experience acquired and following an assessment by the Commission of the Union system of pharmacovigilance, it has become clear that it is necessary to take measures in order to improve the operation of Union law on the pharmacovigilance of medicinal products.

(4) While the fundamental objective of the regulation of medicinal products is to safeguard public health, this aim should nevertheless be achieved by means that do not impede the free movement of safe medicinal products within the Union. It has emerged from the assessment of the Union system of pharmacovigilance that divergent actions by Member States in relation to safety issues pertaining to medicinal products are creating obstacles to the free movement of medicinal products. In order to prevent or eliminate those obstacles the existing pharmacovigilance provisions at Union level should be strengthened and rationalised.

(5) For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. The suspicion of an adverse drug reaction, meaning that there is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting. Therefore, the term 'suspected adverse reaction' should be used when referring to reporting obligations. Without prejudice to the existing Union and national provisions and practices on medical confidentiality, Member States should ensure that reporting and processing of personal data related to suspected adverse reactions, including those associated with medication errors is carried out on a confidential basis. This should not affect Member States' obligations regarding the mutual exchange of

⁽¹⁾ OJ C 306, 16.12.2009, p. 28.

⁽²⁾ OJ C 79, 27.3.2010, p. 50.

⁽³⁾ OJ C 229, 23.9.2009, p. 19.

⁽⁴⁾ Position of the European Parliament of 22 September 2010 [not yet published in the Official Journal] and Council Decision of 29 November 2010.

⁽⁵⁾ OJ L 311, 28.11.2001, p. 67.

- information on pharmacovigilance issues or their obligation to make available to the public important information on pharmacovigilance concerns. Furthermore, the principle of confidentiality should not affect the obligations of the persons concerned to provide information under criminal law.
- (6) The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem. Member States should consider measures to monitor and evaluate the risk of environmental effects of such medicinal products, including those which may have an impact on public health. The Commission should, based, *inter alia*, on data received from the European Medicines Agency, the European Environment Agency and Member States, produce a report on the scale of the problem, along with an assessment on whether amendments to Union legislation on medicinal products or other relevant Union legislation are required.
- (7) The marketing authorisation holder should establish a pharmacovigilance system to ensure the monitoring and supervision of one or more of its authorised medicinal products, recorded in a pharmacovigilance system master file which should be permanently available for inspection. The competent authorities should undertake to supervise those pharmacovigilance systems. Applications for marketing authorisations should therefore be accompanied by a brief description of the corresponding pharmacovigilance system, which should include a reference to the location where the pharmacovigilance system master file for the medicinal product concerned is kept and available for inspection by the competent authorities.
- (8) Marketing authorisation holders should plan pharmacovigilance measures for each individual medicinal product in the context of a risk management system. The measures should be proportionate to the identified risks, the potential risks, and the need for additional information on the medicinal product. It should also be ensured that any key measures included in a risk management system are made conditions of the marketing authorisation.
- (9) It is necessary from a public health perspective to complement the data available at the time of authorisation with additional data about the safety and, in certain cases, the efficacy of authorised medicinal products. Competent authorities should therefore be empowered to impose on the marketing authorisation holder the obligation to conduct post-authorisation studies on safety and on efficacy. It should be possible to impose that obligation at the time of the granting of the marketing authorisation or later, and it should be a condition of the marketing authorisation. Such studies may be aimed at collecting data to enable the assessment of the safety or efficacy of medicinal products in everyday medical practice.
- (10) It is essential that a strengthened system of pharmacovigilance not lead to the premature granting of marketing authorisations. However, some medicinal products are authorised subject to additional monitoring. This includes all medicinal products with a new active substance and biological medicinal products, including biosimilars, which are priorities for pharmacovigilance. Competent authorities may also require additional monitoring for specific medicinal products that are subject to the obligation to conduct a post-authorisation safety study or to conditions or restrictions with regard to the safe and effective use of the medicinal product. Medicinal products subject to additional monitoring should be identified as such by a black symbol and an appropriate standardised explanatory sentence in the summary of product characteristics and in the package leaflet. A publicly available list of medicinal products subject to additional monitoring should be kept up to date by the European Medicines Agency established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency⁽¹⁾ (hereinafter referred to as the 'Agency').
- (11) The Commission should, in collaboration with the Agency and national competent authorities and following consultations with organisations representing patients, consumers, doctors and pharmacists, social health insurers, and other interested parties, present to the European Parliament and the Council an assessment report regarding the readability of the summaries of product characteristics and the package leaflets and their value to the healthcare professionals and the general public. Following an analysis of that data, the Commission should, if appropriate, make proposals to improve the layout and content of the summaries of product characteristics and of the package leaflets to ensure that they represent a valuable source of information for healthcare professionals and the general public respectively.
- (12) Experience has shown that the responsibilities of marketing authorisation holders with regard to pharmacovigilance of authorised medicinal products should be clarified. The marketing authorisation holder should be responsible for continuously monitoring the safety of its medicinal products, for informing the authorities of any changes that might impact on the marketing authorisation, and for ensuring that the product information is kept up to date. As medicinal products could be used outside the terms of the marketing authorisation, the marketing authorisation holder's responsibilities should include providing all available information, including the results of clinical trials or other studies, as well as reporting any use of the medicinal product which is outside the terms of the marketing authorisation. It is also appropriate to ensure that all relevant information

⁽¹⁾ OJ L 136, 30.4.2004, p. 1.

collected on the safety of the medicinal product is taken into account when the marketing authorisation is being renewed.

- (13) In order to ensure close cooperation between the Member States in the area of pharmacovigilance, the mandate of the coordination group set up by Article 27 of Directive 2001/83/EC should be enlarged to include the examination of questions related to the pharmacovigilance of all medicinal products authorised by the Member States. In order to fulfil its new tasks, the coordination group should be further strengthened through the adoption of clear rules as regards the expertise required, the procedures for reaching agreements or positions, transparency, independence and professional secrecy of its members, and the need for cooperation between Union and national bodies.
- (14) With a view to ensuring the same level of scientific expertise in the area of pharmacovigilance decision-making at both Union and national levels, the coordination group should rely on the recommendations of the Pharmacovigilance Risk Assessment Committee when fulfilling its pharmacovigilance tasks.
- (15) In order to avoid duplication of work, the coordination group should agree on a single position for pharmacovigilance assessments concerning medicinal products authorised in more than one Member State. Agreement within the coordination group should suffice for pharmacovigilance measures to be implemented throughout the Union. Where no agreement is reached within the coordination group, the Commission should be authorised to adopt a decision concerning the necessary regulatory action in respect of the marketing authorisation, addressed to the Member States.
- (16) A single assessment should also be conducted in the case of pharmacovigilance issues which concern medicinal products authorised by the Member States and medicinal products authorised in accordance with Regulation (EC) No 726/2004. In such cases, the Commission should adopt harmonised measures for all medicinal products concerned on the basis of an assessment at Union level.
- (17) Member States should operate a pharmacovigilance system to collect information that is useful for the monitoring of medicinal products, including information on suspected adverse reactions arising from use of a medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure. Member States should ensure the quality of the pharmacovigilance system through the follow-up of cases of suspected adverse reactions. For those tasks, Member States should establish a permanent pharmacovigilance system, supported by the appropriate expertise, so that the obligations under this Directive can be fully met.
- (18) In order to further increase the coordination of resources between the Member States, Member State should be authorised to delegate certain pharmacovigilance tasks to another Member State.
- (19) In order to simplify the reporting of suspected adverse reactions, the marketing authorisation holders and the Member States should report those reactions only to the Union pharmacovigilance database and data-processing network referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 (the 'Eudravigilance database'). The Eudravigilance database should be equipped to immediately forward reports on suspected adverse reactions received from marketing authorisation holders to the Member States on whose territory the reaction occurred.
- (20) In order to increase the level of transparency of the pharmacovigilance processes, the Member States should create and maintain medicines web-portals. To the same end, the marketing authorisation holders should provide the competent authorities with prior or simultaneous warnings about safety announcements and the competent authorities should also provide each other with advance notice of safety announcements.
- (21) Union rules in relation to pharmacovigilance should continue to rely on the crucial role of healthcare professionals in monitoring the safety of medicinal products, and should take account of the fact that patients are also well placed to report suspected adverse reactions to medicinal products. It is therefore appropriate to facilitate the reporting of suspected adverse reactions to medicinal products by both healthcare professionals and patients, and to make methods for such reporting available to them.
- (22) As a result of the submission of all suspected adverse reaction data directly to the Eudravigilance database, it is appropriate to amend the scope of periodic safety update reports so that they present an analysis of the risk-benefit balance of a medicinal product rather than a detailed listing of individual case reports already submitted to the Eudravigilance database.

- (23) Obligations imposed in respect of periodic safety update reports should be proportionate to the risks posed by medicinal products. Periodic safety update reporting should therefore be linked to the risk management system for newly authorised medicinal products and routine reporting should not be required for generic medicinal products, for medicinal products containing an active substance for which well-established medicinal use has been demonstrated, for homeopathic medicinal products or for traditional-use registered herbal medicinal products. However, in the interests of public health, the competent authorities should require periodic safety update reports for such medicinal products when concerns arise relating to pharmacovigilance data or as a result of the lack of available safety data when the use of the active substance concerned is concentrated in medicinal products for which periodic safety update reporting is not routinely required.
- (24) It is necessary to increase the shared use of resources between competent authorities for the assessment of periodic safety update reports. A single assessment of periodic safety update reports for medicinal products authorised in more than one Member State should be provided for. Moreover, procedures should be established to set single frequency and submission dates of periodic safety update reports for all medicinal products containing the same active substance or the same combination of active substances.
- (25) Following a single assessment of periodic safety update reports, any resulting measures as regards the maintenance, variation, suspension or revocation of the marketing authorisations concerned should be adopted through a Union procedure leading to a harmonised result.
- (26) The Member States should automatically submit certain safety issues related to medicinal products to the Agency thereby triggering a Union-wide assessment of the issue. Therefore it is appropriate to establish rules for an assessment procedure by the Pharmacovigilance Risk Assessment Committee, and for the subsequent follow-up as regards the marketing authorisations concerned with a view to the adoption of harmonised measures across the Union.
- (27) In connection with the clarification and strengthening of the provisions relating to pharmacovigilance activities in Directive 2001/83/EC, it is also appropriate to further clarify the procedures for all Union-wide post-authorisation assessments of safety issues concerning medicinal products. To that end, the number of procedures for Union-wide assessment should be limited to two, one of which allows for a swift assessment and should be applied when urgent action is considered necessary. Regardless of whether the urgent procedure or the normal procedure is applied, and whether the medicinal product was authorised through the centralised or non-centralised procedure, the Pharmacovigilance Risk Assessment Committee should always give its recommendation when the reason for taking action is based on pharmacovigilance data. It is appropriate that the coordination group and the Committee for Medicinal Products for Human Use should rely on this recommendation when performing their assessment of the issue.
- (28) It is necessary to introduce harmonised guiding principles for, and regulatory supervision of, post-authorisation safety studies that are requested by competent authorities and that are non-interventional, that are initiated, managed or financed by the marketing authorisation holder, and that involve the collection of data from patients or healthcare professionals and that therefore fall outside of the scope of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use⁽¹⁾. The supervision of such studies should be the responsibility of the Pharmacovigilance Risk Assessment Committee. Studies requested after the marketing authorisation of a medicinal product by only one competent authority to be conducted in only one Member State should be supervised by the national competent authority of the Member State in which the study is to be conducted. Provision should also be made for the subsequent follow-up, if appropriate, as regards the marketing authorisations concerned with a view to the adoption of harmonised measures across the Union.
- (29) In order to enforce the provisions relating to pharmacovigilance, the Member States should ensure that effective, proportionate and dissuasive penalties are applied to marketing authorisation holders for non-compliance with pharmacovigilance obligations. If the conditions included in the marketing authorisation are not fulfilled within the given deadline, the national competent authorities should have the power to review the marketing authorisation.

⁽¹⁾ OJ L 121, 1.5.2001, p. 34.

- (30) In order to protect public health, the pharmacovigilance activities of national competent authorities should be adequately funded. It should be ensured that adequate funding is possible for pharmacovigilance activities by empowering the national competent authorities to charge fees to marketing authorisation holders. However, the management of those collected funds should be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.
- (31) It should be possible for Member States to allow the relevant actors, under certain conditions, to deviate from certain provisions of Directive 2001/83/EC related to the requirements for labelling and packaging in order to address severe availability problems related to the potential lack of authorised medicinal products or of medicinal products placed on the market or shortages thereof.
- (32) Since the objective of this Directive, namely to improve the safety of medicinal products placed on the market in the Union in a harmonised way across the Member States, cannot be sufficiently achieved by the Member States and can, by reason of the scale of the measures, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union (TEU). In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary in order to achieve this objective.
- (33) This Directive shall apply without prejudice to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data ⁽¹⁾ and Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data ⁽²⁾. In order to detect, assess, understand and prevent adverse reactions, and to identify and take actions to reduce the risks of, and increase the benefits from, medicinal products for the purpose of safeguarding public health, it should be possible to process personal data within the Eudravigilance system while respecting Union legislation relating to data protection. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data can be justified if identifiable health data are processed only when necessary and only when the parties involved assess this necessity at every stage of the pharmacovigilance process.
- (34) The provisions on the monitoring of medicinal products in Directive 2001/83/EC constitute specific provisions within the meaning of Article 15(2) of Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products ⁽³⁾.
- (35) The pharmacovigilance activities provided for in this Directive require that uniform conditions be established as concerns the contents and maintenance of the pharmacovigilance system master file, as well as the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and marketing authorisation holders, the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities, and the minimum requirements for the monitoring of the data contained in the Eudravigilance database to determine whether there are new risks or whether risks have changed. The format and content of the electronic transmission of suspected adverse reactions by Member States and marketing authorisation holders, the format and content of electronic periodic safety update reports and risk management plans as well as the format of protocols, abstracts and final study reports for the post-authorisation safety studies should also be established. In accordance with Article 291 of the Treaty on the Functioning of the European Union (TFEU), rules and general principles concerning mechanisms for the control by Member States of the Commission's exercise of implementing powers are to be laid down in advance by a regulation adopted in accordance with the ordinary legislative procedure. Pending the adoption of that new regulation, Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission ⁽⁴⁾ continues to apply, with the exception of the regulatory procedure with scrutiny, which is not applicable.
- (36) The Commission should be empowered to adopt delegated acts in accordance with Article 290 TFEU in order to supplement the provisions in Articles 21a and 22a of Directive 2001/83/EC. The Commission should be empowered to adopt supplementary measures laying down the situations in which post-authorisation efficacy studies may be required. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level.
- (37) In accordance with point 34 of the Interinstitutional Agreement on better law-making ⁽⁵⁾, Member States are encouraged to draw up, for themselves and in the interests of the Union, their own tables illustrating, as far as possible, the correlation between this Directive and the transposition measures, and to make them public.
- (38) Directive 2001/83/EC should be amended accordingly,

⁽¹⁾ OJ L 281, 23.11.1995, p. 31.

⁽²⁾ OJ L 8, 12.1.2001, p. 1.

⁽³⁾ OJ L 218, 13.8.2008, p. 30.

⁽⁴⁾ OJ L 184, 17.7.1999, p. 23.

⁽⁵⁾ OJ C 321, 31.12.2003, p. 1.

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Amendments to Directive 2001/83/EC

Directive 2001/83/EC is hereby amended as follows:

1. Article 1 is amended as follows:

(a) point 11 is replaced by the following:

‘11. Adverse reaction: A response to a medicinal product which is noxious and unintended.’;

(b) point 14 is deleted;

(c) point 15 is replaced by the following:

‘15. Post-authorisation safety study: Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.’;

(d) the following points are inserted:

‘28b. Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.

28c. Risk management plan: a detailed description of the risk management system.

28d. Pharmacovigilance system: a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

28e. Pharmacovigilance system master file: A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.’.

2. Article 8(3) is amended as follows:

(a) point (ia) is replaced by the following:

‘(ia) A summary of the applicant’s pharmacovigilance system which shall include the following elements:

— proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,

— the Member States in which the qualified person resides and carries out his/her tasks,

— the contact details of the qualified person,

— a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX,

— a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.’;

(b) the following point is inserted after point (ia):

‘(iaa) The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof.’;

(c) point (l) is replaced by the following:

‘(l) Copies of the following:

— any authorisation, obtained in another Member State or in a third country, to place the medicinal product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination;

— the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21 and the package leaflet proposed in accordance with Article 59 or approved by the competent authorities of the Member State in accordance with Article 61;

— details of any decision to refuse authorisation, whether in the Union or in a third country, and the reasons for such a decision.’;

(d) point (n) is deleted;

(e) the following subparagraphs are added after the second subparagraph:

‘The risk management system referred to in point (iaa) of the first subparagraph shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.

The information referred to in the first subparagraph shall be updated where and when appropriate.’.

3. In Article 11 the following subparagraphs are added:

‘For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary of product characteristics shall include the statement: “This medicinal product is subject to additional monitoring”. This

statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system referred to in Article 107a(1). Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of Article 107a(1).'

4. Article 16g(1) is replaced by the following:

'1. Article 3(1) and (2), Article 4(4), Article 6(1), Article 12, Article 17(1), Articles 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108b, Article 111(1) and (3), Articles 112, 116, 117, 118, 122, 123, 125, the second paragraph of Article 126, and Article 127 of this Directive as well as Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*) shall apply, by analogy, to traditional-use registration granted under this Chapter.

(*) OJ L 262, 14.10.2003, p. 22.'

5. Article 17 is amended as follows:

- (a) in the second subparagraph of paragraph 1, the words 'Articles 27' are replaced by the words 'Articles 28';
- (b) in paragraph 2, the words 'Articles 27' are replaced by the words 'Articles 28';

6. In Article 18, the words 'Articles 27' are replaced by the words 'Articles 28'.

7. In Article 21, paragraphs 3 and 4 are replaced by the following:

'3. The national competent authorities shall, without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with Articles 21a, 22 and 22a, together with any deadlines for the fulfilment of those conditions for each medicinal product which they have authorised.

4. The national competent authorities shall draw up an assessment report and make comments on the file as

regards the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

The national competent authorities shall make the assessment report publicly accessible without delay, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.

The public assessment report shall include a summary written in a manner that is understandable to the public. The summary shall contain, in particular, a section relating to the conditions of use of the medicinal product.'

8. The following Article is inserted:

'Article 21a

In addition to the provisions laid down in Article 19, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

- (a) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;
- (b) to conduct post-authorisation safety studies;
- (c) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Title IX;
- (d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;
- (e) the existence of an adequate pharmacovigilance system;
- (f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The marketing authorisation shall lay down deadlines for the fulfilment of these conditions where necessary.'

9. Article 22 is replaced by the following:

'Article 22

In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.

The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.

Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.'

10. The following Articles are inserted:

'Article 22a

1. After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder:

(a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

(b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The national competent authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify,

if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

3. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

Article 22b

1. In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 21a and 22a of this Directive, the Commission may adopt, by means of delegated acts in accordance with Article 121a, and subject to the conditions of Articles 121b and 121c, measures supplementing the provisions in Articles 21a and 22a.

2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Directive.

Article 22c

1. The marketing authorisation holder shall incorporate any conditions referred to in Articles 21a, 22 or 22a in his risk management system.

2. The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to Articles 21a, 22 or 22a.'

11. Article 23 is replaced by the following:

'Article 23

1. After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I.

In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

4. In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

The national competent authority may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest 7 days after receipt of the request.

12. Article 24 is amended as follows:

(a) in paragraph 2, the second subparagraph is replaced by the following:

'To this end, the marketing authorisation holder shall provide the national competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Title IX, and information on all variations introduced since the marketing authorisation was granted, at least 9 months before the marketing authorisation ceases to be valid in accordance with paragraph 1.;

(b) paragraph 3 is replaced by the following:

'3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the national

competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with paragraph 2.'

13. The title 'Chapter 4 Mutual recognition and decentralised procedure' is deleted.

14. Article 27 is amended as follows:

(a) paragraphs 1 and 2 are replaced by the following:

'1. A coordination group shall be set up for the following purposes:

(a) the examination of any question relating to a marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Chapter 4;

(b) the examination of questions related to the pharmacovigilance of medicinal products authorised by the Member States, in accordance with Articles 107c, 107e, 107g, 107k and 107q;

(c) the examination of questions relating to variations of marketing authorisations granted by the Member States, in accordance with Article 35(1).

The Agency shall provide the secretariat of this coordination group.

For the fulfilment of its pharmacovigilance tasks, including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee provided for in Article 56(1)(aa) of Regulation (EC) No 726/2004.

2. The coordination group shall be composed of one representative per Member State appointed for a renewable period of 3 years. Member States may appoint an alternate for a renewable period of 3 years. Members of the coordination group may arrange to be accompanied by experts.

Members of the coordination group and experts shall, for the fulfilment of their tasks, rely on the scientific and regulatory resources available to national competent authorities. Each national competent authority shall monitor the level of expertise of the evaluations carried out and facilitate the activities of the nominated coordination group members and experts.

Article 63 of Regulation (EC) No 726/2004 shall apply to the coordination group as regards transparency and the independence of its members.;

(b) the following paragraphs are added:

‘4. The Executive Director of the Agency or his representative and representatives of the Commission shall be entitled to attend all meetings of the coordination group.

5. The members of the coordination group shall ensure that there is appropriate coordination between the tasks of that group and the work of national competent authorities, including the consultative bodies concerned with the marketing authorisation.

6. Save where otherwise provided for in this Directive, the Member States represented within the coordination group shall use their best endeavours to reach a position by consensus on the action to be taken. If such a consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall prevail.

7. Members of the coordination group shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.’.

15. After Article 27 the following heading is inserted:

‘CHAPTER 4

Mutual recognition and decentralised procedure’.

16. Article 31(1) is amended as follows:

(a) the first subparagraph is replaced by the following:

‘The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.’;

(b) the following subparagraphs are inserted after the first subparagraph:

‘Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 107j(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 32. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 107k shall apply.

However, where urgent action is considered necessary, the procedure laid down in Articles 107i to 107k shall apply.’.

17. Article 36 is deleted.

18. Article 59 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) point (e) is replaced by:

‘(e) a description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case.’;

(ii) the following subparagraphs are added:

‘For medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included “This medicinal product is subject to additional monitoring”. This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a(1), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Article 107a(1).’;

(b) the following paragraph is added:

‘4. By 1 January 2013, the Commission shall present to the European Parliament and the Council an assessment report on current shortcomings in the summary of product characteristics and the package leaflet and how they could be improved in order to better meet the needs of patients and healthcare professionals. The Commission shall, if appropriate, and on the basis of the report, and consultation with appropriate stakeholders, present proposals in order to improve the readability, layout and content of these documents.’

19. Article 63(3) is replaced by the following:

‘3. When the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in the official language or languages of the Member State in which the medicinal product is placed on the market.’

20. Title IX is replaced by the following:

‘TITLE IX

PHARMACOVIGILANCE

CHAPTER 1

General provisions

Article 101

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients’ or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

2. Member States shall, by means of the pharmacovigilance system referred to in paragraph 1, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action

concerning the marketing authorisation as necessary. They shall perform a regular audit of their pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter.

3. Each Member State shall designate a competent authority for the performance of pharmacovigilance tasks.

4. The Commission may request Member States to participate, under the coordination of the Agency, in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 102

The Member States shall:

(a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority; for these tasks, organisations representing consumers, patients and healthcare professionals may be involved as appropriate;

(b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

(c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary;

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number;

(f) take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in this Title is subject to effective, proportionate and dissuasive penalties.

For the purposes of point (a) and (e) of the first paragraph the Member States may impose specific obligations on doctors, pharmacists and other health-care professionals.

Article 103

A Member State may delegate any of the tasks entrusted to it under this Title to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State.

The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information public.

Article 104

1. The marketing authorisation holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system provided for under Article 101(1).

2. The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.

3. As part of the pharmacovigilance system, the marketing authorisation holder shall:

- (a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;
- (b) maintain and make available on request a pharmacovigilance system master file;
- (c) operate a risk management system for each medicinal product;
- (d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a;
- (e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

The qualified person referred to in point (a) of the first subparagraph shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the competent authority and the Agency.

4. Notwithstanding the provisions of paragraph 3, national competent authorities may request the nomination of a contact person for pharmacovigilance issues at national level reporting to the qualified person responsible for pharmacovigilance activities.

Article 104a

1. Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 104(3)(c), not be required to operate a risk management system for each medicinal product.

2. The national competent authority may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in Article 104(3)(c), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the national competent authority shall also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned.

The imposition of such obligations shall be duly justified, notified in writing and shall include the timeframe for submission of the detailed description of the risk-management system.

3. The national competent authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

4. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority confirms the obligation, the marketing authorisation shall be varied accordingly to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in point (a) of Article 21a.

Article 105

The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.

The first paragraph shall not preclude the national competent authorities from charging fees to marketing authorisation holders for performing those activities by the national competent authorities on the condition that their independence in the performance of those pharmacovigilance activities is strictly guaranteed.

CHAPTER 2

Transparency and communications*Article 106*

Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004. By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

- (a) public assessment reports, together with a summary thereof;
- (b) summaries of product characteristics and package leaflets;
- (c) summaries of risk management plans for medicinal products authorised in accordance with this Directive;
- (d) the list of medicinal products referred to in Article 23 of Regulation (EC) No 726/2004;
- (e) information on the different ways of reporting suspected adverse reactions to medicinal products to national competent authorities by healthcare professionals and patients, including the web-based structured forms referred to in Article 25 of Regulation (EC) No 726/2004.

Article 106a

1. As soon as the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, he shall be required to inform the national competent authorities, the Agency and the Commission.

The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

2. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

3. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public.

Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the Agency, provide advice on those safety announcements.

4. When the Agency or national competent authorities make public information referred to in paragraphs 2 and 3, any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

CHAPTER 3

Recording, reporting and assessment of pharmacovigilance data

Section 1

Recording and reporting of suspected adverse reactions*Article 107*

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.

Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.

By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC.

2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals.

3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the "Eudravigilance database") information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.

4. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information on these reports and submit the updates to the Eudravigilance database.

5. Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports.

Article 107a

1. Each Member State shall record all suspected adverse reactions that occur in its territory which are brought to its attention from healthcare professionals and patients. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 102(c) and (e).

Member States shall ensure that reports of such reactions may be submitted by means of the national medicines web-portals or by other means.

2. For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports.

3. Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.

4. Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

They shall, within 90 days from the receipt of reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

Marketing authorisation holders shall access those reports through the Eudravigilance database.

5. Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that Member State. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004.

6. Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.

Section 2

Periodic safety update reports

Article 107b

1. Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

- (a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;
- (b) a scientific evaluation of the risk-benefit balance of the medicinal product;
- (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

The periodic safety update reports shall be submitted electronically.

2. The Agency shall make available the reports referred to in paragraph 1 to the national competent authorities, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository referred to in Article 25a of Regulation (EC) No 726/2004.

3. By way of derogation from paragraph 1 of this Article, the holders of marketing authorisations for medicinal products referred to in Article 10(1), or Article 10a, and the holders of registrations for medicinal products referred to in Articles 14 or 16a, shall submit periodic safety update reports for such medicinal products in the following cases:

- (a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Article 21a or Article 22; or
- (b) when requested by a competent authority on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted. The assessment reports of the requested periodic safety update reports shall be communicated to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Article 107c(4) and Article 107e.

Article 107c

1. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.

The dates of submission according to the specified frequency shall be calculated from the date of the authorisation.

2. Holders of marketing authorisations which were granted before 21 July 2012, and for which the

frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with paragraphs 4, 5 or 6.

Periodic safety update reports shall be submitted to the competent authorities immediately upon request or in accordance with the following:

- (a) where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;
- (b) where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter.

3. Paragraph 2 shall also apply to medicinal products which are authorised only in one Member State and for which paragraph 4 does not apply.

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates are calculated.

This harmonised frequency for the submission of the reports and the Union reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Committee, by one of the following:

- (a) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004;
- (b) the coordination group, in other cases than those referred to in point (a).

The harmonised frequency for the submission of the reports determined pursuant to the first and second subparagraphs shall be made public by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

5. For the purposes of paragraph 4, the Union reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

- (a) the date of the first marketing authorisation in the Union of a medicinal product containing that active substance or that combination active substances;
- (b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

6. Marketing authorisation holders shall be allowed to submit requests to the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine Union reference dates or to change the frequency of submission periodic safety update reports on one of the following grounds:

- (a) for reasons relating to public health;
- (b) in order to avoid a duplication of the assessment;
- (c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, shall either approve or deny such requests. Any change in the dates or the frequency of submission of periodic safety update reports shall be made public by the Agency. The marketing authorisation holders shall accordingly submit an application for a variation of the marketing authorisation.

7. The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal.

Any change to the dates of submission and frequency of periodic safety update reports specified in the marketing

authorisation as a result of the application of paragraphs 4, 5 and 6 shall take effect 6 months after the date of such publication.

Article 107d

The national competent authorities shall assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

Article 107e

1. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases of paragraphs 4 to 6 of Article 107c, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and frequency of periodic safety update reports has been established.

The single assessment shall be conducted by either of the following:

- (a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004; or
- (b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004.

When selecting the Member State in accordance with point (a) of the second subparagraph, the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Article 28(1).

2. The Member State or rapporteur, as appropriate, shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. The Agency shall send the report to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the Member States and the marketing authorisation holder may submit comments to the Agency and to the rapporteur or Member State.

3. Following the receipt of the comments referred to in paragraph 2, the rapporteur or Member State shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 25a of Regulation (EC) No 726/2004 and forward both to the marketing authorisation holder.

Article 107f

Following the assessment of periodic safety update reports, the national competent authorities shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary.

They shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 107g

1. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement.

In the event of a variation, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a modification, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented

within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

- (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for in this section; and
- (b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the marketing authorisations granted in accordance with the centralised procedure provided for in Regulation (EC) No 726/2004 and concerned by the procedure provided for in this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Section 3

Signal detection

Article 107h

1. Regarding medicinal products authorised in accordance with this Directive, national competent authorities in collaboration with the Agency, shall take the following measures:

- (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 21a, 22 or 22a;
- (b) assess updates to the risk management system;
- (c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

3. The Agency and national competent authorities and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

Member States shall ensure that marketing authorisation holders inform the Agency and national competent authorities in the event of new risks or risks that have changed or when changes to the risk-benefit balance have been detected.

Section 4

Urgent Union procedure

Article 107i

1. A Member State or the Commission, as appropriate, shall initiate the procedure provided for in this section, by

informing the other Member States, the Agency and the Commission when urgent action is considered necessary, as a result of the evaluation of data resulting from pharmacovigilance activities, in any of the following cases:

- (a) it considers suspending or revoking a marketing authorisation;
- (b) it considers prohibiting the supply of a medicinal product;
- (c) it considers refusing the renewal of a marketing authorisation;
- (d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or that he intends to do so;
- (e) it considers that a new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary.

The Agency shall verify whether the safety concern relates to medicinal products other than the one covered by the information, or whether it is common to all products belonging to the same range or therapeutic class.

Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the procedure of the outcome of this verification, and the procedures laid down in Articles 107j and 107k shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make information that the procedure has been initiated available to marketing authorisation holders.

2. Without prejudice to the provisions of paragraph 1 of this Article, and Articles 107j and 107k, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

3. At any stage of the procedure laid down in Articles 107j to 107k, the Commission may request Member States in which the medicinal product is authorised to take temporary measures immediately.

Where the scope of the procedure, as determined in accordance with paragraph 1, includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission may, at any stage of the procedure initiated under this section, take temporary measures immediately in relation to those marketing authorisations.

4. The information referred to in this Article may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the safety concern relates to more medicinal products than those which are covered by the information or that it is common to all medicinal products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.

Where the scope of the procedure initiated under this Article concerns a range of medicinal products or therapeutic class, medicinal products authorised in accordance with Regulation (EC) No 726/2004 which belong to that range or class shall also be included in the procedure.

5. At the time of the information referred to in paragraph 1, the Member State shall make available to the Agency all relevant scientific information that it has at its disposal and any assessment by the Member State.

Article 107j

1. Following receipt of the information referred to in Article 107i(1), the Agency shall publicly announce the initiation of the procedure by means of the European medicines web-portal. In parallel, Member States may publicly announce the initiation on their national medicines web-portals.

The announcement shall specify the matter submitted to the Agency in accordance with Article 107i, and the medicinal products and, where applicable, the active substances concerned. It shall contain information on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter which has been submitted to the Agency in accordance with Article 107i. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use and the Reference Member State for the medicinal products concerned.

For the purposes of that assessment, the marketing authorisation holder may submit comments in writing.

Where the urgency of the matter permits, the Pharmacovigilance Risk Assessment Committee may hold public hearings, where it considers that this is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern. The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web-portal. The announcement shall specify the modalities of participation.

In the public hearing, due regard shall be given to the therapeutic effect of the medicinal product.

The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 78 of Regulation (EC) No 726/2004.

Where a marketing authorisation holder or another person intending to submit information has confidential data relevant to the subject matter of the procedure, he may request permission to present that data to the Pharmacovigilance Risk Assessment Committee in a non-public hearing.

3. Within 60 days of the information being submitted, the Pharmacovigilance Risk Assessment Committee shall make a recommendation, stating the reasons on which it is based, having due regard to the therapeutic effect of the medicinal product. The recommendation shall mention the divergent positions and the grounds on which they are based. In the case of urgency, and on the basis of a proposal by its chairman, the Pharmacovigilance Risk Assessment Committee may agree to a shorter deadline. The recommendation shall include any or a combination of the following conclusions:

- (a) no further evaluation or action is required at Union level;
- (b) the marketing authorisation holder should conduct further evaluation of data together with the follow-up of the results of that evaluation;
- (c) the marketing authorisation holder should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;
- (d) the Member States or marketing authorisation holder should implement risk minimisation measures;

(e) the marketing authorisation should be suspended, revoked or not renewed;

(f) the marketing authorisation should be varied.

For the purposes of point (d) of the first subparagraph, the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject.

Where, in the cases referred to in point (f) of the first subparagraph, it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation shall suggest the wording of such changed or added information and where in the summary of the product characteristics, labelling or package leaflet such wording should be placed.

Article 107k

1. Where the scope of the procedure, as determined in accordance with Article 107i(4), does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position. Where an urgent adoption of the position is necessary, and on the basis of a proposal by its chairman, the coordination group may agree to a shorter deadline.

2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in

Articles 33 and 34. However, by way of derogation from Article 34(1), the procedure referred to in Article 121(2) shall apply.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States represented within the coordination group differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. Where the scope of the procedure, as determined in accordance with Article 107i(4), includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, and on the basis of a proposal by its chairman, the Committee for Medicinal Products for Human Use may agree to a shorter deadline.

Where the opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

(a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations that are granted by the Member States and that are subject to the procedure provided for in this section; and

(b) where the opinion is that regulatory action is necessary, adopt a decision to vary, suspend, revoke or refuse renewal of the marketing authorisations granted in accordance with Regulation (EC) No 726/2004 and subject to the procedure provided for in this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States. However, by way of derogation from Article 34(1) of this Directive, the procedure referred to in Article 121(2) thereof shall apply.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. However, by way of derogation from Article 10(2) of that Regulation, the procedure referred to in Article 87(2) thereof shall apply. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Section 5

Publication of assessments

Article 107l

The Agency shall make public the final assessment conclusions, recommendations, opinions and decisions referred to in Articles 107b to 107k by means of the European medicines web-portal.

CHAPTER 4

Supervision of post-authorisation safety studies

Article 107m

1. This Chapter applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a, and which involve the collection of safety data from patients or healthcare professionals.

2. This Chapter is without prejudice to national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The national competent authority may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.

6. The marketing authorisation holder shall send the final report to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the risk-benefit balance of the medicinal product concerned.

Any new information which might influence the evaluation of the risk-benefit balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 23.

The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107b.

8. Articles 107n to 107q shall apply exclusively to studies referred to in paragraph 1 which are conducted pursuant to an obligation imposed in accordance with Articles 21a or 22a.

Article 107n

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requests the study according to Article 22a. For such studies, the marketing authorisation holder shall submit a draft protocol to the national competent authority of the Member State in which the study is conducted.

2. Within 60 days of the submission of the draft protocol the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:

- (a) a letter endorsing the draft protocol;
- (b) a letter of objection, which shall set out in detail the grounds for the objection, in any of the following cases:
 - (i) it considers that the conduct of the study promotes the use of a medicinal product;
 - (ii) it considers that the design of the study does not fulfil the study objectives; or
- (c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

3. The study may commence only when the written endorsement from the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

Where a letter of endorsement as referred to in paragraph 2(a) has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

Article 107o

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the national competent authority or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform Member States in which the study is conducted.

Article 107p

1. Upon completion of the study, a final study report shall be submitted to the national competent authority or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection unless a written waiver has been granted by the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate.

2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities an application to vary the marketing authorisation.

3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the national competent authority or the Pharmacovigilance Risk Assessment Committee.

Article 107q

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention the divergent positions and the grounds on which they are based.

2. When recommendations for the variation, suspension or revocation of the marketing authorisation are made for a medicinal product authorised by the Member States pursuant to this Directive, the Member States represented within the coordination group shall agree a position on the matter taking into account the recommendation referred to

in paragraph 1 and including a timetable for the implementation of the agreed position.

If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

The agreement shall be made public on the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

CHAPTER 5

Implementation, Delegation and Guidance

Article 108

In order to harmonise the performance of the pharmacovigilance activities provided for in this Directive, the Commission shall adopt implementing measures in the following areas for which pharmacovigilance activities are provided for in Article 8(3), and in Articles 101, 104, 104a, 107, 107a, 107b, 107h, 107n and 107p:

- (a) the content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;
- (b) the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and the marketing authorisation holder;

- (c) the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;
- (d) the minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;
- (e) the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;
- (f) the format and content of electronic periodic safety update reports and risk management plans;
- (g) the format of protocols, abstracts and final study reports for the post-authorisation safety studies.

Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the regulatory procedure referred to in Article 121(2).

Article 108a

In order to facilitate the performance of pharmacovigilance activities within the Union, the Agency shall, in cooperation with competent authorities and other interested parties, draw up:

- (a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;
- (b) scientific guidance on post-authorisation efficacy studies.

Article 108b

The Commission shall make public a report on the performance of pharmacovigilance tasks by the Member States on 21 July 2015 at the latest and then every 3 years thereafter.

21. Article 111 is amended as follows:

- (a) paragraph 1 is amended as follows:
 - (i) the first subparagraph is replaced by the following:

The competent authority of the Member State concerned shall, in cooperation with the Agency, ensure that the legal requirements governing

medicinal products are complied with, by means of inspections, if necessary unannounced, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples. This cooperation shall consist in sharing information with the Agency on both inspections that are planned and that have been conducted. Member States and the Agency shall cooperate in the coordination of inspections in third countries.;

- (ii) in the fifth subparagraph, point (d) is replaced by the following:

‘(d) inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX.’;

- (b) paragraph 3 is replaced by the following:

‘3. After every inspection referred to in paragraph 1, the competent authority shall report on whether the inspected entity complies with the principles and guidelines of good manufacturing practice and good distribution practices referred to in Articles 47 and 84, or whether the marketing authorisation holder complies with the requirements laid down in Title IX.

The competent authority which carried out the inspection shall communicate the content of those reports to the inspected entity.

Before adopting the report, the competent authority shall give the inspected entity concerned the opportunity to submit comments.’;

- (c) paragraph 7 is replaced by the following:

‘7. If the outcome of the inspection as referred to in points (a), (b) and (c) of paragraph 1 or the outcome of an inspection of a distributor of medicinal products or active substances or a manufacturer of excipients used as starting materials is that the inspected entity does not comply with the legal requirements and/or the principles and guidelines of good manufacturing practice or good distribution practices as provided for by Union law, the information shall be entered in the Union database as provided for in paragraph 6.’;

(d) the following paragraph is added:

'8. If the outcome of the inspection referred to in paragraph 1(d) is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Title IX, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give him the opportunity to submit comments.

In such case the Member State concerned shall inform the other Member States, the Agency and the Commission.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties.'

22. Article 116 is replaced by the following:

'Article 116

The competent authorities shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not favourable, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy shall be considered to be lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

A marketing authorisation may also be suspended, revoked or varied where the particulars supporting the application as provided for in Articles 8, 10 or 11 are incorrect or have not been amended in accordance with Article 23, or where any conditions referred to in Articles 21a, 22 or 22a have not been fulfilled or where the controls referred to in Article 112 have not been carried out.'

23. Article 117 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) point (a) is replaced by the following:

'(a) the medicinal product is harmful; or';

(ii) point (c) is replaced by the following:

'(c) the risk-benefit balance is not favourable; or';

(b) the following paragraph is added:

'3. The competent authority may, for a medicinal product for which the supply has been prohibited or which has been withdrawn from the market in accordance with paragraphs 1 and 2, in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product.'

24. The following Articles are inserted:

'Article 121a

1. The power to adopt the delegated acts referred to in Article 22b shall be conferred on the Commission for a period of 5 years from 20 January 2011. The Commission shall draw up a report in respect of the delegated powers not later than 6 months before the end of the 5 year period. The delegation of powers shall be automatically extended for periods of an identical duration, unless the European Parliament or the Council revokes it in accordance with Article 121b.

2. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

3. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in Articles 121b and 121c.

Article 121b

1. The delegation of powers referred to in Article 22b may be revoked at any time by the European Parliament or by the Council.

2. The institution which has commenced an internal procedure for deciding whether to revoke the delegation of powers shall endeavour to inform the other institution and the Commission within a reasonable time before the final decision is taken, indicating the delegated powers which could be subject to revocation and possible reasons for a revocation.

3. The decision of revocation shall put an end to the delegation of the powers specified in that decision. It shall take effect immediately or at a later date specified therein. It shall not affect the validity of the delegated acts already in force. It shall be published in the *Official Journal of the European Union*.

Article 121c

1. The European Parliament or the Council may object to a delegated act within a period of 2 months from the date of notification.

At the initiative of the European Parliament or the Council that period shall be extended by 2 months.

2. If, on expiry of the period referred to in paragraph 1, neither the European Parliament nor the Council has objected to the delegated act, it shall be published in the *Official Journal of the European Union* and shall enter into force on the date stated therein.

The delegated act may be published in the *Official Journal of the European Union* and enter into force before the expiry of that period if the European Parliament and the Council have both informed the Commission of their intention not to raise objections.

3. If either the European Parliament or the Council objects to the delegated act within the period referred to in paragraph 1, it shall not enter into force. The institution which objects shall state the reasons for objecting to the delegated act.'

25. Article 122(2) is replaced by the following:

'2. Upon reasoned request, Member States shall send electronically the reports referred to in Article 111(3) to the competent authorities of another Member State or to the Agency.'

26. Article 123(4) is replaced by the following:

'4. The Agency shall make public annually a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended, whose supply has been prohibited or which have been withdrawn from the market.'

27. In Article 126a, paragraphs 2 and 3 are replaced by the following:

'2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Titles V, VI, VIII, IX and XI. Member States may decide that Article 63(1) and (2) shall not apply to medicinal products authorised under paragraph 1.

3. Before granting such a marketing authorisation, a Member State:

- (a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant a marketing authorisation under this Article in respect of the medicinal product concerned.
- (b) may request the competent authority in that Member State to submit copies of the assessment report referred

to in Article 21(4) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority in that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.'

28. Article 127a is replaced by the following:

'Article 127a

When a medicinal product is to be authorised in accordance with Regulation (EC) No 726/2004, and the Committee for Medicinal Products for Human Use in its opinion refers to recommended conditions or restrictions as provided for in points (c), (ca), (cb) or (cc) of Article 9(4) thereof, the Commission may adopt a decision addressed to the Member States, in accordance with Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.'

Article 2

Transitional provisions

1. With regard to the obligation on the part of the marketing authorisation holder to maintain and make available on request a pharmacovigilance system master file in respect of one or more medicinal products provided for in Article 104(3)(b) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that that obligation applies to marketing authorisations granted before 21 July 2011 as from either:

a) the date on which those marketing authorisations are renewed; or

b) the expiry of a period of 3 years starting from 21 July 2011,

whichever is earlier.

2. The Member States shall ensure that the procedure provided for in Articles 107m to 107q of Directive 2001/83/EC as amended by this Directive applies only to studies which have commenced after 21 July 2011.

3. With regard to the obligation on the part of the marketing authorisation holder to submit information on suspected adverse reactions electronically to the Eudravigilance database, provided for in Article 107(3) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that this obligation applies as from 6 months after the functionalities of the database are established and have been announced by the Agency.

4. Until the Agency can ensure the functionalities of the Eudravigilance database as specified in Article 24 of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010⁽¹⁾ of the European Parliament and of the Council, marketing authorisation holders shall report, within 15 days of the day on which the holder concerned gained knowledge of the event, all serious suspected adverse reactions that occur in the Union, to the competent authority of the Member State on whose territory the incident occurred and shall report all serious suspected adverse reactions that occur on the territory of a third country to the Agency and, if requested, to the competent authorities of the Member States in which the medicinal product is authorised.

5. Until the Agency can ensure the functionalities of the Eudravigilance database as specified in Article 24 of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010, the competent authority of a Member State may require marketing authorisation holders to report to it all non-serious suspected adverse reactions that occur on the territory of that Member State, within 90 days of the day on which the marketing authorisation holder concerned gained knowledge of the event.

6. During this period, Member States shall ensure that the reports referred to in paragraph 4 that relate to events that occurred in their territory are promptly made available to the Eudravigilance database, and in any case within 15 days of the notification of suspected serious adverse reactions.

7. With regard to the obligation on the part of the marketing authorisation holder to submit periodic safety update reports to the Agency as provided for in Article 107b(1) of Directive 2001/83/EC as amended by this Directive, the national competent authorities shall ensure that this obligation applies as from 12 months after the functionalities of the repository have been established and have been announced by the Agency.

Until the Agency can ensure the functionalities agreed for the repository of the periodic safety update reports, the marketing authorisation holders shall submit the periodic safety reports to all Member States in which the medicinal product has been authorised.

Article 3

Transposition

1. Member States shall adopt and publish, by 21 July 2012 at the latest, the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith communicate to the Commission the text of those provisions.

They shall apply those provisions from 21 July 2012.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 4

Entry into force

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

Article 5

Addressees

This Directive is addressed to the Member States.

Done at Strasbourg, 15 December 2010.

For the European Parliament
The President
J. BUZEK

For the Council
The President
O. CHASTEL

⁽¹⁾ See page 1 of this Official Journal.

Appendix D: Guidelines on Good Pharmacovigilance Practices (GVP) Introduction



15 September 2014
EMA/475236/2014

Guidelines on good pharmacovigilance practices (GVP)

Introductory cover note, last updated with revision 1 of module III on pharmacovigilance inspections and of module VI on the management and reporting of adverse reactions reports

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Background to GVP

New legislation for pharmacovigilance applies in the European Union (EU) since July 2012, and to support its implementation, a new set of guidelines for the conduct of pharmacovigilance in the EU has been developed which, as they are adopted, replace the previous set in Volume 9A of the Rules Governing Medicinal Products in the EU.

This new guidance on good pharmacovigilance practices (GVP) is organised into two types of chapters, namely Modules on pharmacovigilance processes and Product- or Population-Specific Considerations.

History of the GVP development process and latest updates

The first seven Modules on prioritised processes were consulted between 21 February and 18 April 2012 and revised, taking into account the comments received from stakeholders. They are available in their final versions which came into force on 2 July 2012.

Module III on pharmacovigilance inspections and Module X on processes for additional monitoring of medicinal products were released on 27 June 2012 for public consultation until 24 August 2012, and Module IV on pharmacovigilance audits and Module XV on safety communication were released on 26 July 2012 for public consultation until 21 September 2012. Modules III and IV were published in their final versions, together with the updated GVP Annex I on definitions, on 13 December 2012. The final Module XV was published on 24 January 2013, together with a template for Direct Healthcare Professional Letters in the GVP Annex II. On 25 April 2013, the final Module X on additional monitoring was published as final, taking into account latest additional legislation.

Since their first release as final, some Modules have been revised as final: Module II was published in its first revision, mainly to provide clarifications for herbal medicinal products, on 12 April 2013.

Module VIII Revision 1 and its Addendum Revision 1 as well as in Annex II – Template for the PSUR Cover Page Revision 1 were published on 25 April 2013.

On 7 June 2013, the draft revision 1 of Module VI on the management and reporting of adverse reactions was released for public consultation, in order to provide more guidance on the clock state for reporting of valid case reports, reporting from post-authorisation safety studies as well as the handling of languages. Also on 7 June 2013, draft Module XVI on risk minimisation measures was released for public consultation. Both consultations closed on 5 August 2013. Module XVI was published in its final version on 28 February 2014.

On 12 December 2013, the first chapter with Product- or Population-Specific Considerations was provided in its final version, i.e. the chapter P.I on vaccines, following its public consultation launched on 12 April 2013. Also, revision 1 of Module VII on periodic safety update reports was provided in its final version following public consultation launched on 25 April 2013. This revision included updates for consistency with the recently finalised ICH-E2C(R2) guideline and on the operations in the EU.

On 8 January 2014, the definitions relating to vaccine pharmacovigilance, launched for public consultation on 12 April 2013, were published without any change post-consultation, together with other amendments to definitions and explanatory notes as detailed on page 2 of the GVP Annex I on definitions in its revision 2.

On 25 April 2014, revision 1 of Module V on risk management system was published, mainly to amend the requirements of part VI of the RMP as published already in the updated RMP templates, to introduce amendments in line with the new requirements for variation applications and to align the definitions of Missing information and Safety concern and their explanatory notes with legal requirements, as well as to amend the definition for Risk minimisation activity. Annex I on definitions

was updated accordingly and published as revision 3, and likewise Module XVI on risk minimisation measures was published as revision 1.

Today, revision 1 of Module VI on the management and reporting of adverse reactions is published, in particular providing updated guidance on reporting from post-authorisation safety studies. Revision 1 of Module III is also published with a reference to the new Union procedures for pharmacovigilance inspections.

For timelines when the remaining Modules and new Considerations will be published for public consultation, please see the GVP webpage of the Agency's website.

Objectives of pharmacovigilance

Pharmacovigilance has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

In line with this general definition, underlying objectives of the applicable EU legislation for pharmacovigilance are:

- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

Pharmacovigilance in the EU: roles of different actors

In the EU, a regulatory network, consisting of the competent authorities in Member States, the European Commission and the European Medicines Agency (in GVP referred to as "the Agency") is responsible for granting marketing authorisations and supervising medicinal products, including the conduct of pharmacovigilance. The Agency has a core role in coordinating these activities for the network.

In addition to the network's responsibilities, EU legislation imposes responsibility for pharmacovigilance, together with specific obligations (i.e. in terms of tasks and responsibilities), on marketing authorisation holders.

In the past, the role of healthcare professionals was mainly seen as contributing to pharmacovigilance through spontaneous reporting of suspected adverse reaction cases and as receiving, together with the patients, advice on minimising risks through updated product information or other information materials. However over time, participation of patients and healthcare professionals in EU regulatory processes, including those for pharmacovigilance, has steadily increased. A large number of Member States have established, over the last years, schemes for reporting of suspected adverse reactions by patients themselves. An EU legal framework for patient reporting in all Member States has now been introduced through the new pharmacovigilance legislation. The new legislation further increases public participation by including patient and healthcare professional representatives in the new Pharmacovigilance and Risk Assessment Committee (PRAC) and through public hearings on pharmacovigilance and benefit-risk matters at the Agency, involving all stakeholders.

Legal basis, scope and process for GVP

The legal framework for pharmacovigilance of medicinal products for human use in the EU is given in Regulation (EC) No 726/2004 and Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended in 2010 by Regulation (EU) No 1235/2010 and Directives 2010/84/EU and 2012/26/EU respectively, as well as by the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC. It should be noted that Chapter 3 of the Regulation (EC) No 726/2004 as amended, Title IX of the Directive 2001/83/EC as amended and the Implementing Regulation contain the majority of pharmacovigilance provisions in the legislation, however, other measures directly relevant to the conduct of pharmacovigilance are found in other Chapters and Titles of this Regulation and Directive.

The aforementioned amending legislation of 2010/12, together with the related Implementing Regulation, is commonly referred to as the new pharmacovigilance legislation in the EU. It was the outcome of a major review of the current pharmacovigilance system in the EU conducted by the European Commission, followed by a formal law-making process in the Council and European Parliament. The legislation has the primary aim to strengthen and rationalise pharmacovigilance and increase patient safety.

The pharmacovigilance legal requirements and GVP apply to all medicinal products authorised in the EU, whether centrally or nationally authorised. While risk proportionality underpins the new legislation, the requirements are generally the same for different types of product unless specific provision or exemptions apply as indicated in the GVP chapters.

GVP is drawn up to facilitate the performance of pharmacovigilance activities within the EU and applies to marketing authorisation holders in the EU, the Agency and competent authorities in Member States. Iceland, Liechtenstein and Norway have so far, through the Agreement of the European Economic Area (EEA), adopted the complete Union *acquis* (i.e. the legislation at EU level, guidelines and judgements) on medicinal products, and are consequently parties to the EU procedures. The new pharmacovigilance Regulation (EU) No 1235/2010 and Directive 2010/84/EU will however only formally apply to these countries once they have been incorporated into the EEA Agreement. In the meantime and thereafter, where in GVP reference is made to Member States of the EU, this should be read to include Norway, Iceland and Liechtenstein¹.

GVP is drawn up based on Article 108a of Directive 2001/83/EC as amended, by the Agency in cooperation with competent authorities in Member States and interested parties.

GVP is being developed within a governance structure set up by the Agency and national competent authorities specifically for the implementation of the new pharmacovigilance legislation. This structure allows for the close collaboration of Member States, the Agency and the European Commission services, with regular stakeholder meetings an integral part of the implementation process.

Each draft chapter of GVP is prepared by a project team (Modules) or author team (Considerations) consisting of experts from Member States and the Agency, taking into account comments collected during the stakeholder meetings. The draft chapters are agreed by the Heads of Medicines Agencies' European Risk Management Strategy Facilitation Group (ERMS FG) and are released for public consultation on behalf of the EU regulatory network. After public consultation, the chapters are finalised within the governance structure, addressing the comments from stakeholders, and then published by the Agency.

¹ The only exemption from this is that legally binding acts from the EU (e.g. Commission Decisions) do not directly confer rights and obligations but have first to be transposed into legally binding acts in Norway, Iceland and Liechtenstein.

Maintenance and further development of GVP

Proposals for corrections, revision/addition of guidance or new GVP chapters can be made by any member of the EU regulatory network as well as any other stakeholder. Members of the public and non-regulatory stakeholder organisations can send proposals to p-pv-helpdesk@ema.europa.eu. There might not be an immediate, individual response, but all proposals will be reviewed regularly and prioritised within the governance structure set up by the Agency and national competent authorities for the implementation of the new pharmacovigilance legislation.

Structure of GVP

Pharmacovigilance activities are organised by distinct but connected processes, and each GVP Module presents one major pharmacovigilance process. In addition, GVP provides guidance on the conduct of pharmacovigilance for specific product types or specific populations in which medicines are used. These GVP Considerations apply in conjunction with the process-related guidance in the Modules.

While the development of GVP is ongoing, some guidelines developed under the previous legislation remain valid in principle (unless any aspect is not compatible with the new legislation) until they are revised at a later point in time for inclusion in GVP. They are published on the Agency's GVP webpage under GVP Annex III.

Within each chapters, Section A provides the legal, technical and scientific context of the respective process. Section B gives guidance which, while based on EU legislation, reflects scientific and regulatory approaches, formats and standards agreed internationally in various for a; or, where such formal agreements or expert consensus do not exist, Section B describes approaches which are considered in line with general current thinking in the field. Section C focusses on the specifics of applying the approaches, formats and standards in the EU and other aspects of operating the respective process in the EU.

In particular in Sections B, the term "competent authority" is to be understood in its generic meaning of an authority regulating medicinal products and/or an authority appointed at national level for being in charge of all or individual pharmacovigilance processes. For the purpose of applying GVP in the EU, the term "competent authority" covers the competent authorities in Member States and the Agency.

A table of contents of GVP is kept up to date on the GVP webpage, accessible under http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c.

Referencing of legal requirements in GVP

In GVP, any reference to Regulation (EC) No 726/2004 and Directive 2001/83/EC refers to the Regulation and Directive respectively, always including their latest amendments. Where reference is made to specific Articles in square brackets "REG" means Regulation (EC) No 726/2004 as amended and "DIR" means Directive 2001/83/EC as amended. If reference is provided to any other Regulation or Directive, its full reference is provided.

Reference to specific Articles of the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC is provided in square brackets with the indication "IR".

Text in GVP describing legal requirements makes reference to the specific article in the legislation and uses the same modal verb as used in the article, which is usually "shall". Guidance for the implementation of legal requirements is presented with the modal verb "should".

Practical advice for the public consultation

Those participating in the public consultation are asked to please submit comments by using the specific templates for each chapter (see page 1 of each draft chapter) and the Definition or Template Annex, when these are under consultation too. Comments will only be processed if submitted as **completed templates in open word format**. Participants may additionally submit pdf-files of their comments, if they wish to do so, if they accompany them by a statement that the open and pdf-files are identical in content.

The public consultation relates to the guidance proposed for the practical implementation of the applicable legislation. Participants are therefore asked not to comment on the underlying legal requirements (identified in the draft chapters by reference to the respective Articles), as these cannot be altered through the GVP consultation process.

Participants should note that their comments will be published on the Agency's website, identifying the sender's organisation (but not the sender's name). Where a sender does not represent an organisation but submits comments as an individual, the sender's name will be published unless the sender objects against the publication. In the absence of a legitimate interest to oppose the publication of the name, the contribution will not be published nor will, in principle, its content be taken into account. Please consult the Agency's Privacy Policy (http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid) and the specific privacy statement for this consultation (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf)

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The European Medicines Agency thanks all those participating in the public consultation for their contributions.

Appendix E: Pharmacovigilance Systems and Their Quality Systems

22 June 2012
EMA/541760/2011

Guideline on good pharmacovigilance practices (GVP)

Module I – Pharmacovigilance systems and their quality systems

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	19 January 2012
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See websites for contact details

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I.A. Introduction

This Module contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorisation holders, competent authorities of Member States and the Agency. How the systems of these organisations interact while undertaking specific pharmacovigilance processes is described in each respective Module of GVP.

The definition of a pharmacovigilance system is provided in Article 1 of Directive 2001/83/EC as a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance. The Agency likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.

For performing their pharmacovigilance activities, marketing authorisation holders, competent authorities of Member States and the Agency shall establish and use quality systems that are adequate and effective for this performance. The legal requirement for quality systems was introduced by Directive 2010/84/EU amending Directive 2001/83/EC (the latter is referenced as DIR) and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (the latter is referenced as REG) to strengthen pharmacovigilance in the EU. The minimum requirements of these quality systems are set out in the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (the Implementing Regulation is referenced as IR).

While there has to be compliance with these legal requirements, the implementation of a quality system should be adapted to the respective organisation.

By following the overall quality objectives in I.B.4. and the guiding principle in I.B.5. to meet the needs of patients, healthcare professionals and the public in relation to the safety of medicines, the application of the quality system should be adapted to how crucial each pharmacovigilance task is for fulfilling the quality objectives for each medicinal product covered by a quality system.

The guidance on quality systems in this Module is consistent with the general principles of the ISO 9000 Standards on good quality management practices, specifically the ISO 9001-2008 Standards on quality management systems, issued by the International Organization for Standardization (ISO). The general application of quality management to pharmacovigilance systems is described under I.B. and requirements specific to the operation of the EU network in I.C..

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

I.B. Structures and processes

I.B.1. Pharmacovigilance system

A pharmacovigilance system is defined as a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [DIR Art 1(28d)].

A pharmacovigilance system, like any system, is characterised by its structures, processes and outcomes. For each specific pharmacovigilance process, including its necessary structures, a dedicated Module is included in GVP.

1.B.2. Quality, quality objectives, quality requirements and quality system

For the purpose of GVP, which provides guidance on structures and processes of a pharmacovigilance system, the quality of a pharmacovigilance system can be defined as all the characteristics of the system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.

In general terms, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives. The overall quality objectives for pharmacovigilance systems are provided under **1.B.4.**

Specific quality objectives and quality requirements for the specific structures and processes of the pharmacovigilance systems are provided in each Module of GVP as appropriate.

The quality system is part of the pharmacovigilance system and consists of its own structures and processes. It shall cover organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management [IR Art 8(2)].

1.B.3. Quality cycle

The quality system shall be based on all of the following activities:

- quality planning: establishing structures and planning integrated and consistent processes;
- quality adherence: carrying out tasks and responsibilities in accordance with quality requirements ;
- quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; and
- quality improvements: correcting and improving the structures and processes where necessary [IR Art 8(3)].

1.B.4. Overall quality objectives for pharmacovigilance

The overall quality objectives of a pharmacovigilance system are:

- complying with the legal requirements for pharmacovigilance tasks and responsibilities;
- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure;
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and
- contributing to the protection of patients' and public health.

1.B.5. Principles for good pharmacovigilance practices

With the aim of fulfilling the overall quality objectives in **1.B.4.**, the following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

- The needs of patients, healthcare professionals and the public in relation to the safety of medicines should be met.

- Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
- All persons within the organisation should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- All persons involved with the entire organisation should engage in continuous quality improvement following the quality cycle in I.B.3..
- Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
- All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, should be considered for decision-making.
- Good cooperation should be fostered between marketing authorisation holders, competent authorities, public health organisations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions.

I.B.6. Responsibilities for the quality system within an organisation

A sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities [IR Art 10(1), Art 14(1)]. Their responsibility should include adherence to the principles defined in I.B.5..

For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for:

- ensuring that the organisation documents the quality system as described in I.B.11.;
- ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
- ensuring that adequate resources are available and that training is provided (see I.B.7.);
- ensuring that suitable and sufficient premises, facilities and equipment are available (see I.B.8.);
- ensuring adequate compliance management (see I.B.9.);
- ensuring adequate record management (see I.B.10.);
- reviewing the pharmacovigilance system including its quality system at regular intervals in risk-based manner to verify its effectiveness (see I.B.12.) and introducing corrective and preventive measures where necessary;
- ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to medicinal products within an organisation;
- identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- ensuring that audits are performed (see I.B.12.).

In relation to the management responsibilities described above, upper management within an organisation should provide leadership through:

- motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organisation; and
- assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

For competent authorities, all persons involved in the procedures and processes of the quality system established for the performance of pharmacovigilance activities shall be responsible for the good functioning of that quality system and shall ensure a systematic approach towards quality and towards the implementation and maintenance of the quality system [IR Art 8(5)].

1.B.7. Training of personnel for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel (see 1.B.6.).

All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training [IR Art 10(3), Art 14(2)]. For marketing authorisation holders, this training shall relate to the roles and responsibilities of the personnel [IR Art 10(3)].

The organisation shall keep training plans and records for documenting, maintaining and developing the competences of personnel [IR Art 10(3), Art 14(2)]. Training plans should be based on training needs assessment and should be subject to monitoring.

The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organisation should receive and be able to seek information about what to do if they become aware of a safety concern.

There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organisations as well as the individual staff members.

Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Appropriate instructions on the processes to be used in case of urgency, including business continuity (see 1.B.11.3.), shall be provided by the organisation to their personnel [IR Art 10(4), Art 14(3)].

1.B.8. Facilities and equipment for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see 1.B.4.) and

also be available for business continuity (see I.B.11.3.). Facilities and equipment which are critical for the conduct of pharmacovigilance (see I.B.11.3.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep awareness of the valid terminologies (see Module VI) in their valid versions and to keep the IT systems up-to-date accordingly.

I.B.9. Specific quality system procedures and processes

I.B.9.1. Compliance management by marketing authorisation holders

For the purpose of compliance management, marketing authorisation holders shall have specific quality system procedures and processes in place in order to ensure the following:

- the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the marketing authorisation holder [IR Art 11(1)(a)] (see Modules IX and XII);
- the scientific evaluation of all information on the risks of medicinal products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorisation or associated with occupational exposure [IR Art 11(1)(b)] (see Modules VI, VII, VIII, IX);
- the submission of accurate and verifiable data on serious and non-serious adverse reactions to the competent authorities within the legally required time-limits [IR Art 11(1)(c)] (see Modules VI and IX);
- the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals [IR Art 11(1)(d)] (see Modules V, VI, VII, VIII and IX);
- effective communication by the marketing authorisation holder with competent authorities, including communication on new or changed risks (see Module XII and XV), the pharmacovigilance system master file (see Module II), risk management systems (see Module V), risk minimisations measures (see Modules V and XVI), periodic safety update reports (see Module VII), corrective and preventive actions (see Modules II, III and IV) and post-authorisation safety studies (see Module VIII) [IR Art 11(1)(e)];
- the update of product information by the marketing authorisation holder in the light of scientific knowledge [IR Art 11(1)(f)] (see Module XII);
- appropriate communication of relevant safety information to healthcare professionals and patients (see Module XII and XV) [IR Art 11(1)(g)].

I.B.9.2. Compliance management by competent authorities

For the purpose of compliance management, competent authorities shall establish specific quality system procedures and processes in order to achieve all of the following objectives:

- ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted [IR Art 15(1)(a)];
- ensuring the assessment of pharmacovigilance data and its processing in accordance with the legal timelines [IR Art 15(1)(b)];
- ensuring independence in the performance of pharmacovigilance activities [IR Art 15(1)(c)];

- ensuring effective communication with patients, healthcare professionals, marketing authorisation holders and the general public [IR Art 15(1)(d)];
- conducting inspections, including pre-authorisation inspections [IR Art 15(1)(f)].

Independence in the performance of pharmacovigilance activities is interpreted in the sense that all regulatory decisions on medicinal products should be taken in the sole interest of patients' and public health.

1.B.10. Record management

The organisation shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information [IR Art 12(1), Art 16(1)].

A record management system shall be put in place for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process [IR Art 12(1), Art 16(1)].

The record management system should support:

- the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
- timely access to all records;
- effective internal and external communication; and
- the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.

In addition, marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports [IR Art 12(1)].

In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process (IR Recital 17). As part of a record management system, specific measures should therefore be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the medical and administrative confidentiality of the data.

There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.

The record management system should be described in a record management policy.

I.B.11. Documentation of the quality system

All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records [IR Art 8(4)].

A quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them. A procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction or quality manual. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two. A quality record is a document stating results achieved or providing evidence of activities performed.

In order to have a systematic approach, the organisation should define in advance:

- quality objectives specific to their organisations in accordance with the overall quality objectives provided under I.B.4. and the structure- and process-specific quality objectives in accordance with each Module of GVP; and
- methods for monitoring the effectiveness of the pharmacovigilance system (see I.B.12.).

The quality system shall be documented by:

- documents on organisational structures and assignments of tasks to personnel (see I.B.11.1. and I.B.11.2.);
- training plans and records (see I.B.7.) [IR Art 10(3), Art 14(2)];
- instructions for the compliance management processes (see I.B.9.) [IR Art 11(1), Art 15(1)];
- appropriate instructions on the processes to be used in case of urgency, including business continuity (see I.B.11.3.) [IR Art 10(4), Art 14(3)];
- performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities [IR Art 9(1)];
- reports of quality audits and follow-up audits, including their dates and results [IR Art 13(2), Art 17(2)].

Training plans and records shall be kept and made available for audit and inspection [IR Art 10(3), Art 14(2)].

It is recommended that the documentation of the quality system also includes:

- the methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;
- a record management policy;
- records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;
- records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
- records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been

applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

I.B.11.1. Additional quality system documentation by marketing authorisation holders

In addition to the quality system documentation in accordance with I.B.11., marketing authorisation holders shall document:

- their human resource management in the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 2(5)(b)];
- job descriptions defining the duties of the managerial and supervisory staff [IR Art 10(2)];
- an organisational chart defining the hierarchical relationships of managerial and supervisory staff [IR Art 10(2)];
- instructions on critical processes (see I.B.11.3.) in the pharmacovigilance system master file (PSMF) (see Module II); and
- their record management system in the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 2(5)(c)].

It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

For the requirements of documenting the quality system in the pharmacovigilance system master file (PSMF) or its annexes, see Module II.

I.B.11.2. Additional quality system documentation by competent authorities

In addition to the quality system documentation in accordance with I.B.11., the organisational structures and the distribution of tasks and responsibilities shall be clear and, to the extent necessary, accessible [IR Art 14(1)].

It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

Contact points shall be established [IR Art 14(1)], in particular to facilitate interaction between competent authorities, marketing authorisation holders and persons reporting information on the risks of medicinal products as regards patients' or public health.

I.B.11.3. Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes should be considered as critical include:

- continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;

- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
- interaction between the pharmacovigilance and product quality defect systems;
- communication about safety concerns between marketing authorisation holders and competent authorities, in particular notifying changes to the risk-benefit balance of medicinal products;
- communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of medicinal products;
- keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the applicable competent authority;
- implementation of variations to marketing authorisations for safety reasons according to the urgency required.

Business continuity plans should be established in a risk-based manner and should include:

- provisions for events that could severely impact on the organisation's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
- back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks as well as between marketing authorisation holders and competent authorities.

I.B.12. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

Processes to monitor the performance and effectiveness of a pharmacovigilance system and its quality system should include:

- reviews of the systems by those responsible for management;
- audits;
- compliance monitoring;
- inspections;
- evaluating the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use in patients.

The organisation may use performance indicators to continuously monitor the good performance of pharmacovigilance activities [IR Art 9(1)] in relation to the quality requirements. The quality requirements for each pharmacovigilance process are provided in each Module of GVP as appropriate.

The requirements for the quality system itself are laid out in this Module and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system (see **I.B.11.**) at regular intervals, with the frequency and the extent of the reviews to be determined in a

risk-based manner. Pre-defined programmes for the review of the system should therefore be in place. Reviews of the quality system should include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.

Risk-based audits of the quality system shall be performed at regular intervals to ensure that it complies with the requirements for the quality system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness [IR Art 13(1), Art 17(1)]. Audits of the quality system should include audit of the pharmacovigilance system which is the subject of the quality system. The methods and processes for the audits are described in **Module IV**. In relation to the pharmacovigilance system of a marketing authorisation holder, a report shall be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited [IR Art 13(2)]. The report should include the results of audits of organisations or persons the marketing authorisation holder has delegated tasks to, as these are part of the marketing authorisation holder's pharmacovigilance system. For competent authorities, the audit report shall be sent to the management responsible for the matters audited [IR Art 17(2)].

As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary [IR Art 13(2), Art 17(2)]. Additionally, the competent authorities should have in place arrangements for monitoring the compliance of marketing authorisations holders with legally required pharmacovigilance tasks and responsibilities. They shall further ensure compliance with the legal requirements by means of conducting inspections of marketing authorisation holders [DIR Art 111(1)] (see **Module III**). Guidance on compliance monitoring for each pharmacovigilance process is provided in each Module of GVP as appropriate.

Requirements and methods for evaluating the effectiveness of actions taken upon medicinal products for the purpose of minimising risks and supporting the safe and effective use of medicines in patients are described in **Module XVI**.

I.B.13. Preparedness planning for pharmacovigilance in public health emergencies

Any pharmacovigilance system should be adaptable to public health emergencies and preparedness plans should be developed as appropriate.

For preparedness planning in the EU, see **I.C.4.**

I.C. Operation of the EU network

I.C.1. Overall pharmacovigilance responsibilities of the applicant and marketing authorisation holder in the EU

The marketing authorisation holder in the EU is responsible for the respective pharmacovigilance tasks and responsibilities laid down in Directive 2001/83/EC, Regulation (EC) No 726/2004 and the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC in order to assure responsibility and liability for its authorised medicinal products and to ensure that appropriate action can be taken, when necessary.

For this purpose, the marketing authorisation holder shall operate a pharmacovigilance system [DIR 104(1)] and shall establish and use a quality system that is adequate and effective for performing its pharmacovigilance activities [IR Art 8(1)].

There may be circumstances where a marketing authorisation holder may establish more than one pharmacovigilance system, e.g. specific systems for particular types of products (e.g. vaccines, products available without medical prescription).

A description of the pharmacovigilance system shall be developed by the applicant for a marketing authorisation in the format of a pharmacovigilance system master file (PSMF) and be maintained by the marketing authorisation holder for all authorised medicinal products (see **Module II**). The applicant or the marketing authorisation holder is also responsible for developing and maintaining product-specific risk management systems (see **Module V**).

Guidance on the structures and processes on how the marketing authorisation holder should conduct the pharmacovigilance tasks and responsibilities is provided in the respective GVP Modules.

I.C.1.1. Responsibilities of the marketing authorisation holder in relation to the qualified person responsible for pharmacovigilance in the EU

As part of the pharmacovigilance system, the marketing authorisation holder shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU (QPPV) [DIR Art 104(3)(a)].

The marketing authorisation holder shall submit the name and contact details of the QPPV to the competent authorities in Member States and the Agency [DIR Art 104(3) last paragraph]. Changes to this information should be submitted in accordance with Regulation (EC) No 1234/2008 on variations to the terms of marketing authorisation and the **Communication from the Commission - Guideline on the Details of the Various Categories of Variations to the Terms of Marketing Authorisations for Medicinal Products for Human Use and Veterinary Medicinal Products**¹.

The duties of the QPPV shall be defined in a job description [IR Art 10(2)]. The hierarchical relationship of the QPPV shall be defined in an organisational chart together with those of other managerial and supervisory staff [IR Art 10(2)].

Information relating to the QPPV shall be included in the pharmacovigilance systems master file (PSMF) [IR Art 2(1)] (see **Module II**).

Each pharmacovigilance system can have only one QPPV. A QPPV may be employed by more than one marketing authorisation holder, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorisation holder, provided that the QPPV is able to fulfil all obligations.

In addition to the QPPV, competent authorities in Member States are legally provided with the option to request the nomination of a pharmacovigilance contact person at national level reporting to the QPPV. Reporting in this context relates to pharmacovigilance tasks and responsibilities and not necessarily to line management. A contact person at national level may also be nominated as the QPPV.

The marketing authorisation holder shall ensure that the QPPV has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorisation holder [IR Art 10(2)]. The marketing authorisation holder should therefore ensure that the QPPV has

¹ See Volume 2C of the Rules Governing Medicinal Products in the EU; http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it in accordance with **Module II** (see **I.C.1.3**). The authority over the pharmacovigilance system and the PSMF should allow the QPPV to implement changes to the system and to provide input into risk management plans (see **Module V**) as well as into the preparation of regulatory action in response to emerging safety concerns (see **Module XII**).

Overall, the marketing authorisation holder should ensure that structures and processes are in place, so that the QPPV can fulfil the responsibilities listed in **I.C.1.3**. In order to do this, the marketing authorisation holder should ensure that mechanisms are in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant, in particular on:

- emerging safety concerns and any other information relating to the benefit-risk evaluation of the medicinal products covered by the pharmacovigilance system;
- ongoing or completed clinical trials and other studies the marketing authorisation holder is aware of and which may be relevant to the safety of the medicinal products;
- information from sources other than from the specific marketing authorisation holder, e.g. from those with whom the marketing authorisation holder has contractual arrangements; and
- the procedures relevant to pharmacovigilance which the marketing authorisation holder has in place at every level in order to ensure consistency and compliance across the organisation.

The outcome of the regular reviews of the quality system referred to in **I.B.6** and **I.B.12** and the measures introduced should be communicated by the managerial staff to the QPPV.

Compliance information should be provided to the QPPV on a periodic basis. Such information may also be used to provide assurance to the QPPV that commitments in the framework of risk management plans and post-authorisation safety systems are being adhered to.

The managerial staff should also inform the QPPV of scheduled pharmacovigilance audits. The QPPV should be able to trigger an audit where appropriate. The managerial staff should provide the QPPV with a copy of the corrective and preventive action plan following each audit relevant to the pharmacovigilance system the QPPV is responsible for, so that the QPPV can assure that appropriate corrective actions are implemented.

In particular with regard to its adverse reaction database (or other systems to collate adverse reaction reports), the marketing authorisation holder should implement a procedure to ensure that the QPPV is able to obtain information from the database, for example, to respond to urgent requests for information from the competent authorities or the Agency, at any time. If this procedure requires the involvement of other personnel, for example database specialists, then this should be taken into account in the arrangements made by the marketing authorisation holder for supporting the QPPV outside of normal working hours.

When a marketing authorisation holder intends to expand its product portfolio, for example, by acquisition of another company or by purchasing individual products from another marketing authorisation holder, the QPPV should be notified as early as possible in the due diligence process in order that the potential impact on the pharmacovigilance system can be assessed and the system be adapted accordingly. The QPPV may also have a role in determining what pharmacovigilance data should be requested from the other company, either pre- or post-acquisition. In this situation, the QPPV should be made aware of the sections of the contractual arrangements that relate to responsibilities for pharmacovigilance activities and safety data exchange and have the authority to request amendments.

When a marketing authorisation holder intends to establish a partnership with another marketing authorisation holder, organisation or person that has a direct or indirect impact on the pharmacovigilance system, the QPPV should be informed early enough and be involved in the preparation of the corresponding contractual arrangements (see I.C.1.5.) so that all necessary provisions relevant to the pharmacovigilance system are included.

I.C.1.2. Qualifications of the qualified person responsible for pharmacovigilance in the EU

The marketing authorisation holder shall ensure that the QPPV has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities [IR Art 10(1)]. The QPPV should have skills for the management of pharmacovigilance systems as well as expertise or access to expertise in relevant areas such as medicine, pharmaceutical sciences as well as epidemiology and biostatistics. Where the QPPV has not completed basic medical training in accordance with Article 24 of Directive 2005/36/EC, the marketing authorisation holder shall ensure that the QPPV is assisted by a medically trained person (i.e. in accordance with Article 24 of Directive 2005/36/EC) and this assistance shall be duly documented [IR Art 10(1)].

The expectation is that the applicant or marketing authorisation holder will assess the qualification of the QPPV prior to appointment by, for example, reviewing university qualifications, knowledge of EU pharmacovigilance requirements and experience in pharmacovigilance.

The applicant or marketing authorisation holder should provide the QPPV with training in relation to its pharmacovigilance system, which is appropriate for the role prior to the QPPV taking up the position and which is appropriately documented. Consideration should be given to additional training, as needed, of the QPPV in the medicinal products covered by the pharmacovigilance system.

I.C.1.3. Role of the qualified person responsible for pharmacovigilance in the EU

The qualified person responsible for pharmacovigilance in the EU (QPPV) is a natural² person.

The QPPV appointed by the marketing authorisation holder shall be appropriately qualified (see I.C.1.2.) and shall be at the marketing authorisation holder's disposal permanently and continuously (see I.C.1.1.) [DIR Art 104 (3)(a)]. The QPPV shall reside and operate in the EU [DIR Art 104 (3) last paragraph]. Following European Economic Area (EEA) agreements, the QPPV may also reside and operate in Norway, Iceland or Liechtenstein. Back-up procedures in the case of absence of the QPPV shall be in place [IR Art 2(1)(d)] and should be accessible through the QPPV's contact details. The QPPV should ensure that the back-up person has all necessary information to fulfil the role.

The QPPV shall be responsible for the establishment and maintenance of the marketing authorisation holder's pharmacovigilance system [DIR Art 104 (3) last paragraph] and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities [IR Art 10(2)] and to promote, maintain and improve compliance with the legal requirements [IR Art 2(1)(a)]. Hence, the QPPV should have access to the pharmacovigilance system master file (PSMF) (see Module II) and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility.

In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV should include:

² A natural person is a real human being, as distinguished from a corporation which is often treated at law as a fictitious person.

- having an overview of medicinal product safety profiles and any emerging safety concerns;
- having awareness of any conditions or obligations adopted as part of the marketing authorisations and other commitments relating to safety or the safe use of the products;
- having awareness of risk minimisation measures;
- being aware of and having sufficient authority over the content of risk management plans;
- being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in the EU or pursuant to a risk management plan agreed in the EU;
- having awareness of post-authorisation safety studies requested by a competent authority including the results of such studies;
- ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP;
- ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the competent authorities in Member States and the Agency;
- ensuring a full and prompt response to any request from the competent authorities in Member States and from the Agency for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product;
- providing any other information relevant to the benefit-risk evaluation to the competent authorities in Member States and the Agency;
- providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);
- acting as a single pharmacovigilance contact point for the competent authorities in Member States and the Agency on a 24-hour basis and also as a contact point for pharmacovigilance inspections.

This responsibility for the pharmacovigilance system means that the QPPV has oversight over the functioning of the system in all relevant aspects, including its quality system (e.g. standard operating procedures, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance). Specifically for the adverse reaction database, if applicable, the QPPV should be aware of the validation status of the database, including any failures that occurred during validation and the corrective actions that have been taken to address the failures. The QPPV should also be informed of significant changes that are made to the database (e.g. changes that could have an impact on pharmacovigilance activities).

The QPPV may delegate specific tasks, under supervision, to appropriately qualified and trained individuals, for example, acting as safety experts for certain products, provided that the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.

I.C.1.4. Specific quality system processes of the marketing authorisation holder in the EU

In applying the requirements set out in **I.B.9.1.** in the EU, the marketing authorisation holder shall put in place the following additional specific quality system processes for ensuring:

- the submission of adverse reaction data to EudraVigilance within the legal timelines [IR Art 11(c)];

- the monitoring of the use of terminology referred to in IR Art 25(1) either systematically or by regular random evaluation [IR Art 25(3)];
- the retention of minimum elements of the pharmacovigilance system master file (PSMF) (see IR Art 2 and Module II) as long as the system described in the PSMF exists and for at least further 5 years after it has been formally terminated by the marketing authorisation holder [IR Art 12(2)];
- the retention of pharmacovigilance data and documents relating to individual authorised medicinal products as long as the marketing authorisation exists and for at least further 10 years after the marketing authorisation has ceased to exist [IR Art 12(2)];
- that the product information is kept up-to-date by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal [IR Art 11(1)(g)].

The retention periods above apply unless the documents shall be retained for a longer period where EU or national law so requires [IR Art 12(2)].

During the retention period, retrievability of the documents should be ensured. Documents can be retained in electronic format, provided that the electronic system has been appropriately validated and appropriate arrangements exist for system security, access and back-up of data. If documents in paper format are transferred into an electronic format, the transfer process should ensure that all of the information present in the original format is retained in a legible manner and that the media used for storage will remain readable over time.

Documents transferred in situations where the business of the marketing authorisation holder is taken over by another organisation should be complete.

I.C.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the marketing authorisation holder

The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties [IR Art 6(1)], i.e. to another organisation or person (where the same requirements apply to a person as for an organisation). This may include the role of the QPPV. The marketing authorisation holder shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file (PSMF) (see Module II) [IR Art 6(1)]. The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the marketing authorisation holder.

Where a marketing authorisation holder has subcontracted some tasks of its pharmacovigilance tasks, it shall retain responsibility for ensuring that an effective quality system is applied in relation to those tasks [IR Art 11(2)]. All guidance provided in GVP is also applicable to the other organisation to which the tasks have been subcontracted.

When subcontracting tasks to another organisation, the marketing authorisation holder shall draw up subcontracts [IR Art 6(2)] and these should be detailed, up-to-date and clearly document the contractual arrangements between the marketing authorisation holder and the other organisation, describing arrangements for delegation and the responsibilities of each party. A description of the subcontracted activities and/or services shall be included in the pharmacovigilance system master file (PSMF) [IR Art 2(6)] and a list of the subcontracts shall be included in an annex to the PSMF, specifying the product(s) and territory(ies) concerned [IR Art 6(2)] (see Module II). The other

organisation may be subject to inspection at the discretion of the competent or supervisory authority in the relevant Member State.

Contractual arrangements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. When preparing contractual arrangements, the marketing authorisation holder should include sufficiently detailed descriptions of the delegated tasks, the related interactions and data exchange, together with, for example, agreed definitions, tools, assignments and timelines. The contractual arrangements should also contain clear information on the practical management of pharmacovigilance as well as related processes, including those for the maintenance of pharmacovigilance databases. Further, they should indicate which processes are in place for checking whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organisation by the marketing authorisation holder or introduction of other methods of control and assessment are recommended.

With respect to centrally authorised products, contractual arrangements between different marketing authorisation holders should also be in place in relation to separately authorised medicinal products with the application of Article 82(1) of Regulation (EC) No 726/2004 in order to ensure conduct of pharmacovigilance on the basis of complete worldwide data sets.

For responsibilities of the marketing authorisation holder towards the QPPV in this context, see I.C.1.1..

I.C.2. Overall pharmacovigilance responsibilities within the EU regulatory network

The competent authorities in Member States and the Agency are responsible for the respective pharmacovigilance tasks and responsibilities imposed on them by Directive 2001/83/EC, Regulation (EC) No 726/2004 and the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC in order to ensure that appropriate action can be taken, when necessary.

For this purpose each competent authority in a Member State as well as the Agency shall operate a pharmacovigilance system [DIR 101(1)] and shall establish and use an adequate and effective quality system for performing their pharmacovigilance activities [IR Art 8(1)].

The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available within the EU [REG Art 28e].

The requirement in I.B.11.2. according to which competent authorities shall keep accessible clear descriptions of the organisational structures, assignment of tasks and responsibilities as well as contact points [IR Art 14(1)], should relate to the interaction between competent authorities in Member States, the Agency, the European Commission, marketing authorisation holders and persons reporting information on the risks of medicinal products.

Guidance on the structures and processes to enable the competent authorities in Member States and the Agency to conduct the pharmacovigilance tasks and responsibilities is provided in the respective Modules of GVP.

I.C.2.1. Role of the competent authorities in Member States

Each Member State shall designate a competent authority for the performance of pharmacovigilance [DIR Art 101(3)]. This authority is usually the same as the competent authority responsible for granting national marketing authorisations.

Each competent authority in a Member State must operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in EU pharmacovigilance activities [DIR Art 101(1)]. In this context, the competent authority in a Member State is responsible for the safety monitoring of each medicinal product, independent of its route of authorisation, in the territory of that Member State. In particular, the competent authority in each Member State shall be responsible for monitoring data originating in their territory [IR Art 18(4)].

For nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, the competent authority in a Member State is responsible for granting, varying, suspending and revoking a marketing authorisation. The pharmacovigilance tasks and responsibilities of competent authorities in Member States for each process in relation to such products, are detailed in the respective Modules of GVP.

For products authorised through the mutual recognition or the decentralised procedure, one Member State acts as the Reference Member State. For practical reasons, the competent authority of the Reference Member State should coordinate communication with the marketing authorisation holder on pharmacovigilance matters and monitor the compliance of the marketing authorisation holder with legal pharmacovigilance requirements. These arrangements do not replace the legal responsibilities of the marketing authorisation holder with respect to individual competent authorities and the Agency.

Nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, may become subject to regulatory procedures at EU level on pharmacovigilance grounds. If a Commission Decision for a nationally authorised product exists as an outcome of such a procedure, the competent authorities in Member States are responsible for the implementation of the Commission Decision and also for its follow-up, unless exceptionally further action by the Agency and the European Commission has been foreseen in the Commission Decision reflecting the outcome of the regulatory procedure (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons).

The pharmacovigilance tasks and responsibilities of competent authorities in Member States in relation to centrally authorised products are also detailed in the respective Modules of GVP. They include the collaboration in signal detection (see Module IX) and implementation of Commission Decisions regarding risk management of centrally authorised products addressed to Member States (see Module V). Where urgent action is essential to protect human health or the environment, the competent authority in a Member State, on its own initiative or at the European Commission's request, may suspend the use of a centrally authorised product in its territory (see Modules XII).

Competent authorities in Member States are responsible for pharmacovigilance inspections of organisations in their territory in relation to medicinal products. This is independent of the route of marketing authorisation as well as which competent authority granted the marketing authorisation for the respective medicinal product (see Module III).

In relation to the various aspects of the role described above, each Member State's competent authority should ensure that all pharmacovigilance data are shared between competent authorities in other Member States, the European Commission and the Agency for each process in accordance with the legislation and the guidance in the respective GVP Modules.

I.C.2.2. Role of the European Commission

The European Commission is the competent authority for medicinal products authorised through the centralised procedure and is responsible for granting, varying, suspending and revoking their marketing authorisations by adoption of Commission Decisions on the basis of Opinions adopted by the Committee for Medicinal Products for Human Use (CHMP) (see I.C.2.3.3.).

Further, the European Commission adopts Commission Decisions in relation to nationally authorised medicinal products subject to regulatory procedures at EU level, including on pharmacovigilance grounds. The European Commission may also initiate such procedures (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons).

I.C.2.3. Role of the European Medicines Agency

I.C.2.3.1. General role of the Agency and the role of the Agency's secretariat

The role of the Agency is to coordinate the monitoring of medicinal products for human use authorised in the EU and to provide advice on the measures necessary to ensure their safe and effective use, in particular, by coordinating the evaluation and implementation of legal pharmacovigilance requirements and the monitoring of such implementation. The tools established and maintained by the Agency for the coordination are presented in the GVP Modules for each process.

The Agency provides coordination and technical, scientific and administrative support to the Pharmacovigilance Risk Assessment Committee (PRAC) (see I.C.2.3.2.) and the Committee for Medicinal Products for Human Use (CHMP) (see I.C.2.3.3.) and coordination and technical and administrative support to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) (see I.C.2.3.4.), as well as coordination between the committees and the CMDh.

Pharmacovigilance for centrally authorised products is conducted by the Agency with the involvement of the Rapporteurs, the PRAC and the CHMP. The Agency should take the lead for communicating with the marketing authorisation holders of centrally authorised products. The respective responsibilities for each pharmacovigilance process are detailed in the GVP Modules.

For nationally authorised products, the Agency coordinates regulatory procedures at EU level on pharmacovigilance grounds through providing support to the CMDh and CHMP (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons).

The Agency also cooperates with other EU bodies as necessary.

Specific pharmacovigilance tasks of the Agency include:

- running the EudraVigilance database [REG Art 57(d)];
- monitoring selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances [REG Art 27] (see Module VI);
- running processes for the EU coordination of the assessment of periodic safety update reports (see Module VII) and oversight of post-authorisation safety studies (see Module VIII);
- tasks relating to signal detection [REG Art 28a(1)(c), IR Art 18-24] (see Module IX);
- tracking of follow-up of safety concerns and other pharmacovigilance matters at EU level (see Module XII);

- assisting Member States with the rapid communication of information on safety concerns to healthcare professionals and coordinating the safety announcements of the national competent authorities [REG Art 57(e)] (see Module XV);
- distributing appropriate information on safety concerns to the general public, in particular by setting up and maintaining the European medicines web-portal [REG Art 57(f)] (see Module XV);
- coordination of safety announcements between national competent authorities for active substances contained in medicinal products authorised in more than one Member State, including providing timetables for the publication of information [DIR 106a(3)] (see Module XV);

and specifically in relation to centrally authorised products:

- assessing updates to risk management systems [REG Art 28a(1)(b)] (see Module V);
- monitoring the outcome of risk minimisation measures [REG Art 28a(1)(a)] (see Module XVI).

1.C.2.3.2. Role of the Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for providing recommendations to the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems, including the monitoring of the effectiveness of those risk management systems [REG Art 56(1)(aa)]. The Details on the responsibilities for each process are presented in the respective GVP Modules. The Mandate and Rules of Procedure of the PRAC are published on the Agency's website³.

1.C.2.3.3. Role of the Committee for Medicinal Products for Human Use (CHMP)

The Committee for Medicinal Products for Human Use (CHMP) is responsible for evaluating applications and formulating Opinions serving as a basis for granting, varying, suspending or withdrawing marketing authorisations for centrally authorised products. The CHMP also prepares Opinions on safety concerns emerging after a marketing authorisation has been granted for centrally authorised products or, for nationally authorised products, including those through the mutual recognition or the decentralised procedure, in the framework of regulatory procedures at EU level in which at least one centrally authorised product is involved (see Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons), procedures for the assessment of periodic safety update reports (PSURs) (see Module VII) and procedures for post-authorisation safety studies (see Module VIII). For questions related to pharmacovigilance activities and risk management systems, the CHMP relies on the recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC). The specific responsibilities of each party for each pharmacovigilance process are described in the GVP Modules. The Rules of Procedure of the CHMP are published on the Agency's website⁴.

1.C.2.3.4. Role of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)

The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) is responsible for examining any question relating to marketing authorisations for medicinal products authorised through the mutual recognition or the decentralised procedure and questions on the

³ <http://www.ema.europa.eu>

⁴ http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c7a

variation of marketing authorisations granted by the Member States as well as questions arising for nationally authorised products from assessments of periodic safety update reports (see **Module VII**), post-authorisation safety studies (see **Module VIII**) and during regulatory procedures at EU level. The CMDh shall reach a position, based on a PRAC recommendation, on regulatory procedures at EU level when only nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, are involved [DIR Art 107k](see **Chapter 3 of the Notice to Applicants and the Agency's and HMA Procedural Advice on Referral Procedures for Safety Reasons**). The responsibilities of the CMDh for each pharmacovigilance process are described in the respective GVP Modules. The **Rules of Procedure of the CMDh** and the **Functions and Tasks for CMDh** are published on the HMA website⁵.

I.C.2.4. Specific quality system processes of the quality systems of competent authorities in Member States and the Agency

In applying the requirements set out in **I.B.9.2.** in the EU, the competent authorities in Member States and the Agency shall put in place the following additional specific quality system processes for:

- monitoring and validating the use of terminology referred to in IR Art 25(1), either systematically or by regular random evaluation [IR Art 25(3)];
- assessing and processing pharmacovigilance data in accordance with the timelines provided by legislation [IR Art 15(1)(b)];
- ensuring effective communication within the EU regulatory network in accordance with the provisions on safety announcements in Article 106a of Directive 2001/83/EC [IR Art 15(1)(d)] (see **Module XV**);
- guarantying that competent authorities in Member States and the Agency inform each other and the European Commission of their intention to make announcements relating to the safety of a medicinal product or an active substance contained in a medicinal product authorised in several Member State (see **Modules XII** and **XV**) [IR Art 15(1)(e)];
- arranging for the essential documents describing their pharmacovigilance systems to be kept as long as the system exists and for at least further 5 years after they have been formally terminated [IR Art 16(2)];
- ensuring that pharmacovigilance data and documents relating to individual authorised medicinal products are retained as long as the marketing authorisation exists or for at least further 10 years after the marketing authorisation has expired [IR Art 16(2)].

In this context, documents relating to a medicinal product include documents of a reference medicinal product where this is applicable.

The retention periods above apply unless the documents shall be retained for a longer period where EU or national law so requires [IR Art 16(2)].

During the retention periods referred to above, retrievability of the documents should be ensured.

Documents can be retained in electronic format, provided that the electronic system has been appropriately validated and appropriate arrangements exist for system security, access and back-up of data. If pharmacovigilance documents in paper format are transferred into an electronic format, the transfer process should ensure that all of the information present in the original format is retained in a legible manner and that the media used for storage will remain readable over time.

⁵ <http://www.hma.eu/205.html>

The legal requirements for record management (see I.B.10.) imply accessibility to the records from within the EU, preferably at a single point.

In addition to the above, competent authorities in Member States shall establish procedures for collecting and recording all suspected adverse reactions that occur in their territory (see Module VI) [IR Art 15(2)].

In addition to the above, the Agency shall establish procedures for literature monitoring in accordance with Article 27 of Regulation (EC) No 726/2004 (see Module VI) [IR Art 15(3)].

In addition to the quality system documentation in accordance with I.B.11. and I.B.11.2., competent authorities in Member States and the Agency shall clearly determine, and to the extent necessary, keep accessible the organisational structures and the distribution of tasks and responsibilities [IR Art 14(1)] as well as establish contact points [IR Art 14(1)], in particular to facilitate interaction between competent authorities in Member States, the Agency, marketing authorisation holders and persons reporting information on the risks of medicinal products as regards patients' or public health.

Quality audits of the Member States' and Agency 's pharmacovigilance systems (see I.B.12.) shall be performed according to a common methodology [IR Art 17(1)]. The results of audits shall be reported by competent authorities in Member States in accordance with Article 101(2) of Directive 2001/83/EC and by the Agency in accordance with Article 28f of Regulation (EC) No 726/2004 (see Module IV).

I.C.2.5. Quality system requirements for pharmacovigilance tasks delegated or transferred by competent authorities in Member States

A competent authority in a Member State may delegate any pharmacovigilance task to another Member State subject to a written agreement of the latter Member State [DIR Art 103]. The written agreement should be reflected by exchange of letters, defining the scope of the delegation.

A competent authority in a Member State may transfer any or all of the pharmacovigilance tasks to another organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the competent authority in a Member State.

Where tasks are transferred to another organisation, the competent authority in a Member State should ensure that the tasks are subject to a quality system compliant with the legal requirements applicable to their own organisation.

I.C.2.6. Transparency of the quality system of the EU regulatory network

The European Commission (EC) shall publish every three years a report on the performance of pharmacovigilance based on the reports submitted by the competent authorities in Member States (first EC report due on 21 July 2015) and by the Agency (first EC report due on 2 January 2014) on the results of their regular pharmacovigilance system audits (see Module IV) [DIR Art 101(2), Art 108b, REG Art 28f, Art 29].

I.C.3. Data protection in the EU

All legal requirements of the IR, including those relating to the record management described in I.B.10., shall apply without prejudice to the obligations of national competent authorities and marketing authorisation holders relating to their processing of personal data under Directive 95/46/EC or the obligations of the Agency relating to its processing of personal data under Regulation (EC) No 45/2001 [IR Art 39].

I.C.4. Preparedness planning in the EU for pharmacovigilance in public health emergencies

The pharmacovigilance systems of marketing authorisation holders, competent authorities in Member States and the Agency should be adaptable to public health emergencies. Preparedness plans should be developed as appropriate (see I.B.13.).

A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Community in the framework of Decision No. 2119/98/EC of the European Parliament and of the Council.

Pharmacovigilance requirements for public health emergencies should be considered by the competent authorities in Member States, the European Commission and the Agency on a case-by-case basis and appropriately notified to marketing authorisation holders and the public. The Agency publishes its notifications on the Agency's website.

Appendix F: Pharmacovigilance System Master File

9 April 2013
EMA/816573/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module II – Pharmacovigilance system master file (Rev 1)

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*Note: Revision 1 contains the following:

- a correction of the text with regard to the requirements for herbal and homeopathic medicinal products in II.B.2.1. on page 5;
- an emphasis on the requirements of IR Art 2 in a first new sentence of II.B.4. on page 8;
- emphasis on legal references to IR Art 3 and IR Art 5(4) in II.3.4.8. on page 14.

See websites for contact details



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II.A. Introduction

The legal requirement for marketing authorisation holders to maintain and make available upon request a pharmacovigilance system master file (PSMF) was introduced by Directive 2010/84/EU amending Directive 2001/83/EC (Recitals (7) and (35), Article 23(4), Article 104(3)(b)) and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (Recitals (22) and (25), Article 16(4), to harmonise and strengthen the conduct of pharmacovigilance activities in the EU.

The pharmacovigilance system master file definition is provided in Article 1(28e) of Directive 2001/83/EC and the minimum requirements for its content and maintenance are set out in the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (the Implementing Regulation is referenced as IR). The detailed requirements provided by the Commission Implementing Regulation are further supported by the guidance in this Module of the Good Vigilance Practice(s).

The pharmacovigilance system master file shall be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the EU where the qualified person responsible for pharmacovigilance operates [IR Art 7(1)].

It is a requirement of the marketing authorisation application that summary information about the pharmacovigilance system is submitted to the competent authorities. This summary includes information on the location of the pharmacovigilance system master file (see [II.B.2.1](#)). There is no requirement for variations for changes in the content of the pharmacovigilance system master file.

This Module provides detailed guidance regarding the requirements for the pharmacovigilance system master file, including its maintenance, content and associated submissions to competent authorities, applicable from July 2012, during the transition period (as described in Article 2 of Directive 2010/84/EU and Article 3 of Regulation (EU) No 1235/2010), and after 2015.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

II.B. Structures and processes

The pharmacovigilance system master file is a legal requirement in the EU. This guidance concerns the requirements for the pharmacovigilance system master file and is applicable for any medicinal product authorised in the EU, irrespective of the marketing authorisation procedure. The required content and management of the pharmacovigilance system master file applies irrespective of the organisational structure of a marketing authorisation holder, including any subcontracting or delegation of activities, or their location. Irrespective of the location of other activities, the qualified person for pharmacovigilance (QPPV's) residence, the location at which he/she carries out his/her tasks and the pharmacovigilance system master file location must be within the EU. Following European Economic Area (EEA) agreements, the QPPV may also reside and operate in Norway, Iceland or Liechtenstein.

The content of the pharmacovigilance system master file should reflect global availability of safety information for medicinal products authorised in the EU, with information on the pharmacovigilance system not just confined to local or regional activities.

II.B.1. Objectives

The pharmacovigilance system master file shall describe the pharmacovigilance system and support/document its compliance with the requirements. As well as fulfilling the requirements for a pharmacovigilance system master file laid down in the legislation and guidance, it shall also contribute to the appropriate planning and conduct of audits by the applicant or marketing authorisations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by national competent authorities. The pharmacovigilance system master file provides an overview of the pharmacovigilance system, which may be requested and assessed by national competent authorities during marketing authorisation application(s) or post-authorisation.

Through the production and maintenance of the pharmacovigilance system master file, the marketing authorisation holder and the QPPV should be able to:

- gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements;
- confirm aspects of compliance in relation to the system;
- obtain information about deficiencies in the system, or non-compliance with the requirements;
- obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

The use of this information should contribute to the appropriate management of and improvement(s) to the pharmacovigilance system.

The requirements for submission of a summary of the marketing authorisation holder's pharmacovigilance system, provision of the content of pharmacovigilance system master file and the history of changes to the relevant authority(ies) should enable the appropriate co-ordination of inspections by the Agency, and the planning and effective conduct of inspections by national competent authorities, based on a risk assessment approach.

Responsibilities, in terms of the pharmacovigilance system master file, for marketing authorisation holders and applicants, national competent authorities and the Agency are described in detail in Section C (see II.C.1.).

II.B.2. Registration and maintenance

II.B.2.1. Summary of the applicant's pharmacovigilance system

Article 8(3)(ia) of Directive 2001/83/EC requires a summary of the applicant's pharmacovigilance system to be included in the marketing authorisation application, which shall include the following elements in module 1.8.1 of the dossier:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance;
- the Member States in which the qualified person resides and carries out his/her tasks;
- the contact details of the qualified person;
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX;
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

The requirement for submission of a detailed description of the pharmacovigilance system (DDPS) with each marketing authorisation application is no longer applicable. For new applications, the summary of the pharmacovigilance system must be included in the application.

As required by Article 16 of Regulation (EC) No 726/2004 and Article 23 of Directive 2001/83/EC, amendments to the particulars or documents referred to in the summary of the applicant's pharmacovigilance system shall be submitted in accordance with Commission Regulation (EC) No 1234/2008 and the associated Guideline.

Applicants for, and holders of simplified registrations of traditional herbal medicinal products are not required to submit a pharmacovigilance system summary, however, they are required to operate a pharmacovigilance system and prepare, maintain and make available on request a pharmacovigilance system master file.

For other herbal medicinal products, not falling within the scope of the traditional use registration, the requirements to operate a pharmacovigilance system, to prepare, maintain and make available on request a pharmacovigilance system master file and to submit a summary of the pharmacovigilance system apply.

For homeopathic medicinal products registered via the simplified registration procedure the requirements to operate a pharmacovigilance system, to maintain and make available on request a pharmacovigilance system master file and to submit a summary of the pharmacovigilance system do not apply.

For other homeopathic medicinal products, not falling within the scope of the simplified registration, the requirements to operate a pharmacovigilance system, to prepare, maintain and make available on request a pharmacovigilance system master file and to submit a summary of the pharmacovigilance system apply.

II.B.2.2. Location

The pharmacovigilance system master file shall be located within the EU, either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates [IR Art 7(1)], irrespective of the format (paper-based or electronic format file). Following European Economic Area (EEA) agreements, the PSMF may also be located in Norway, Iceland or Liechtenstein.

Details about the location of the pharmacovigilance system master file are required to be entered in the extended Eudravigilance Medicinal Product Dictionary (XEVMPPD), and any change to the location shall be notified immediately to the Agency in order to have the information in the XEVMPPD and on the European medicines web-portal referred to in Article 26(1) of Regulation (EC) No 726/2004 updated. [IR Art 4(4), REG Art 57(2)(c)] (see Eudravigilance guidance and EMA website guidance on electronic submission of information on medicines). The required location information for the PSMF is a physical office address of the marketing authorisation holder or a contracted third party. Where the pharmacovigilance system master file is held in electronic form, the location stated must be a site where the data stored can be directly accessed, and this is sufficient in terms of a practical electronic location [IR Art 7(3)].

When determining the main site of pharmacovigilance activity, the marketing authorisation holder should consider the most relevant EU site for the pharmacovigilance system as a whole, since the relative importance of particular activities may vary according to products and fluctuate in the short term. The marketing authorisation holder should have an appropriate rationale for the location decision. In the situation where the main activities take place outside the EU, or where a main site cannot be determined, the location should default to the site where the QPPV operates.

II.B.2.3. Registration

All pharmacovigilance system master files must be registered in XEVMPD. The MAH shall update the database with the location of the pharmacovigilance system master file for each product, and update the information immediately upon change, as XEVMPD must be correctly populated with the pharmacovigilance system master file location [IR Art 4(4)].

At the time of marketing authorisation application, the applicant should submit electronically the pharmacovigilance system master file location information using the agreed format as referred to in chapter IV, Article 26, paragraph 1(a) of the Commission Implementing Regulation (EU) No 520/2012, and subsequently include in the application, the pharmacovigilance system master file reference number, which is the unique code assigned by the Eudravigilance (EV) system to the master file when the XEVPRM is processed (guidance on electronic submission of information on medicines is published on the EMA website). On grant of a marketing authorisation application, the pharmacovigilance system master file will be linked by the marketing authorisation holder to the EVMPD product code(s).

Submission of information about the location of the pharmacovigilance system master file that occurs at times other than a marketing authorisation application or a renewal application must be submitted in accordance with Commission Regulation (EC) No 1234/2008 and the associated Guideline. In order to facilitate the submission of master file location information for more than one product covered by a single pharmacovigilance system (and therefore with a common pharmacovigilance system master file), the variations can be grouped.

II.B.2.4. Transfers of responsibilities for the pharmacovigilance system master file

The pharmacovigilance system may change with time. Transfer or delegation of responsibilities and activities concerning the master file should be documented (see II.B.4.2. and II.B.4.8.) and managed to ensure that the marketing authorisation holder fulfils their responsibilities. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system. The types of changes that should be routinely and promptly notified to the QPPV are:

- Updates to the pharmacovigilance system master file or its location that are notified to the competent authorities;
- The addition of corrective and/or preventative actions to the pharmacovigilance system master file (e.g. following audits and inspections). The QPPV should also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance;
- Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
- Changes in arrangements for the provision of the pharmacovigilance system master file to competent authorities;
- Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR production);
- Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
- Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications, studies or the addition of territories.

Any recipient QPPV should explicitly accept the following changes in writing:

- Transfer of responsibility for a pharmacovigilance system to a QPPV.

The QPPV should be in a position to ensure and to verify that the information contained in the pharmacovigilance system master file is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility (see **Module I**).

II.B.3. The representation of pharmacovigilance systems

The pharmacovigilance system master file, as per definition in Article 1(28e) of the Directive 2001/83/EC, shall describe the pharmacovigilance system for one or more medicinal products of the marketing authorisation holder. For different categories of medicinal products the marketing authorisation holder may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate pharmacovigilance system master file. Those files shall cumulatively cover all medicinal products of the marketing authorisation holder for which a marketing authorisation has been issued in accordance with Directive 2001/83/EC or an authorisation has been granted in accordance with Regulation (EC) No 726/2004.

- It is anticipated that there will be circumstances where a single marketing authorisation holder may establish more than one pharmacovigilance system e.g. specific systems for particular types of products (vaccines, consumer health, etc.), or that the pharmacovigilance system may include products from more than one marketing authorisation holder. In either case, a single and specific pharmacovigilance system master file shall be in place to describe each system.
- In accordance with Articles 8 and 104 of the Directive 2001/83/EC, a single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file.
- Where a pharmacovigilance system is shared by several marketing authorisation holders each marketing authorisation holder is responsible ensuring that a pharmacovigilance system master file exists to describe the pharmacovigilance system applicable for his products. For a particular product(s) the marketing authorisation holder may delegate through written agreement (e.g. to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the marketing authorisation holder is responsible. In this case the pharmacovigilance system master file of the marketing authorisation holder may cross refer to all or part of the pharmacovigilance system master file managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the marketing authorisation holder and the authorities. The marketing authorisation holder should be able to assure the content of the referenced file(s) in relation to the pharmacovigilance system applicable to their product(s). Activities for maintaining the pharmacovigilance system master file in a current and accessible state can be delegated.
- Where applicable, a list of all pharmacovigilance system master files held by the same marketing authorisation holder shall be provided in the annex (see **II.B.4.8.**) [IR Art 3(7)]; this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).
- Submission of summary information to competent authorities cannot contain multiple locations for a single pharmacovigilance system master file. The address of the location of the pharmacovigilance system master file provided to fulfil the requirement of Article 8(3) of the Directive 2001/83/EC (and within XEVMPD) should be an office address which reflects either the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or the site where the qualified person responsible for pharmacovigilance operates. This address may be different to that of the applicant/marketing authorisation holder, for example,

a different office of the marketing authorisation holder or when a third party undertakes the main activities.

- Similarly, the QPPV details aligned to a product in XEVMPD may be those of a contract QPPV responsible for the pharmacovigilance system for a particular medicinal product, and not necessarily a QPPV directly employed by the marketing authorisation holder.
- When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorisation holder retains ultimate responsibility for the pharmacovigilance system, submission of information about the pharmacovigilance system master file location, maintenance of the pharmacovigilance system master file and its provision to competent authorities upon request [IR Art 6]. Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place [IR Art 6].
- When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own pharmacovigilance system master files. Accessibility of the pharmacovigilance system master file to all the applicable marketing authorisation holder(s), and its provision to competent authorities should be defined in written agreements. It is vital that marketing authorisation holder(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

II.B.4. Information to be contained in the pharmacovigilance system master file

The pharmacovigilance system master file shall contain at least all of the documents listed in Article 2 of the Commission Implementing Regulation (EU) No 520/2012.

The pharmacovigilance system master file shall include documents to describe the pharmacovigilance system. The content of the pharmacovigilance system master file should reflect the global availability of safety information for medicinal products authorised in the EU. The content shall be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex headings described in **II.B.6.1**. The main principle for the structure of the content of the pharmacovigilance system master file is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the Annexes. The control associated with change of content is described in section **II.B.5**.

It is accepted that, where no marketing authorisation (and master file) previously existed in the EU, there may be information that cannot be initially provided, for example, compliance information, however, descriptions of what will be implemented should be provided instead.

II.B.4.1. PSMF section on qualified person responsible for pharmacovigilance (QPPV)

For the QPPV, contact details shall be provided in the marketing authorisation application [DIR Art 8(3)(ia)] and/or via the XEVMPD.

The information relating to the QPPV provided in the PSMF [IR Art 2(1)] shall include:

- a description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;

- a summary curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance, including proof of registration with the Eudragilance database;
- contact details;
- details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance; and
- information relating to the contact person for pharmacovigilance where such a person has been nominated at national level in accordance with Article 104(4) of Directive 2001/83/EC, including contact details.

A list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes (see II.B.4.8.). This should outline the activities that are delegated and to whom, and include the access to a medically qualified person if applicable (Module I and [IR Art 10(1)]). This list may be supplied as a copy of a written procedural document provided the required content is covered.

The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance (including registration with Eudragilance). The contact details supplied should include name, postal, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorisation holder address. If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorisation holder, this should be indicated and the name of the company the QPPV works for provided.

II.B.4.2. PSMF section on the organisational structure of the marketing authorisation holder

A description of the organisational structure of the marketing authorisation holder relevant to the pharmacovigilance system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between organisations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. Specifically, the pharmacovigilance system master file shall describe:

- The organisational structure of the marketing authorisation holder(s), showing the position of the QPPV in the organisation.
- The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to product particulars [IR Art 2(2)].

Diagrams may be particularly useful; the name of the department or third party should be indicated.

Delegated activities

The pharmacovigilance system master file, where applicable, shall contain a description of the delegated activities and/or services relating to the fulfilment of pharmacovigilance obligations [IR Art 2 (6)]. This includes arrangements with other parties in any country, Worldwide and if applicable, to the pharmacovigilance system applied to products authorised in the Community.

Links with other organisations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements

relating to the fulfilment of pharmacovigilance obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s) and territories. The list should be organised according to; service providers (e.g. medical information, auditors, patient support programme providers, study data management etc.), commercial arrangements (distributors, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.). Individual contractual agreements shall be made available at the request of national competent authorities and the Agency or during inspection and audit and the list provided in the Annexes (see II.B.4.8.).

II.B.4.3. PSMF section on the sources of safety data

The description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorised in the EU. This should include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and e-mail) for the site. The list may be located in the Annexes of the pharmacovigilance system master file. Information about third parties (licence partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements (see II.B.4.2. and II.B.4.8.).

Flow diagrams indicating the main stages, timeframes and parties involved may be used. However represented, the description of the process for ICSRs from collection to reporting to competent authorities should indicate the departments and/or third parties involved.

For the purposes of inspection and audit of the pharmacovigilance system, sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the marketing authorisation holder through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight. In the interests of harmonisation, it is recommended that the list should be comprehensive for products authorised in the EU, irrespective of indication, product presentation or route of administration. The list should describe, on a worldwide basis, the status of each study/programme, the applicable country(ies), the product(s) and the main objective. It should distinguish between interventional and non-interventional studies and should be organised per active substance. The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex or provided separately.

II.B.4.4. PSMF section on computerised systems and databases

The location, functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the pharmacovigilance system master file [IR Art 2(3)].

Where multiple computerised systems/databases are used, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerisation within the pharmacovigilance system can be understood. The validation status of key aspects of computer system functionality should also be described; the change control, nature of testing, back-up procedures and electronic data repositories vital to pharmacovigilance compliance should be included in summary, and the nature of the documentation available described. For paper-based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, should be described.

II.B.4.5. PSMF section on pharmacovigilance processes

An essential element of any pharmacovigilance system is that there are clear written procedures in place. **Module I** describes the required minimum set of written procedures for pharmacovigilance. A description of the procedural documentation available (standard operating procedures, manuals, at a global and/or National level etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the pharmacovigilance system master file.

A description of the process, data handling and records for the performance of pharmacovigilance, covering the following aspects shall be included in the pharmacovigilance system master file:

- Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc;
- Risk management system(s) and monitoring of the outcome of risk minimisation measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;
- PSUR scheduling, production and submission, if applicable (see **Module VII**);
- Communication of safety concerns to consumers, healthcare professionals and the competent authorities;
- Implementation of safety variations to the summary of product characteristics (SmPC) and patient information leaflets; procedures should cover both internal and external communications [IR Art 2(4)].

In each area, the marketing authorisation holder should be able to provide evidence of a system that supports appropriate and timely decision making and action.

The description must be accompanied by the list of processes referred to in article 11(1) of the Commission Implementing Regulation (EU) No 520/2012 under the topic compliance management, as well as interfaces with other functions. Interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to competent authority requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. The list, which may be located in the Annexes, should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified. Documents relating to specific local/country procedures need not be listed, but a list may be requested on a per country basis. If no or only some countries use specific local procedures, this should be indicated (and the names of the applicable countries provided).

II.B.4.6. PSMF section on pharmacovigilance system performance

The pharmacovigilance system master file should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The pharmacovigilance system master file should include a description of the monitoring methods applied and contain as a minimum:

- An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;
- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by competent authorities regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timeliness of PSUR reporting to competent authorities in the EU (the annex should reflect the latest figures used by the marketing authorisation holder to assess compliance);
- An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and competent authority deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorisation(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance system shall be described and explained. A list of performance indicators must be provided in the Annex to the pharmacovigilance system master file [IR Art 3(6) and Art 9], alongside the results of (actual) performance measurements.

II.B.4.7. PSMF section on quality system

A description of the quality management system should be provided, in terms of the structure of the organisation and the application of the quality to pharmacovigilance. This shall include:

Document and Record Control

A description of the archiving arrangements for electronic and/or hardcopy versions of the pharmacovigilance system master file should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents (see also **Module I**).

Procedural documents

- A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc), the applicability of the various documents at global, regional or local level within the organisation, and the controls that are applied to their accessibility, implementation and maintenance.
- Information about the documentation systems applied to relevant procedural documents under the control of third parties.

A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed [IR Art 2(5)(a)] must be provided, and the detailed guidance for the inclusion of these is in section **II.B.4.5**.

Training

- A description of the resource management for the performance of pharmacovigilance activities:
 - the organisational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organisational structure (see **II.B.4.3**)
- Information about sites where the personnel are located (this is described under sections **II.B.4.2** and **II.B.4.3**) whereby the sites are provided in the PSMF in relation to the organisation of specific pharmacovigilance activities and in the Annexes which provide the list of site contacts for sources

of safety data. However, a description should be provided in order to explain the training organisation in relation to the personnel and site information;

- A summary description of the training concept, including a reference to the location training files.

Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports.

Auditing

Information about quality assurance auditing of the pharmacovigilance system should be included in the pharmacovigilance system master file. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to **II.B.4.8.** [IR Art 3(5)]. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations in the Directive 2001/83/EC, and cover a rolling 5 year period.

The pharmacovigilance system master file shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the EU criteria for major or critical findings must be indicated (see Module IV). The audit report must be documented within the quality system; in the pharmacovigilance system master file it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). In the annex, in the list of audits conducted, those associated with unresolved notes in the pharmacovigilance system master file, should be identified. The note and associated corrective and preventative action(s), shall be documented in the pharmacovigilance system master file until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified [DIR Art 104(2)]. The addition, amendment or removal of the notes must therefore be recorded in the logbook.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the pharmacovigilance system master file should also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved [IR Art 4(3)]. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

II.B.4.8. Annex to the PSMF

An annex to the pharmacovigilance system master file shall contain the following documents:

- A list of medicinal products covered by the pharmacovigilance system master file including the name of the medicinal product, the name of the active substance(s), and the Member State(s) in which the authorisation is valid [IR Art 3];

The list of medicinal products authorised in the EU should also include the authorisation number(s) including, per authorisation:

- the type of procedure for authorisation and procedure number (e.g. centrally authorised, nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure);
- the Rapporteur country or Reference Member State;
- the presence on the market in the EU;
- other (non EU) territories where the product is authorised or on the market.

The list should be organised per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimisation measures contained in the risk management plan or laid down as conditions of the marketing authorisation, non-standard PSUR periodicity, referral under Article 31 of the Directive 2001/83/EC, or included in the list described in Article 23 of the Regulation (EC) No 726/2004). The monitoring information may be provided as a secondary list.

For marketing authorisations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third party agreements exist to delegate the system, reference to the additional pharmacovigilance system master file(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of pharmacovigilance system master files.

Where pharmacovigilance systems are shared, all products that utilise the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organised per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

- A list of written policies and procedures for the purpose of complying with Article 11(1) of the Commission Implementing Regulation (EU) 520/2012 [IR Art 3];
- A list of contractual agreements covering delegated activities including the medicinal products and territory(ies) concerned in accordance with Article 6(2) of the Commission Implementing Regulation No 520/2012 (see II.B.4.3.) [IR Art 3];
- A list of tasks that have been delegated by the qualified person for pharmacovigilance [IR Art 3];
- A list of all completed audits, for a period of five years, and a list of audit schedules [IR Art 3];
- Where applicable, a list of performance indicators in accordance with Article 9 of the Commission Implementing Regulation No 520/2012 [IR Art 3];
- Where applicable, a list of other pharmacovigilance system master files held by the same marketing authorisation holder [IR Art 3];

This list should include the pharmacovigilance system master file number(s), and the name of MAH of the QPPV responsible for the pharmacovigilance system used. If the pharmacovigilance system is managed by another party that is not a marketing authorisation holder, the name of the service provider should also be included.

- A logbook in accordance with Article 5(4) of the Commission Implementing Regulation No 520/2012 [IR Art 3] and other change control documentation should be included as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change [IR Art 5(4)].

II.B.5 Change control, logbook, versions and archiving

It is necessary for marketing authorisation holders to implement change control systems and to have robust processes in place to continuously be informed of relevant changes in order to maintain the pharmacovigilance system master file accordingly. The competent authorities may solicit information about important changes to the pharmacovigilance system, such as, but not limited to:

- Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- Changes in the provision of significant services for pharmacovigilance, especially major contractual arrangements concerning the reporting of safety data;
- Organisational changes, such as takeovers, mergers, the sites at which pharmacovigilance is conducted or the delegation/transfer of pharmacovigilance system master file management.

In addition to these changes being documented in the pharmacovigilance system master file for the purpose of change control (in the logbook), the QPPV should always be kept informed of these changes.

Changes to the pharmacovigilance system master file should be recorded, such that a history of changes is available (specifying the date and the nature of the change), changes to the PSMF must be recorded in the logbook described in Article 5(4) of the Commission Implementing Regulation No 520/2012. Descriptive changes to the content of the master file must be recorded in the logbook.

Change history for the information contained in the Annexes may be 'on demand', in which case the logbook would indicate the date of the revision of PSMF content and/or Annex update(s), the history of changes for Annex content would also be updated. Information that is being regularly updated and is contained in the Annexes, such as product and standard operating procedure lists or compliance figures, may include outputs from controlled systems (such as electronic document management systems or regulatory databases). The superseded versions of such content may be managed outside of the pharmacovigilance system master file content itself, provided that the history of changes is maintained and available to competent authorities and the Agency on request. If the pharmacovigilance system master file has not been requested, or has remained unchanged for a period of time (for example, if the changes in the content of Annexes are managed outside of the pharmacovigilance system master file), it is recommended that a review is conducted periodically. Marketing authorisation holders need to ensure that the obligations concerning the timely provision of the pharmacovigilance system master file can be met. It is also noted that the QPPV must be able to gain access to current and accurate information about the pharmacovigilance system, hence permanent access to the pharmacovigilance system master file must be enabled, including the information contained in the Annexes (either via the pharmacovigilance master file itself or via access to the systems used to generate the Annex content).

Marketing authorisation holders should be able to justify their approach and have document control procedures in place to govern the maintenance of the pharmacovigilance system master file. As a basis for audit and inspections, the pharmacovigilance system master file provides a description of the pharmacovigilance system at the current time, but the functioning and scope of the pharmacovigilance system in the past may need to be understood.

Changes to the pharmacovigilance system master file should also account for shared pharmacovigilance systems and delegated activities. A record of the date and nature of notifications of the changes made available to the competent authorities, the QPPV and relevant third parties should be kept in order to ensure that change control is fully implemented.

The pharmacovigilance system master file should be retained in a manner that ensures its legibility and accessibility [IR Art 5 and Art 7].

II.B.6. Pharmacovigilance system master file presentation

The pharmacovigilance system master file shall be continuously accessible to the QPPV [IR Art 7(2)] and to the competent authorities on request [REG Art 16(4), DIR Art 23(4), IR Art 7]. The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements [IR Art 4(1)]. Although provision of the document within 7 days of request by a competent authority is stated in the Article 23(4) of Directive 2001/83/EC, marketing authorisation holders should be aware that immediate access to the pharmacovigilance system master file may also be required by the competent authorities, at the stated pharmacovigilance system master file location or QPPV site (if different).

II.B.6.1. Format and layout

The pharmacovigilance system master file may be in electronic form on condition that a clearly arranged printed copy can be made available to competent authorities if requested [IR Art 5(3)]. In any format, the pharmacovigilance system master file should be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes. Therefore, it may be appropriate to restrict access to the pharmacovigilance system master file in order to ensure appropriate control over the content and to assign specific responsibilities for the management of pharmacovigilance system master file in terms of change control and archiving.

The pharmacovigilance system master file should be written in English (unless the marketing authorisation holder only holds approvals in one Member State when it can be written in the EU official language for that territory), indexed in a manner consistent with the headings described in this Module [IR Art 5], and allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

The documents and particulars of the pharmacovigilance system master file shall be presented with the following headings and, if hardcopy, in the order outlined:

Cover Page to include:

- The unique number assigned by the EV System to the pharmacovigilance system master file when the XEVPRM is processed in the XEVMPD.
- The name of the MAH, the MAH of the QPPV responsible for the pharmacovigilance system described (if different), as well as the relevant QPPV third party company name (if applicable).
- The name of other concerned MAH(s) (sharing the pharmacovigilance system)
- The list of pharmacovigilance system master files for the MAH (concerning products with a different pharmacovigilance system)
- The date of preparation / last update

The headings used in **II.B.4** should be used for the main content of the pharmacovigilance system master file. The minimum required content of the Annexes is outlined in **II.B.4.8**, and additional information may be included in the Annexes, provided that the requirements for the content of the

main sections (II.B.1-7) are also met. The positioning of content in the Annexes is further outlined; the bulleted points are descriptions of possible content (and not required headings):

The Qualified Person responsible for pharmacovigilance, Annex A

- The list of tasks that have been delegated by the QPPV, or the applicable procedural document
- The curriculum vitae of the QPPV and associated documents
- Contact details supplementary to those contained in XEVMPD, if appropriate

The Organisational Structure of the MAH, Annex B

- The lists of contracts and agreements

Sources of safety data, Annex C

- Lists associated with the description of sources of safety data e.g. affiliates and third party contacts

Computerised systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E

- Lists of procedural documents

Pharmacovigilance System Performance, Annex F

- Lists of performance indicators
- Current results of performance assessment in relation to the indicators

Quality System, Annex G

- Audit schedules
- List of audits conducted and completed

Products, Annex H

- List(s) of products covered by the pharmacovigilance system
- Any notes concerning the MAH per product

Document and Record Control, Annex I

- Logbook
- Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself

Documentation to support notifications and signatures concerning the pharmacovigilance system master file, as required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided should still be named according to the format described. For example, Annex E should not be renamed to Annex D in circumstances where no Annex concerning computerised systems and databases is used, Annex D should simply be described as 'unused' in the indexing, in order that recipients of the pharmacovigilance system master file are assured that missing content is intended.

II.C. Operation of the EU network

II.C.1. Responsibilities

II.C.1.1. Marketing authorisation holders and applicants

Marketing authorisation holders shall have a pharmacovigilance system in place to ensure the monitoring and supervision of one or more medicinal products. They are also responsible for introducing and maintaining a pharmacovigilance system master file that records the pharmacovigilance system in place with regard to one or more authorised products [DIR Art 23(4), Art 104(3)(b), REG Art 16(4)]. In accordance with Articles 8 and 104 of the Directive 2001/83/EC a single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file.

Applicants are required, at the time of initial marketing authorisation application, to have in place a description of the pharmacovigilance system that records the system that will be in place and functioning at the time of grant of the marketing authorisation and placing of the product on the market. During the evaluation of a marketing authorisation application the applicant may be requested to provide a copy of the pharmacovigilance system master file for review.

The applicant/marketing authorisation holder is responsible for establishing the pharmacovigilance system master file in an EU country (at any marketing authorisation holder or contractual partner site including the site of a contractor or marketing partner) and for registering the master file location with the competent authorities in the marketing authorisation application (as applicable) and in the XEVMPD. The pharmacovigilance system master file shall describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.

The pharmacovigilance system master file creation, maintenance in a current and accessible state (permanently available for audit and inspection purposes) and provision to competent authorities can be outsourced to a third party, but the marketing authorisation holder retains ultimate responsibility for compliance with the legal requirements.

When the QPPV and related contact details change or when the location of the pharmacovigilance system master file changes, the marketing authorisation holder is required to submit the appropriate variation application(s) to the national competent authorities or the Agency, as applicable. Marketing authorisation holders will also be responsible for notifying the Agency immediately of any change in the QPPV details and the pharmacovigilance system master file address details so that the Eudravigilance database referred to in Article 24(1) of Regulation (EC) No 726/2004 and when necessary, the European medicines web-portal, are updated accordingly by the Agency [IR Art 4(4)].

II.C.1.2. National competent authorities

The national competent authorities are obliged to supervise the pharmacovigilance systems of marketing authorisation holders [DIR Recital 7]. As part of this requirement, they will review the summary information about the pharmacovigilance system included in the marketing authorisation application. The full pharmacovigilance system master file may be requested at any time, for example, to review the description of a pharmacovigilance system of an applicant that has not previously held a marketing authorisation in the EU or where specific concerns about the pharmacovigilance system and/or the product safety profile exist, and in preparation for an inspection (see [Module III](#)). Information concerning changes to the summary information or content of the pharmacovigilance system master file will also be used to inform inspection planning and conduct.

For centrally authorised products, the Member State where the master file is located will become the supervisory authority [REG Recital 22, Art 18(3)]. For pharmacovigilance systems that include centrally authorised products, as well as nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure, national competent authorities will supervise the pharmacovigilance system in co-operation with the supervisory authority and the Agency. For pharmacovigilance systems that do not include centrally authorised products, individual national competent authorities remain responsible for supervision of the pharmacovigilance system and will work together to minimise duplication of effort.

National competent authorities will share information about pharmacovigilance systems and use the information to inform national risk-based inspection programmes. Inspectors from national competent authorities will report non-compliance with the requirements of legislation and guidance, including both non-compliance with the requirements for the pharmacovigilance system master file and the pharmacovigilance system (see [Module III](#)).

II.C.1.3. The European Medicines Agency

For centrally authorised products, the Agency co-ordinates the inspections of marketing authorisation holders or their service providers. Supervision of the pharmacovigilance system is based on the location of the pharmacovigilance system master file, with the Member State where the master file is held becoming the supervisory authority [REG Art 18(3)]. The Agency may request the pharmacovigilance system master file in order to fulfil its co-ordination role.

The main responsibility of the Agency, in relation to pharmacovigilance system master files, is the maintenance of EU wide databases, dissemination of information and coordination of EU wide activities. To this effect, the Agency, in collaboration with the Member States and the European Commission, is responsible for the set up and maintenance of the European medicines web-portal for the dissemination of information on medicinal products authorised in the EU [REG Art 26]. The Agency will manage the product list described in Article 57 of Regulation (EC) No 726/2004 which provides a practical mechanism for maintaining up-to-date information about the location of the pharmacovigilance system master file, the QPPV contact information and the products relevant to the pharmacovigilance system described in the pharmacovigilance system master file. The list of the locations in the EU where pharmacovigilance system master files are kept will be made public via the web-portal [REG Art 26(1)(e)].

II.C.2. Accessibility of the pharmacovigilance system master file

The pharmacovigilance system master file shall be maintained in a current state and be permanently available to the QPPV [IR Art 4(1) and Art7(2)]. It shall also be permanently available for inspection, at the site where it is kept (the stated location), irrespective of whether the inspection has been notified in advance or is unannounced [IR Art 7(3)].

According to Article 104 (3)(b) of the Directive the marketing authorisation holder shall maintain and make available on request a copy of the pharmacovigilance system master file. The marketing authorisation holder must submit the copy 7 days at the latest after receipt of the request from a national competent authority or the Agency. The pharmacovigilance system master file should be submitted in a readable electronic format or clearly arranged printed copy.

In the situation where the same pharmacovigilance system master file is used by more than one marketing authorisation holder (where a common pharmacovigilance system is used) the concerned pharmacovigilance system master file should be accessible to each, as any of the applicable marketing

authorisation holders shall be able to provide the file to the competent authorities within 7 days, upon request [DIR Art 23(4), IR Art 7(4)].

The pharmacovigilance system master file should not routinely be requested during the assessment of new marketing authorisation applications (i.e. pre-authorisation), but may be requested on an ad hoc basis, particularly if a new pharmacovigilance system is being implemented, or if product specific safety concerns or issues with compliance with pharmacovigilance requirements have been identified.

II.C.3. Transparency

Information on the pharmacovigilance system master file location should be made available to the public via the Agency web-portal [REG Art 26] for transparency and communication purposes.

Appendix G: Pharmacovigilance Inspections

8 September 2014
EMA/119871/2012 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module III – Pharmacovigilance inspections (Rev 1)

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	25 May 2012
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Date for coming into effect of Revision 1	16 September 2014

*Note: Revision 1 contains the following:

- Reference to the new Union procedures for pharmacovigilance inspections in III.B.5..

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

The European Medicines Agency is
an agency of the European Union



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III.A. Introduction

This Module contains guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in the EU and outlines the role of the different parties involved. General guidance is provided under III.B., while III.C. covers the overall operation of pharmacovigilance inspections in the EU.

In order to determine that marketing authorisation holders comply with pharmacovigilance obligations established within the EU, and to facilitate compliance, competent authorities of the Member States concerned shall conduct, in cooperation with the Agency, pharmacovigilance inspections of marketing authorisation holders or any firms employed to fulfil marketing authorisation holder's pharmacovigilance obligations. Such inspections shall be carried out by inspectors appointed by the national competent authorities and empowered to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX of Directive 2001/83/EC in accordance with Articles 111(1) and 111(1)(d) (Directive is referenced as DIR). In particular, marketing authorisation holders are required to provide, on request, the pharmacovigilance system master file, which will be used to inform inspection conduct [DIR Art 23(4) and Regulation (EC) No 726/2004 Article 16(4) (Regulation is referenced as REG) (see Module II).

The objectives of pharmacovigilance inspections are:

- to determine that the marketing authorisation holder has personnel, systems and facilities in place to meet their pharmacovigilance obligations;
- to identify, record and address non-compliance which may pose a risk to public health;
- to use the inspection results as a basis for enforcement action, where considered necessary.

For marketing authorisation holders of centrally authorised products, it is the responsibility of the supervisory authority for pharmacovigilance to verify, on behalf of the EU, that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Directive 2001/83/EC [REG Art 19]. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is located [REG Art 18(3)]. According to Article 7(1) of the Commission Implementation Regulation (EU) No 520/2012 (Implementing Regulation is referenced as IR) the pharmacovigilance system master file shall be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the qualified person responsible for pharmacovigilance operates. The supervisory authority may conduct pre-authorisation inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system [REG Art 18(3)].

For marketing authorisation holders of non-centrally authorised products (i.e. nationally authorised products, including those authorised through the mutual recognition or the decentralised procedure), it is the responsibility of the competent authority of the Member State concerned, in cooperation with the Agency, to ensure by means of inspection that the legal requirements governing medicinal products are complied with. This cooperation shall consist of the sharing of information between national competent authorities and the Agency concerning inspections that are planned and those that have been conducted [DIR Art 111(1)].

Pharmacovigilance inspection programmes will be implemented, which will include routine inspections scheduled according to a risk-based approach and will also incorporate "for cause" inspections, which

have been triggered to examine suspected non-compliance or potential risks, usually with impact on a specific product(s).

There shall be cooperation between national competent authorities and the Agency to minimise duplication and maximise the use of available resources. National competent authorities and the Agency will make use of the shared information on planned and conducted inspections to facilitate this and to adapt the scope and/or timing of their inspections.

The results of an inspection will be provided to the inspected entity [DIR Art 111(3) and 111(8)], who will be given the opportunity to comment on any non-compliance identified [DIR Art 111(8)]. Any non-compliance should also be rectified by the marketing authorisation holder in a timely manner through the implementation of a corrective and preventive action plan.

If the outcome of the inspection is that the marketing authorisation holder does not comply with the pharmacovigilance obligations, the Member State concerned shall inform the other Member States, the Agency and the Commission in accordance with section III.C.1 [DIR Art 111(8)].

Sharing of information and communication between inspectors and assessors from the Pharmacovigilance Risk Assessment Committee (PRAC) and from the Committee for Medicinal Products for Human Use (CHMP), is very important in relation to issues of Union interest and, where considered appropriate, for the proper follow-up of inspections and the provision of recommendations on actions to be taken.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties [DIR Art 111(8)]. Regulation (EC) No 658/2007 also empowers the Commission to impose financial penalties on marketing authorisations holders to ensure the enforcement of certain obligations connected with marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004.

Information on the conduct and outcome of pharmacovigilance inspections and the follow-up and evaluation of the consequences may be made publicly available as part of the overall transparency of pharmacovigilance activities.

III.B. Structures and processes

III.B.1. Inspection types

III.B.1.1. System and product-related inspections

Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.

Product-related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g. the system used for that product).

III.B.1.2. Routine and “for cause” pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

For cause pharmacovigilance inspections are undertaken when a trigger is recognised, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. For cause inspections may arise when, for example, one or more of the triggers listed below are identified:

- risk-benefit balance of the product:
 - change in the risk-benefit balance where further examination through an inspection is considered appropriate;
 - delays or failure to identify or communicate a risk or a change in the risk-benefit balance;
 - communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the national competent authorities or Agency, as applicable;
 - non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the national competent authorities and/or the Agency;
 - suspension or product withdrawal with no advance notice to the competent authorities;
- reporting obligations (expedited and periodic):
 - delays or omissions in reporting;
 - poor quality or incomplete reports;
 - inconsistencies between reports and other information sources;
- requests from competent authorities:
 - failure to provide the requested information or data within the deadline specified by the competent authorities;
 - poor quality or inadequate provision of data to fulfil requests for information from the competent authorities;
- fulfilment of commitments:
 - concerns about the status or fulfilment of risk management plan (RMP) commitments;
 - delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorisation;
 - poor quality of reports requested as specific obligations;
- inspections:

- delays in the implementation or inappropriate implementation of corrective and preventive actions;
- information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP) ;
- inspection information received from other authorities (EU or non-EU), which may highlight issues of non-compliance;
- others:
 - concerns following review of the pharmacovigilance system master file;
 - non-inspection related information received from other authorities, which may highlight issues of non-compliance;
 - other sources of information or complaints.

III.B.1.3. Pre-authorisation inspections

Pre-authorisation pharmacovigilance inspections are inspections performed before a marketing authorisation is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorisation application [REG Art 19]. Pre-authorisation inspections are not mandatory, but may be requested in specific circumstances. Principles and procedures for requesting pre-authorisation inspections should be developed to avoid performing unnecessary inspections which may delay the granting of a marketing authorisation. The following aspects shall be considered during the validation phase and/or early during the assessment phase:

- the applicant has not previously operated a pharmacovigilance system within the EU or is in the process of establishing a new pharmacovigilance system;
- previous information (e.g. inspection history and non-compliance notifications or information from other authorities) indicates that the applicant has a poor history or culture of compliance. If the marketing authorisation holder has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorisation pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorisation is granted;
- due to product-specific safety concerns, it may be considered appropriate to examine the applicant's ability:
 - to implement product specific risk-minimisation activities; or
 - to meet specific safety conditions which may be imposed; or
 - to manage routine pharmacovigilance for the product of concern (e.g. anticipated significant increase in adverse reaction reports when compared to previous products).

In most cases, a risk assessment based on a combination of product-specific and system-related issues should be performed before a pre-authorisation pharmacovigilance inspection is requested.

If the outcome of the pre-authorisation inspection raises concerns about the applicant's ability to comply with the requirements laid down in the Regulation and the Directive, the following recommendations may be considered:

- non approval of the marketing authorisation;

- a re-inspection prior to approval of the marketing authorisation to confirm that critical findings and recommendations have been addressed;
- granting of the marketing authorisation with the recommendation to perform an early post-authorisation pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the EU routine programme of pharmacovigilance inspections (see III.B.2.);
- imposition of safety conditions to the marketing authorisation based on DIR Art 21a and REG Art 14.8.

III.B.1.4. Post-authorisation inspections

Post-authorisation pharmacovigilance inspections are inspections performed after a marketing authorisation is granted and are intended to examine whether the marketing authorisation holder complies with its pharmacovigilance obligations. They can be any of the types mentioned under III.B.1.1 and III.B.1.2.

III.B.1.5. Announced and unannounced inspections

It is anticipated that the majority of inspections will be announced i.e. notified in advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on occasion, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice (e.g. when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

III.B.1.6. Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritise re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriately corrective and preventive actions in response to an earlier inspection.

III.B.1.7. Remote inspections

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorisation holder or firms employed by the marketing authorisation holder. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside the EU or a third party service provider is not available at the actual inspection site, but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and pharmacovigilance system master file, via remote access. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the inspection. The logistical aspects of the remote inspection should be considered following liaison with the marketing authorisation holder. Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the

remote inspection has revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

III.B.2. Inspection planning

Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

In order to ensure that inspection resources are used in an efficient way, the scheduling and conduct of inspections will be driven by the preparation of inspection programmes. Sharing of information and communication between inspectors and assessors is important to ensure successful prioritisation and targeting of these inspections.

Factors which may be taken into consideration, as appropriate, by the competent authorities when establishing pharmacovigilance inspection programmes include, but are not limited to:

- inspection related:
 - compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP);
 - re-inspection date recommended by the inspectors or assessors as a result of a previous inspection;
- product related:
 - product with additional pharmacovigilance activities or risk-minimisation activities;
 - authorisation with conditions associated with safety, e.g. requirement for post-authorisation safety studies (PASS) or designation for additional monitoring;
 - product(s) with large sales volume, i.e. products associated with large patient exposure in the EU;
 - product(s) with limited alternative in the market place;
- marketing authorisation holder related:
 - marketing authorisation holder that has never been subject to a pharmacovigilance inspection;
 - marketing authorisation holder with many products on the market in the EU;
 - resources available to the marketing authorisation holder for the pharmacovigilance activities they undertake;
 - marketing authorisation holder with no previous marketing authorisations in the EU;
 - negative information and/or safety concerns raised by competent authorities, other bodies outside the EU or other areas (i.e. GCP, GMP, GLP and GDP);
 - changes in the marketing authorisation holder organisation, such as mergers and acquisitions;
- pharmacovigilance system related:
 - marketing authorisation holder with sub-contracted pharmacovigilance activities (function of the qualified person responsible for pharmacovigilance in the EU (QPPV), reporting of safety data etc.) and/or multiple firms employed to perform pharmacovigilance activities;

- change of QPPV since the last inspection;
- changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted;
- delegation or transfer of pharmacovigilance system master file management.

National competent authorities and the Agency may solicit information from marketing authorisation holders for risk-based inspection planning purposes if it is not readily available elsewhere.

III.B.3. Sites to be inspected

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorisation holder may be inspected, in order to confirm their capability to support the marketing authorisation holder's compliance with pharmacovigilance obligations.

The sites to be inspected may be located in the EU (e.g. EU QPPV site) or outside the EU. Inspections of sites outside the EU might be appropriate where the main pharmacovigilance centre, databases and/or activities are located outside the EU and it would be otherwise inefficient or impossible to confirm compliance from a site within the EU. Member States and the Agency shall cooperate in the coordination of inspections in third countries [DIR Art 111(1)].

The type and number of sites to be inspected should be selected appropriately to ensure that the key objectives within the scope of the inspection are met.

III.B.4. Inspection scope

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by competent authorities of Member States and whether it is a system or product-related inspection (a description of the types of inspection, inspection triggers and points to consider for the different types of inspection is provided in III.B.1.).

The following elements should be considered when preparing the scope of the inspection, as applicable:

- information supplied in the pharmacovigilance system master file;
- information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the Agency such as EudraVigilance reporting and data quality audits;
- specific triggers (see III.B.1.2. for examples of triggers);

It may be appropriate for additional data to be requested in advance of an inspection in order to select appropriate sites or clarify aspects of the pharmacovigilance system.

III.B.4.1. Routine pharmacovigilance inspections

Routine pharmacovigilance inspections conducted on behalf of the EU should examine compliance with EU legislation and guidance, and the scope of such inspections should include the following elements, as appropriate:

- individual case safety reports (ICSRs):

- collecting, receiving and exchanging reports - from all types of sources, sites and departments within the pharmacovigilance system, including from those firms employed to fulfil marketing authorisation holder's pharmacovigilance obligations and departments other than drug safety;
- assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality. In addition to examples of ICSRs from within the EU, examples of ICSRs reported from outside the EU should be examined as part of this review (if applicable);
- follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
- reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
- record keeping and archiving for ICSRs;
- periodic safety update reports (PSURs), (as applicable):
 - completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
 - addressing safety topics, providing relevant analyses and actions;
 - formatting according to requirements;
 - timeliness of submissions;
- ongoing safety evaluation;
 - use of all relevant sources of information for signal detection;
 - appropriately applied methodology concerning analysis;
 - appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
 - implementation of the RMP, or other commitments, e.g. conditions of marketing authorisation;
 - timely identification and provision of complete and accurate data to the competent authority(ies), in particular in response to specific requests for data;
 - implementation of approved changes to safety communications and product information, including internal distribution and external publication;
- interventional (where appropriate) and non-interventional clinical trials:
 - reporting suspected unexpected serious adverse reactions (SUSARs) according to Directive 2001/20/EC and non-interventional study cases according to Directive 2001/83/EC;
 - receiving, recording and assessing cases from interventional and non-interventional trials (see ICSRs);
 - submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PSURs), where applicable, PASS or post-authorisation efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
 - appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;

- the inclusion of study data in ongoing safety evaluation;
- pharmacovigilance system:
 - QPPV roles and responsibilities, e.g. access to the quality system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
 - the roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system;
 - accuracy, completeness and maintenance of the pharmacovigilance system master file;
 - quality and adequacy of training, qualifications and experience of staff;
 - coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
 - fitness for purpose of computerised systems;
 - contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.

The inspection may include the system for the fulfilment of conditions of a marketing authorisation and the implementation of risk–minimisation activities, as they relate to any of the above safety topics.

III.B.4.2. For cause inspections

The scope of the inspection will depend on the specific trigger(s). Some, but not all of the elements listed in III.B.4.1 and below, may be relevant:

- QPPV involvement and awareness of product-specific issues;
- in-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

III.B.4.3. Re-inspections

For the scope of a re-inspection, the following aspects should be considered:

- review of the status of the system and/or corrective and preventive action plan(s) resulting from previous pharmacovigilance inspection(s);
- review of significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection (e.g. change in the pharmacovigilance database, company mergers or acquisitions, significant changes in contracted activities, change in QPPV);
- review of process and/or product-specific issues identified from the assessment of information provided by the marketing authorisation holder, or not covered in a prior inspection.

The scope of re-inspection will depend on inspection history. It may be appropriate to conduct a complete system review, for example if a long time has elapsed since the previous inspection, in which case the elements listed in **III.B.4.1**, may be considered for the inspection scope, as appropriate.

III.B.5. Inspection process

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures consistent with agreed Union

pharmacovigilance inspection procedures developed by the PhVIWG to support harmonisation for the mutual recognition of pharmacovigilance inspections within the EU. The Union procedures on pharmacovigilance inspections are published on the webpage "Pharmacovigilance inspection procedures: human" of the Agency's website¹. Improvement and harmonisation of inspection conduct is promoted by agreed processes and procedures, joint inspection(s) and sharing of experience and training by national competent authority inspectorates.

The Union procedures on pharmacovigilance inspections cover, at least, the following processes:

- sharing of information;
- inspection planning;
- pre-authorisation inspections;
- coordination of pharmacovigilance inspections in the EU;
- coordination of third country inspections (including inspections of contractors in third countries);
- preparation of pharmacovigilance inspections;
- conduct of pharmacovigilance inspections;
- reporting of pharmacovigilance inspections and inspection follow-up;
- communication and prioritisation of pharmacovigilance inspections and findings;
- interaction with PRAC in relation to inspections and their follow-up;
- record-keeping and archiving of documents obtained or resulting from pharmacovigilance inspections;
- unannounced inspections;
- sanctions and enforcement in case of serious non-compliance;
- recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

These procedures will be revised and updated as deemed necessary. New procedures may also be developed when the need is identified in relation to the inspection process.

III.B.6. Inspection follow-up

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. The following follow-up actions should be considered, as appropriate:

- review of the marketing authorisation holder's corrective and preventive action plan;
- review of the periodic progress reports, when deemed necessary;
- re-inspection to assess appropriate implementation of the corrective and preventive action plan;
- requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities;

¹ See:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000164.jsp&mid=WC0b01ac0580029754

- requests for issuing safety communications, including amendments of marketing and/or advertising information;
- requests for a meeting with the marketing authorisation holder to discuss the deficiencies, the impact of the deficiencies and action plans;
- communication of the inspection findings to other regulatory authorities (including outside the EU);
- other product-related actions depending on the impact of the deficiencies and the outcome of follow-up actions (this may include recalls or actions relating to the marketing authorisations or clinical trial authorisations).

Sharing information and communication between inspectors and assessors is important for the proper follow-up of inspections. Details of the processes relating to interaction between inspectors and assessors and inspection follow-up will be elaborated further in the compilation of Union procedures on pharmacovigilance inspections mentioned in III.B.5.

III.B.7. Regulatory actions and sanctions

Under EU legislation, in order to protect public health, competent authorities are obliged to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action. Action may be taken by the Agency, the Commission or the competent authorities of the Member States as appropriate. As stated in Article 111(8) of Directive 2001/83/EC, where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties. Moreover Regulation (EC) No 658/2007 also empowers the Commission, to impose financial penalties on the holders of marketing authorisations to ensure the enforcement of certain obligations connected with marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004.

In the event of non-compliance, possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

- education and facilitation: national competent authorities may communicate with marketing authorisation holder representatives (e.g. in a meeting) to summarise the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the marketing authorisation holder's proposals for corrective and preventive actions;
- provision of information to other competent authorities, the Agency or third country regulators under the framework of confidentiality arrangements;
- inspection: non-compliant marketing authorisation holders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- warning letter, non-compliance statement or infringement notice: these are non-statutory or statutory instruments in accordance with national legislation which competent authorities may issue stating the legislation and guideline that has been breached, reminding marketing authorisation holders of their pharmacovigilance obligations or specifying the steps that the marketing authorisation holder must take and in what timeframe in order to rectify the non-compliance and in order to prevent a further case of non-compliance;
- competent authorities may consider making public a list of marketing authorisation holders found to be seriously or persistently non-compliant;

- actions against a marketing authorisation(s) or authorisation application(s) e.g.
 - Urgent Safety Restriction;
 - variation of the marketing authorisation;
 - suspension or revocation of the marketing authorisation;
 - delays in approvals of new marketing authorisation applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorisations;
 - requests for pre-authorisation inspections;
- product recalls e.g. where important safety warnings have been omitted from product information;
- action relating to marketing or advertising information;
- amendments or suspension of clinical trials due to product-specific safety issues;
- administrative penalties, usually fixed fines or based on company profits or levied on a daily basis;
- referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

III.B.8. Record management and archiving

The principles and requirements to be followed will be described in the Union procedure on **Record Keeping and Archiving of Documents Obtained or Resulting from the Pharmacovigilance Inspections** referred to in **III.B.5**.

III.B.9. Qualification and training of inspectors

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by their Member States or by the CHMP should be officials of, or appointed by, the Member State in accordance with national regulation and follow the provisions of the national competent authority.

It is recommended that inspectors are appointed based upon their experience and the minimum requirements defined by the national competent authority. In addition, consideration should be given to the recommendations for training and experience described in the compilation of Union procedures on pharmacovigilance inspections mentioned in **III.B.5**.

The inspectors should undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting and reporting inspections. They should also be trained in pharmacovigilance processes and requirements in such way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

Documented processes should be in place in order to ensure that inspection competencies are maintained. In particular, inspectors should be kept updated with the current status of pharmacovigilance legislation and guidance.

Training and experience should be documented individually and evaluated according to the requirements of the applicable quality system of the concerned competent authority.

III.B.10. Quality management of pharmacovigilance inspection process

Quality of the pharmacovigilance inspection process is managed by the national competent authorities and covered by their pharmacovigilance systems and associated quality systems, meaning that the

process is also subject to audit. Guidance on establishment and maintenance of a quality assured pharmacovigilance system is provided in [Module I](#).

Quality and consistency of the inspections is facilitated by the Union procedures for pharmacovigilance inspections developed by the PhVIWG to support the mutual recognition of inspections within the EU mentioned in [III.B.5](#).

III.C. Operation of the EU network

III.C.1. Sharing of information

The Agency and the Member States shall cooperate to facilitate the exchange of information on inspections and in particular:

- information on inspections planned and conducted in order to avoid unnecessary repetition and duplication of activities in the EU and optimise the inspection resources;
- information on the scope of the inspection in order to focus future inspections;
- information on the outcome of the inspection, in particular when the outcome is that the marketing authorisation holder does not comply with the requirements laid down in legislation and relevant guidance. A summary of the critical and/or major findings and a summary of the corresponding corrective and preventive actions with their follow-up(s) should be exchanged.

Tools and procedures will be developed at EU level to facilitate and optimise the exchange and sharing of information and the communication across the Union.

III.C.2. Role of the European Medicines Agency

III.C.2.1. General role of the Agency

Regarding the monitoring of compliance with regulatory pharmacovigilance obligations and pharmacovigilance inspections, the roles of the Agency are set out in Article 57(1)(c) and Article 57(1)(i) of Regulation (EC) No 726/2004 and can be summarised as follows:

- coordination of the monitoring of medicinal products for human use which have been authorised within the Union, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;
- coordination of the verification of compliance with pharmacovigilance obligations.

Pharmacovigilance inspections coordinated by the Agency are performed by the supervisory authority concerned as outlined in [III.C.3.2](#). The supervisory authority may be assisted by other national competent authorities, when required.

As part of this coordination role the Agency is responsible for:

- establishing and maintaining processes through the PhVIWG to support the consistency and quality of pharmacovigilance inspections of marketing authorisation holders with centrally authorised products conducted by inspectorates of the national competent authorities;
- coordinating and ensuring the implementation of a risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products (see [III.B.2](#).) enabling the timely sharing of information on planned and conducted

pharmacovigilance inspections between Member States, with the aim of reducing duplication of inspection activity and facilitating mutual recognition of inspection findings;

- coordinating “for cause” inspections, as requested by the CHMP. If a “for cause” inspection has been or will be conducted in a similar timeframe as a routine one, it may replace the need for the planned routine inspection and the programme shall be revised to reflect this;
- coordinating third country inspections: according to Article 111(1) of the Directive 2001/83/EC, the Agency shall cooperate in the coordination of inspections in third countries. Member States should liaise with the Agency when the need for an inspection of a third country site is identified in order to ensure productive use of pharmacovigilance inspection resource in the interests of the Union;
- communication and follow-up of inspections of Union interest across the Agency, the PRAC, the CHMP, the CMD(h), the EU regulatory network and with third country regulators, whenever confidentiality arrangements are in place to facilitate this.

III.C.2.2. Role of the PRAC

The PRAC may make recommendations on the need and scope of “for cause” pharmacovigilance inspections related to medicinal products of Union interest.

The PRAC may, in relation to issues of Union interest and where considered appropriate, review the outcome of pharmacovigilance inspections and assess marketing authorisation holder-related corrective and preventive action plan submission(s) in order to make or endorse further recommendations on actions to be taken and their follow-up.

The PRAC is also responsible for providing input in the preparation of and agreeing on the risk-based programme for routine pharmacovigilance inspections of marketing authorisation holders with centrally authorised products outlined in III.B.2 and III.C.3.3.

III.C.2.3. Role of the CHMP

The CHMP is responsible for the request of pharmacovigilance inspections in the context of the centralised procedure and for the endorsement of the recommendations made by the PRAC in relation to the outcome of these inspections and their follow-up. The CHMP is also responsible for the adoption of the risk-based programme for routine pharmacovigilance inspections outlined in III.B.2. and III.C.3.3.

III.C.3. Role of the European Commission

For medicinal products authorised under Regulation (EC) No 726/2004, the European Commission may request at any point in time the Agency to coordinate the conduct of a pharmacovigilance inspection if public health information in the possession of the Commission so mandates.

III.C.4. Role of the Member States

III.C.4.1. General considerations

Member States should establish the legal and administrative framework within which pharmacovigilance inspections operate, including the definition of the rights of inspectors for inspecting pharmacovigilance sites and access to pharmacovigilance data.

Member States should provide sufficient resources and appoint adequately qualified inspectors to ensure effective determination of compliance with good pharmacovigilance practice. The inspector(s) appointed may be accompanied, when needed, by expert(s) on relevant areas. A Member State may also request assistance from another Member State, in which case, access to the inspection sites and data by the Member State providing assistance is desirable.

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures consistent with agreed Union pharmacovigilance inspection procedures developed by the PhVIWG to support harmonisation for the mutual recognition of pharmacovigilance inspections within the EU as mentioned in section III.B.5.

The scheduling and conduct of these inspections will be driven by the preparation of inspection programmes based on a systematic and risk-based approach as outlined in III.B.2. and III.C.3.3.

The national competent authorities, when preparing inspection programmes, should verify the inspection status of the marketing authorisation holders they plan to inspect by considering the information shared on planned or conducted inspections under the programmes in other Member States in order to assure coordination of inspection activities, prevent unnecessary duplication and to make the most efficient use of inspection resources.

When the pharmacovigilance system a national competent authority plans to inspect is the same as that already inspected by another national competent authority, sharing of information on the scope and outcomes of previous inspections and consideration of the national supervisory requirements, can help to define the objective, scope and timing of that national inspection.

A common repository, accessible to all Member States, the Agency and the Commission, should be created to facilitate this information sharing on pharmacovigilance inspections.

III.C.4.2. Role of the supervisory authority

The concept of the supervisory authority applies only in relation to centrally authorised products. According to Article 18 of Regulation (EC) 726/2004, the supervisory authority for the conduct of pharmacovigilance inspections shall be the competent authority of the Member State in which the pharmacovigilance system master file is located.

The supervisory authorities for pharmacovigilance are responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Directive 2001/83/EC and Regulation 726/2004/EC. They may, if this is considered necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system [REG Art 19].

Where the sites selected to be inspected are located outside the EU, the same supervisory authority as above will be responsible for the inspection on behalf of the Union. Where relevant or on request, and in particular for product-specific issues, the inspection may be conducted or assisted by inspector(s) from the Rapporteur or Co-Rapporteur Member State and/or expert(s) from the Rapporteur or Co-Rapporteur Member State or from other Member States as appropriate.

III.C.4.3. Inspection programmes

A programme for routine inspections for centrally authorised products will be determined by the Agency in conjunction with the supervisory authorities of the Member States, the PhVIWG, the PRAC and the CHMP. These inspections will be prioritised based on the potential risk to public health, considering the factors listed in III.B.5. As a general approach, a marketing authorisation holder should be inspected on the basis of risk-based considerations, but at least once every 4 years.

If the same pharmacovigilance system is used for a variety of authorisation types (centralised and national, mutual recognition and decentralised), then the results of a supervisory authority inspection may be applicable for all products covered by that system.

This routine inspection programme will be separate from any “for cause” inspections, but if a “for cause” inspection takes place it may replace the need for one under this programme, dependent on its scope.

Member States are also responsible for the planning and coordination of pharmacovigilance inspections within their territory in relation to products authorised nationally or via the mutual recognition or decentralised procedures in order to ensure compliance with the legislation within their own Member States and to verify the effectiveness of the marketing authorisation holder’s pharmacovigilance system at national level.

As indicated in **III.C.3.1.**, based on the information from other inspections, the national competent authority will prioritise the inspections in its national programme and will use the information for the preparation of an appropriate scope for the national inspection. For example, national competent authorities may seek to verify the fulfilment of requirements concerning the national implementation of specific risk-minimisation measures, national communications concerning safety, locally conducted safety studies, or issues linked to national health care systems. A broader examination of pharmacovigilance applied to particular products of national interest may also be appropriate if this was not covered within the scope of a supervisory authority inspection.

III.C.5. Role of marketing authorisation holders and applicants

Marketing authorisation holders with authorised products and applicants who have submitted new applications under the centralised procedure are subject to pharmacovigilance inspections (see **III.B.1.**). Therefore both have responsibilities in relation to inspections, including but not limited to the following:

- always to be inspection-ready as inspections may be unannounced;
- to maintain and make available to the inspectors on request, no later than 7 calendar days after the receipt of a request, the pharmacovigilance system master file as required by Article 23(4) of Directive 2001/83/EC and Article 16(4) of Regulation (EU) 726/2004;
- to ensure that the sites selected for inspection, which may include firms employed by the marketing authorisation holder to perform pharmacovigilance activities, agree to be inspected before the inspection is performed;
- to make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection;
- to ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;
- to ensure that relevant pharmacovigilance data is accessible from at least one point in the Union [DIR Art 107(1)];
- to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings.

III.C.6. Inspection fees

For inspections requested by the CHMP, an inspection fee(s) (and inspectors' expenses where applicable) will be charged in accordance with the Council Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products as amended and implementing rules applicable at the time. For pharmacovigilance inspections performed in the context of national, mutual recognition and decentralised procedures similar fees may or may not apply depending on the legal requirements of the Member State carrying out the inspection.

III.C.7. Transparency

Information on the conduct and outcome of pharmacovigilance inspections and their follow-up may be made publicly available. This will then be elaborated further in the compilation of Union procedures on pharmacovigilance inspections mentioned in [III.B.5.](#)

Appendix H: Pharmacovigilance Audits

12 December 2012
EMA/228028/2012

Guideline on good pharmacovigilance practices (GVP)

Module IV – Pharmacovigilance audits

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See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

The European Medicines Agency is
an agency of the European Union



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IV.A. Introduction

The entry into force of the new legislation on pharmacovigilance in July 2012, established legal requirements for competent authorities in the Member States and the European Medicines agency (the Agency) and marketing authorisation holders to perform audits of their pharmacovigilance systems [DIR Art 101(2), Art 104(2), REG Art 28f], including risk based audits of their quality systems [IR Art 13 (1), Art 17 (1).]

For the purposes of this module reference to pharmacovigilance audit(s) and pharmacovigilance audit activity(ies) are deemed to include pharmacovigilance system audits and audit(s) of the quality system for pharmacovigilance activities.

The minimum requirements of the pharmacovigilance systems and the quality system are set out in the Commission Implementing Regulation (EU) No 520/2012 (IR) on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC. Risk-based audits of the pharmacovigilance system should cover all areas listed in Directive 2001/83/EC (DIR) and Regulation (EC) 726/2004 (REG). The specificities of the risk-based audits of the quality system [for pharmacovigilance activities] are as described in the Implementing Measures [IR Art 8,10, 11,12,13(1) for marketing authorisation holders, and IR Art 8,14,15,16,17(1) for national competent authorities and the Agency.]

The overall description and objectives of pharmacovigilance systems and quality systems for pharmacovigilance activities are referred to in **Module I**, while the specific pharmacovigilance processes are described in each respective Module of GVP.

In this Module, all applicable legal requirements are referenced in the way explained in the **GVP Introductory Cover Note** and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

This Module provides guidance on planning and conducting the legally required audits, and in respect of the operation of the EU regulatory network, the role, context and management of pharmacovigilance audit activity. This Module is intended to facilitate the performance of pharmacovigilance audits, especially to promote harmonisation, and encourage consistency and simplification of the audit process. The principles in this Module are aligned with internationally accepted auditing standards*, issued by relevant international auditing standardisation organisations*¹ and support a risk-based approach to pharmacovigilance audits.

Section **IV.B.** outlines the general structures and processes that should be followed to identify the most appropriate pharmacovigilance audit engagements and describes the steps which can be undertaken by marketing authorisation holders, competent authorities in Member States and the European Medicines Agency, to plan, conduct and report upon an individual pharmacovigilance audit engagements. This Section also provides an outline of the general quality system and record management practices for pharmacovigilance audit processes.

Section **IV.C.** provides an outline of the operation of the EU network in respect of pharmacovigilance audits.

¹ More details regarding **The Institute of Internal Auditors** (IIA) www.theiia.org; the **International Organisation for Standardisation** (ISO) www.iso.org; **Information Systems Audit and Control Association** (ISACA) www.isaca.org; **The International Auditing and Assurance Standards Board** (IAASB) www.ifac.org; **The International Organisation of Supreme Audit Institutions** (INTOSAI) www.issai.org.

IV.A.1. Terminology

Audit, Audit findings, Audit plan, Audit programme, Audit recommendations,

Upper management: see in Annex I.

Auditee: [entity]_being audited (ISO 19011 (3.7) ²).

Compliance: Conformity and adherence to policies, plans, procedures, laws, regulations, contracts, or other requirements (*IIA International Standards for the Professional Practice of Internal Auditing*²).

Control(s): Any action taken by management and other parties to manage risk and increase the likelihood that established objectives and goals will be achieved. Management plans, organises, and directs the performance of sufficient actions to provide reasonable assurance that objectives and goals will be achieved (*IIA International Standards for the Professional Practice of Internal Auditing*³).

Evaluation (of audit activities): Professional auditing bodies promote compliance with standards, including in quality assurance of their own activities, and codes of conduct, which can be used to address adequate fulfilment of the organisation's basic expectations of Internal Audit activity and its conformity to internationally accepted auditing standards.

Finding(s): see Audit findings

Head of the organisation: see Upper management

Auditors' independence: The freedom from conditions that threaten objectivity or the appearance of objectivity. Such threats to objectivity must be managed at the individual auditor, engagement, functional and organisational levels. (*IIA International Standards for the Professional Practice of Internal Auditing*)

Internal Control: Internal control is an integral process that is effected by an entity's management and personnel and is designed to address risk and provide reasonable assurance that in pursuit of the entity's mission, the following general objectives are being achieved: executing orderly, ethical, economical, efficient and effective operations, fulfilling accountability obligations, complying with applicable laws and regulations and safeguarding resources against loss, misuse and damage (for further information refer to COSO standards).

International Auditing Standards: issued by International Auditing Standardisation Organisations*.

International Auditing Standardisation Organisations: More details regarding **The Institute of Internal Auditors** (IIA) standards can be found at <http://www.theiia.org/guidance/standards-and-guidance/ippf/standards/full-standards>; the **International Organisation for Standardisation** (ISO) standard 19011 "Guidelines for quality and/or environmental management systems auditing. <http://www.iso.org/iso/home.html>; **Information Systems Audit and Control Association** (ISACA) standards can be found at <http://www.isaca.org/Standards> ; **The International Auditing and Assurance Standards Board** (IAASB) standards can be found at <http://www.ifac.org/auditing-assurance/clarity-center/clarified-standards>; The International Organisation of Supreme Audit Institutions (INTOSAI) can be found at <http://www.issai.org/composite-347.htm>.

Auditors' objectivity: An unbiased mental attitude that allows internal auditors to perform engagements in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires internal auditors not to subordinate their judgment on audit matters to that of others. (*IIA International Standards for the Professional Practice of Internal Auditing*) ⁵ .

² **The Institute of Internal Auditors** (IIA) www.theiia.org

IV.B. Structures and processes

IV.B.1. Pharmacovigilance audit and its objective

Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.

In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes. Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and verifiable. Audit criteria are, for each audit objective, the standards of performance and control against which the auditee and its activities will be assessed. In the context of pharmacovigilance, audit criteria should reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in the legislation and guidance.

IV.B.2. The risk-based approach to pharmacovigilance audits

A risk-based approach is one that uses techniques to determine the areas of risk, where risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking account of the severity of its outcome and/or likelihood of non-detection by other methods. The risk-based approach to audits focuses on the areas of highest risk to the organisation's pharmacovigilance system, including its quality system for pharmacovigilance activities. In the context of pharmacovigilance, the risk to public health is of prime importance. Risk can be assessed at the following stages:

- strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by upper management;
- tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme; and
- operational level audit planning resulting in an audit plan for individual audit engagements, prioritising audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system [see [IV.B.2.3.1.](#)]

Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organisation (see [IV.B.2.1.](#), [IV.B.2.2.](#) and [IV.B.2.3.](#) respectively).

IV.B.2.1.Strategic level audit planning

The audit strategy is a high level statement of how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.

The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system including:

- all pharmacovigilance processes and tasks;

- the quality system for pharmacovigilance activities;
- interactions and interfaces with other departments, as appropriate;
- pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties, such as contract organisations and other vendors).

This is a non-prioritised, non-exhaustive list of examples of risk factors that could be considered for the purposes of a risk assessment:

- changes to legislation and guidance;
- major re-organisation or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically for marketing authorisation holders, this may lead to a significant increase in the number of products for which the system is used);
- change in key managerial function(s);
- risk to availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, re-organisation, increase in volumes of work;
- significant changes to the system since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities in order to address new or amended regulatory requirements;
- first medicinal product on the market (for a marketing authorisation holder);
- medicinal product(s) on the market with specific risk minimisation measures or other specific safety conditions such as requirements for additional monitoring;
- criticality of the process, e.g.:
 - for competent authorities: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;
 - for marketing authorisation holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the marketing authorisation holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the marketing authorisation holder, in addition to considering the other factors included in this list;
- outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritised depending on criticality); if the area/process has previously been audited, the audit findings* are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;
- identified procedural gaps relating to specific areas/processes;
- other information relating to compliance* with legislation and guidance, for example:
 - for competent authorities: information from compliance* metrics (as described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC),

- from complaints, from external sources, e.g. audits/assessments of the competent authority conducted by external bodies;
- for marketing authorisation holders: information from compliance* metrics (as described in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC), from inspections see **Module III**, from complaints, from other external sources, e.g. audits;
- other organisational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively impact upon pharmacovigilance activities.

IV.B.2.2. Tactical level audit planning

An audit programme is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long term audit strategy. The audit programme should be approved by upper management with overall responsibility for operational and governance structure.

The risk-based audit programme should be based on an appropriate risk assessment and should focus on:

- the quality system for pharmacovigilance activities;
- critical pharmacovigilance processes (see for example **Module I** and IR Art 11, 15);
- key control systems relied on for pharmacovigilance activities;
- areas identified as high risk, after controls have been put in place or mitigating action taken.

The risk-based audit programme should also take into account historical areas with insufficient past audit coverage, and high risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.

The audit programme documentation should include a brief description of the plan for each audit to be delivered, including an outline of scope and objectives.

The rationale for the timing, periodicity and scope of the individual audits which form part of the audit programme should be based on the documented risk assessment. However, risk-based pharmacovigilance audit(s) should be performed at regular intervals, which are in line with legislative requirements.

Changes to the audit programme may happen and will require proper documentation.

IV.B.2.3. Operational level audit planning and reporting

IV.B.2.3.1. Planning and fieldwork

The organisation should ensure that written procedures are in place regarding the planning and conduct of individual audits that will be delivered. Timeframes for all the steps required for the performance of an individual audit should be settled in the relevant audit related procedures, and the organisation should ensure that audits are conducted in accordance with the written procedures, in line with this GVP Module.

Individual pharmacovigilance audits should be undertaken in line with the approved risk-based audit programme (see **IV.B.2.2.**). When planning individual audits, the auditor identifies and assesses the

risks relevant to the area under review and employs the most appropriate risk-based sampling and testing methods, documenting the audit approach in an audit plan*.

IV.B.2.3.2. Reporting

The findings* of the auditors should be documented in an audit report and should be communicated to management in a timely manner. The audit process should include mechanisms for communicating the audit findings* to the auditee* and receiving feedback, and reporting the audit findings* to management and relevant parties, including those responsible for pharmacovigilance systems, in accordance with legal requirements and guidance on pharmacovigilance audits. Audit findings should be reported in line with their relative risk level and should be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes. The grading system should be defined in the description of the quality system for pharmacovigilance, and should take into consideration the thresholds noted below which would be used in further reporting under the legislation as set out in [section IV.C.2](#):

- **critical** is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.
- **major** is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.
- **minor** is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.

Issues that need to be urgently addressed should be communicated in an expedited manner to the auditee*'s management and the upper management.

IV.B.2.4. Actions based on audit outcomes and follow-up of audits

Actions referenced in this section of the guideline, i.e., immediate action, prompt action, action within a reasonable timeframe, issues that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the pharmacovigilance system. Corrective and preventive actions to address critical and major issues should be prioritised. The precise timeframe for action(s) related to a given critical finding, for example, may differ depending on nature of findings and the planned action(s).

The management of the organisation is responsible for ensuring that the organisation has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.

Upper management and those charged with governance, should ensure that effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to upper management.

Evidence of completion of actions should be recorded in order to document that issues raised during the audit have been addressed.

Capacity for follow-up audits should be foreseen in the audit programme. They should be carried out as deemed necessary, in order to verify the completion of agreed actions. [IR Art 13(2), Art 17(2)]

IV.B.3. Quality system and record management practices

IV.B.3.1. Competence of auditors and quality management of audit activities

IV.B.3.1.1. Independence and objectivity of audit work and auditors

The organisation should assign the specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities should be independent. The organisation's management should ensure this independence and objectivity in a structured manner and document this.

Auditors should be free from interference in determining the scope of auditing, performing pharmacovigilance audits and communicating audit results. The main reporting line should be to the upper management with overall responsibility for operational and governance structure that allows the auditor(s) to fulfil their responsibilities and to provide independent, objective audit opinion. Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and with the person responsible for pharmacovigilance; however auditors should maintain an unbiased attitude that allows them to perform audit work in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires auditors not to subordinate their judgement on audit matters to that of others.

IV.B.3.1.2. Qualifications, skills and experience of auditors and continuing professional development

Auditors should demonstrate and maintain proficiency in terms of the knowledge, skills and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. The proficiency of audit team members will have been gained through a combination of education, work experience and training and, as a team, should cover knowledge, skills and abilities in:

- audit principles, procedures and techniques;
- applicable laws, regulations and other requirements relevant to pharmacovigilance;
- pharmacovigilance activities, processes and system(s);
- management system(s);
- organisational system(s).

IV.B.3.1.3. Evaluation of the quality of audit activities

Evaluation of audit work can be undertaken by means of ongoing and periodic assessment of all audit activities, auditee* feedback and self-assessment of audit activities (e.g. quality assurance of audit activities, compliance to code of conduct, audit programme, and audit procedures).

IV.B.3.2. Audits undertaken by outsourced audit service providers

Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organisation (i.e. within the Agency, competent authority or marketing authorisation

holder). Where the organisation decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of this GVP module and perform pharmacovigilance audits:

- the requirements and preparation of the audit risk assessment, the audit strategy and audit programme and individual engagements should be specified to the outsourced service providers, by the organisation, in writing;
- the scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organisation, in writing;
- the organisation should obtain and document assurance of the independence and objectivity of outsourced service providers;
- the outsourced audit service provider should also follow the relevant parts of this GVP module.

IV.B.3.3. Retention of audit reports

Retention of the audit report and evidence of completion of action needs to be in line with the requirements stipulated in Module I section I.B.10.IV.C. Operation of the EU network.

IV.C. Pharmacovigilance audit policy framework and organisational structure

IV.C.1. Marketing authorisation holders in the EU

IV.C.1.1. Requirement to perform an audit

The marketing authorisation holder in the EU is required to perform regular risk-based audit(s) of their pharmacovigilance system [DIR Art 104(2)], including audit(s) of its quality system to ensure that the quality system complies with the quality system requirements [IR Art 8,10,11,12,13(1)]. The dates and results of audits and follow-up audits shall be documented [IR Art 13(2)]

See [IV.C.2.](#) for further details of the requirements for audit reporting by the marketing authorisation holder.

IV.C.1.1.1. The qualified person responsible for pharmacovigilance in the EU (QPPV)

The responsibilities of the QPPV in respect of audit are provided in [Module I](#). Furthermore, the QPPV should receive pharmacovigilance audit reports, and provide information to the auditors relevant to the risk assessment, including knowledge of status of corrective and preventive actions.

The QPPV should be notified of any audit findings relevant to the pharmacovigilance system in the EU, irrespective of where the audit was conducted.

IV.C.1.2. Competent authorities in Member States and the European Medicines Agency

IV.C.1.2.1. Requirement to perform an audit

The Agency shall perform regular independent audits of its pharmacovigilance tasks [REG Art 28f] and competent authorities in Member States shall perform a regular audit of their pharmacovigilance system [DIR Art 101(2)]. Included in their obligation to perform audits of their pharmacovigilance

system/tasks, competent authorities in the Member States and the Agency shall perform risk-based audits of the quality system as well, at regular intervals according to a common methodology to ensure that the quality system complies with the requirements [IR Art 8,14,15,16,17(1)]. The dates and results of audits and follow-up audits shall be documented [IR Art 17(2)].

IV.C.1.2.2. Common methodology

In order to have a useful audit system, all audits at the competent authorities in the Member States and the European Medicines Agency should have a common ground in terms of methodology. This should ensure harmonised planning, implementation and reporting by every competent authority in Member States and at the Agency.

IV.C.1.2.3. The Pharmacovigilance Risk Assessment Committee (PRAC)

The mandate of the Pharmacovigilance Risk Assessment Committee (PRAC) shall cover all aspects of the risk management of the use of medicinal products for human use, having due regard to the design and evaluation of pharmacovigilance audits [REG Art 61a(6)].

IV.C.2. Requirements for audit reporting in the EU

IV.C.2.1. Reporting by the marketing authorisation holder

The marketing authorisation holder shall place a note concerning critical and major audit findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file (PSMF) (see Module II). Based on the audit findings*, the marketing authorisation holder shall ensure that an appropriate plan detailing corrective and preventative action is prepared and implemented. Once the corrective and preventive actions have been fully implemented, the note may be removed [DIR Art 104(2), IR Art 13(2)]. Objective evidence is required in order that any note of audit findings can be removed from the pharmacovigilance system master file (see **Module II**).

The marketing authorisation holders should ensure that a list of all scheduled and completed audits is kept in the annex to the pharmacovigilance system master file (IR Art 3(5)) and that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies. The dates and results of audits and follow-up audits shall be documented [IR Art 13(2)].

IV.C.2.2. Reporting by competent authorities in Member States and the Agency

Competent authorities in Member States, and the Agency should ensure that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies.

Competent authorities in Member States shall report the results [of their pharmacovigilance system audits] to the Commission on 21 September 2013 at the latest and then every 2 years thereafter [DIR Art 101(2)].

The Agency shall report the results [of its pharmacovigilance system audits] to its Management Board on a 2-yearly basis [REG Art 28f].

The reports to the European Commission will follow an agreed format.

IV.C.3. Confidentiality

Documents and information collected by the internal auditor should be treated with appropriate confidentiality and discretion, and also respect Directive 95/46/EC [Regulation (EC) No. 45/2001 for Community institutions and bodies] and national legislation on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

IV.C.4. Transparency

The European Commission shall make public a report on the performance of pharmacovigilance tasks by the Agency on 2 January 2014 at the latest and subsequently every 3 years thereafter [REG Art 29] and on the performance of pharmacovigilance tasks by the competent authorities in Member States on 21 July 2015 at the latest and then every 3 years thereafter [DIR Art 108(b)].

Appendix I: Risk Management Systems

15 April 2014
EMA/838713/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module V – Risk management systems (Rev 1)

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	19 January 2012
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Date for coming into effect of Revision 1	28 April 2014

*Note: Revision 1 contains the following:

- Amendments to the definitions of Missing information and Safety concern in V.B.1. and subsequent amendments of terms throughout the Module and in particular in V.B.8.9.;
- Amendment to the definition of Risk minimisation activity;
- Amendments to V.B.12. regarding part VI of the RMP (already implemented in published RMP templates for MAHs);
- Amendments to V.C.4 and V.C.5. as regards requirements for variation applications;

See websites for contact details



- Updates with regard to references to and implementation of legislation in V.A., V.B.2., V.B.5., V.B.9.2.1.c., V.B.10. and V.B.11.2.;
- Clarified wording in V.B.11.2.;
- Editorial improvements throughout the Module without impact on its content.

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V.A. Introduction

It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited. This is due to many factors including the relatively small numbers of subjects in clinical trials compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the risk-benefit balance is judged to be positive for the target population. A typical medicinal product will have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post-authorisation. Planning of the necessary pharmacovigilance activities to characterise the safety profile of the medicinal product will be improved if it is more closely based on specific issues identified from pre- or post-authorisation data and from pharmacological principles.

However, the purpose of risk identification and characterisation is to allow for risk minimisation or mitigation wherever possible. Therefore risk management has three stages which are inter-related and re-iterative:

1. characterisation of the safety profile of the medicinal product including what is known and not known;
2. planning of pharmacovigilance activities to characterise risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal product;
3. planning and implementation of risk minimisation and mitigation and assessment of the effectiveness of these activities.

The chapter on risk management systems for medicinal products for human use in Volume 9A, which this guidance replaces, was based solely on managing risks. However, when considering how to maximise, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit. In assessing the risk-benefit balance at the time of authorisation, the assumption is made that these benefits and risks apply to the whole target population. However, there may be subsets of patients for whom the risk is greater than that for the target population as a whole, or in whom the benefit may not be as great. In addition, efficacy in the clinical trial setting may not reflect the true effectiveness of the medicinal product in everyday medical practice and so the risk-benefit balance of a medicinal product as assessed at the time of authorisation will inevitably change post-authorisation. Regulation (EC) No 726/2004 and Directive 2001/83/EC include provisions for both post-authorisation safety studies and post-authorisation efficacy studies to be a condition of the marketing authorisation in certain circumstances [REG Art 9(4), Art 10a(1), DIR Art 21a, Art 22a(1)] and for these studies to be included in the risk management plan (RMP) [DIR Art 22c].

Risk management is a global activity. However, because of differences in indication and healthcare systems, target populations may be different across the world and risk minimisation activities will need to be tailored to the system in place in a particular country or global region. In addition, differences in disease prevalence and severity, for example, may mean that the benefits of a medicinal product may also vary between regions. Therefore a product may have different versions of a RMP for each region although there will be core elements which are common to all. For example much of the safety specification will be the same regardless of where the medicinal product is being used but the

epidemiology of the disease may vary between e.g. Africa and Europe, and there may be additional or fewer safety concerns depending upon the target population and indication,

The move to a modular format of the risk management plan (RMP) came into force in July 2012 and should facilitate submission to different regulatory authorities. . Guidance on templates and submission of RMPs is kept up-to-date on the Agency's website¹ (see [Annex II Related links](#)).

Risk management, is applicable to medicinal products at any point in their lifecycle. However, this module concentrates on peri- and post-authorisation risk management and is applicable to all products regardless of the procedure (centralised, decentralised, mutual recognition or national) leading to authorisation in the EU.

The risks addressed in this guidance are those related to non-clinical and clinical safety. In addition, quality issues may be relevant if they impact on the safety and/or efficacy of the product. Where the disposal of the product might pose a particular risk because of remaining active substance (e.g. patches) this should also be addressed.

Although this module includes the principles of risk minimisation, and details of routine risk minimisation measures, more detail on, in particular, additional risk minimisation tools and the measurement of the effectiveness of risk management can be found in [Module XVI](#).

V.B. Structures and processes

V.B.1. Terminology

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include:

- an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

In a clinical trial, the comparator may be placebo, active substance or non-exposure.

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples include:

- toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of an association, but is not large enough to suggest a causal relationship;

¹ www.ema.europa.eu

- a signal arising from a spontaneous adverse reaction reporting system;
- an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.

Missing information

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.

Important identified risk and important potential risk

An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.

What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.

Risk management system

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions [DIR Art 1(28b)].

Risk management plan

A detailed description of the risk management system [DIR Art 1(28c)].

Risk minimisation activity (used synonymously with risk minimisation measure)

An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur.

Safety concern

An important identified risk, important potential risk or missing information.

Target population (treatment)

The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information.

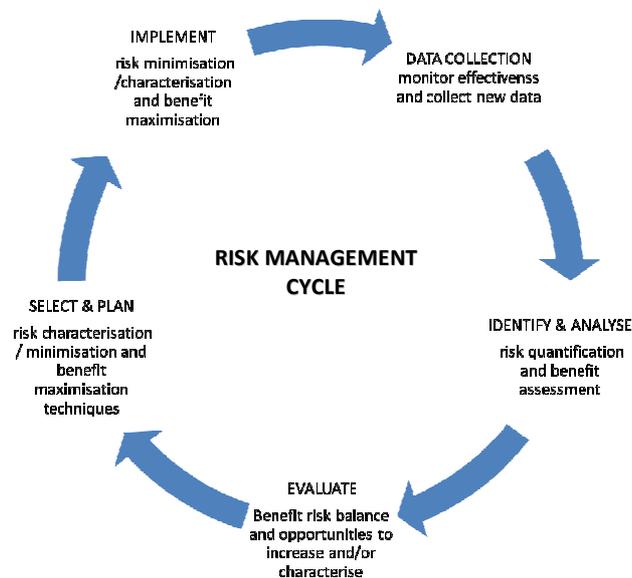
V.B.2. Principles of risk management

The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks. Although the primary aim and focus of the RMP remains that of risk management, the evaluation of the need for efficacy studies (including those linked to the Safety Specification section on Missing Information) and their integration, where necessary, in the RMP may

enable resources to be used more efficiently and for risks to be put into context. The RMP therefore includes the planning of such studies and is without prejudice to the specific efficacy guidance foreseen in Article 108a of Directive 2001/83/EC.

The principles of risk management are the same regardless of stakeholder or territory (see below).

Figure V.1. The risk management cycle



However, the actions and responsibilities within each step of the cycle will vary according to whether the stakeholder is an applicant/marketing authorisation holder, competent authority, healthcare professional or patient. Other players may be involved in risk-benefit management such as: patient organisations, learned societies, health economists, health authorities, national safety organisations, environmental advisors, occupational health professionals and pharmaceutical distributors but their roles will usually be smaller and complementary to that of the main players.

For applicants/marketing authorisation holders and competent authorities in the EU, there is specific mention of risk management in the legislation. In the EU, as well as complying with the legislation, the primary document and process for risk management adheres to the principles in the **International Conference for Harmonisation (ICH) Guideline E2E on Pharmacovigilance Planning**. Outside of the EU, some territories may have local legislation enshrining either risk management in general or adopting the specific ICH E2E guidance or have developed local guidance. For healthcare professionals, product information, medical treatment guidelines and any materials produced by marketing authorisation holders, competent authority or health authorities will direct prescribing, dispensing, treatment and management of both benefit and risks. For patients, the majority of medicinal products will be prescribed by doctors and dispensed by pharmacists so that management of benefits and risks will primarily involve complying with treatment schedules and recommendations, being aware of important risks and what actions to take, and reporting to their doctor, pharmacist, and national competent authority any untoward effects. However, in some countries patients may buy medicines directly without guidance from healthcare practitioners so will need to understand the potential benefits and risks of the product and what measures they need to comply with to use the medicine safely and effectively. Whatever the setting, patients who understand the potential benefits and risks of a

medicinal product are better equipped to decide whether or not to be treated and to comply with suggested risk minimisation activities.

V.B.3. Responsibilities for risk management within an organisation

The principle organisations directly involved in medicinal products' risk management planning are applicants/marketing authorisation holders and the competent authorities who regulate them. Within the EU, responsibility for authorisation and supervision of medicinal products is shared between the national competent authorities in Member States, the European Commission and the European Medicines Agency, with the balance of responsibilities depending upon the route of authorisation.

V.B.3.1. Marketing authorisation holders and applicants

In relation to risk management of its medicinal products, an applicant/marketing authorisation holder is responsible for:

- ensuring that it constantly monitors the risks of its medicinal products in compliance with relevant legislation and reports the results of this, as required, to the appropriate competent authorities;
- taking all appropriate actions to minimise the risks of the medicinal product and maximise the benefits including ensuring the accuracy of all information produced by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available;

Other Modules within GVP deal with specific aspects of the above so this Module is confined to the risk management plan and its contents.

ICH-E2E defines two basic parts of a RMP: the safety specification and the pharmacovigilance plan. It does not include risk minimisation. However it was acknowledged at the time of development of ICH-E2E that risk minimisation was an integral part of risk management planning. Details of how the safety specification and pharmacovigilance plan are integrated within the RMP and the detailed structure and format are provided in [V.B.5 to V.B.7](#).

Producing a RMP requires the input of different specialists and departments within and/or outside an organisation. The safety specification may require involvement of toxicologists, clinical pharmacologists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts. The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimisation activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals. Since a risk management plan is primarily a pharmacovigilance document, ideally the production of it should be managed by personnel with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the marketing authorisation applicant/holder who should ensure oversight by someone with the appropriate scientific background within the company.

Further guidance on individual risk minimisation activities is provided in [Module XVI](#).

V.B.3.2. Competent authorities

The general responsibilities of competent authorities are discussed in [Module I](#). In relation to risk management, the principal responsibilities of competent authorities are:

- constantly monitoring the benefits and risks of medicinal products including assessing the reports submitted by pharmaceutical companies, healthcare professionals, patients and, where appropriate, other sources of information;
- taking appropriate regulatory actions to minimise the risks of the medicinal product and maximise the benefits including ensuring the accuracy and completeness of all information produced by the company in relation to its medicinal products;
- ensuring the implementation of risk minimisation activities at a national level;
- effectively communicating with stakeholders when new information becomes available. This includes providing information in an appropriate format to patients, healthcare physicians, patient groups and learned societies;
- when necessary, ensuring that marketing authorisation holders of generic and/or similar biological medicinal products make similar changes to their risk minimisation measures when changes are made to those of the reference medicinal product;
- providing information to other regulatory authorities, this includes notification of any safety activities in relation to a product, including changes to the product information of originator and/or reference medicinal products.

Many of the associated tasks and activities are described elsewhere in GVP and in other scientific guidances. One of the principle tasks of regulatory authorities in relation to risk management is the assessment of risk management plans. The different parts of the RMP need different areas of expertise so ideally assessment of risk management plans should be performed by a multi-disciplinary team. How this can be achieved will depend upon the organisational structure of the competent authority but could include multi-disciplinary meetings or pharmacovigilance experts reviewing RMPs alongside expert assessment reports relating to different sections of the submitted dossier.

V.B.4. Objectives of a risk management plan

As per the Commission Implementing Regulation (EU) No 520/2012 [IR], the RMP must contain the following elements which:

- identify or characterise the safety profile of the medicinal product(s) concerned;
- indicate how to characterise further the safety profile of the medicinal product(s) concerned;
- document measures to prevent or minimise the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;
- document post-authorisation obligations that have been imposed as a condition of the marketing authorisation [IR Art 30].

There is an implicit requirement that to fulfil these obligations a RMP should also:

- describe what is known and not known about the safety profile of the concerned medicinal product(s);
- indicate the level of certainty that efficacy shown in clinical trial populations will be seen when the medicine is used in the wider target populations seen in everyday medical practice and document the need for studies on efficacy in the post-authorisation phase (also known as effectiveness studies);
- include a description of how the effectiveness of risk minimisation measures will be assessed.

The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the products. For products requiring periodic safety update reports (PSURs), certain (parts of) modules may be used for both purposes (see [V.B.14.](#)).

V.B.5. Structure of the risk management plan

The RMP consists of seven parts. Certain parts of the RMP, in particular the safety specification, are subdivided into modules [IR Annex 1] so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PSURs). RMP part II modules generally follow the section titles in the Safety Specification of ICH-E2E, whilst RMP part III follows the Pharmacovigilance Plan. Differences between indications, formulations and target populations, if several medicinal products have the same active substance, will be similarly accommodated by dividing the relevant parts of the RMP into modules and/or sections. The modular structure also means that the RMP can be updated easily. As the product matures, some RMP modules or sections may cease changing – for example non clinical studies may stop at a certain time as may clinical trials. These RMP modules can be effectively “locked” until new data needs to be added. In addition, certain RMP modules may be omitted in specific circumstances (see [V.C.3.1.](#)).

The submitted RMP should follow the RMP template (see [Annex II Related links](#)). The amount of information, particularly in RMP part II, which can be provided will depend on the type of medicinal product and where it is in its lifecycle but this guidance provides an overview of the level of information needed and its format.

The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data [DIR Art 8(3)]. This proportionality can be achieved in three ways: by reducing the number of modules which need to be submitted for products meeting certain conditions (such as well-established products/generics see table V.3), and by ensuring that requirements for post-authorisation studies and risk minimisation activities reflect the important risks and important uncertainties of the product.

An overview of the parts and modules of the RMP is provided below [IR Annex I]:

Figure V.2. Overview of the parts and modules of the RMP

- Part I** Product(s) overview
- Part II** Safety specification
 - Module SI** Epidemiology of the indication(s) and target population(s)
 - Module SII** Non-clinical part of the safety specification
 - Module SIII** Clinical trial exposure
 - Module SIV** Populations not studied in clinical trials
 - Module SV** Post-authorisation experience
 - Module SVI** Additional EU requirements for the safety specification
 - Module SVII** Identified and potential risks
 - Module SVIII** Summary of the safety concerns
- Part III** Pharmacovigilance plan
- Part IV** Plans for post-authorisation efficacy studies
- Part V** Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
- Part VI** Summary of the risk management plan
- Part VII** Annexes

Where a RMP concerns more than one medicinal product, a separate RMP part VI must be provided for each medicinal product [IR Art 31].

Information should be provided in enough detail to enable an assessor to understand the issues being presented. Unless specifically mentioned in this guidance, cross references to other parts of the dossier should be avoided since it is intended that the RMP should be a largely stand-alone document that is a scientific synopsis of the relevant parts of the dossier, emphasising the important clinically relevant facts. To aid consistency between the information provided in the common technical document (CTD) and the RMP, the table below indicates the location of information in the CTD is summarised for the RMP:

Table V.1 Mapping between RMP modules and CTD

RMP	CTD
Part I Active substance information	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the target population	Module 2.5 Clinical overview
Module SII Non-clinical part of safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module SIII Clinical trial exposure	Module 2.7 Clinical summary - briefly Module 5 Clinical Study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview

RMP	CTD
Module SV Post authorisation experience	Module 2.5 Clinical overview - briefly
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit risk conclusion) Module 2.7 Clinical summary (SPC)
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance activities	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post authorisation efficacy studies (including presentation of efficacy data)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimisation measures	Module 2.5 Clinical overview Module 2.7 Clinical summary

Copies of literature referenced in the RMP should be included in RMP annex 12.

V.B.6. Detailed description of each part of the risk management plan

The description of the parts and modules of an RMP provide guidance on the main topics which should be covered within each specific area. However, some sections may not be relevant to all medicinal products and there may be additional topics which need to be included but are not mentioned. The RMP is part of the scientific dossier of a product and as such should be scientifically based and not be promotional.

Under Regulation (EC) No 1394/2007², certain products for human medicinal use are categorised within the EU as advanced therapy medicinal products (ATMPs). These products are fully defined in the above Regulation but broadly comprise:

- gene therapy medicinal products;
- somatic cell therapy medicinal products;
- tissue engineered products.

Because of the nature of these products, risks may occur which are not normally a consideration with other medicinal products including risks to living donors, risks of germ line transformation and transmission of vectors. For this reason, for ATMPs, RMP module VII *Identified and potential risks (ATMP)* should replace RMP module VII *Identified and potential risks* as this provides greater flexibility in consideration of the additional risks.

V.B.7. RMP part I "Product overview"

This should provide the administrative information on the RMP and an overview of the product(s) covered within it.

The information should include:

² Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products

Active substance information:

- active substance(s);
- pharmacotherapeutic group(s) (ATC code);
- name of marketing authorisation holder or applicant;
- date and country of first authorisation worldwide (if applicable);
- date and country of first launch worldwide (if applicable);
- number of medicinal product(s) to which this RMP refers.

Administrative information on the RMP:

- data lock point of the current RMP;
- date submitted and the version number;
- list of all parts and modules of the RMP with date and version of the RMP when the part/module was last (updated and) submitted.

and

for each medicinal product included in the RMP:

- authorisation procedure (central, mutual recognition, decentralised, national);
- invented name(s) in the European Economic Area (EEA);
- brief description of the product including:
 - chemical class;
 - summary of mode of action;
 - important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
- indications:
 - current (if applicable) in the EEA;
 - proposed (if applicable) in the EEA;
- dosage:
 - current (if applicable) in the EEA;
 - proposed (if applicable) in the EEA;
- pharmaceutical forms and strengths:
 - current (if applicable) in the EEA ;
 - proposed (if applicable) in the EEA;
- whether the product is the subject of additional monitoring in the EU.

V.B.8. RMP part II "Safety specification"

The purpose of the safety specification is to provide a synopsis of the safety profile of the medicinal product(s) and should include what is known and not known about the medicinal product(s). It should be a summary of the important identified risks of a medicinal product, important potential risks, and missing information. Missing information is defined as: gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant (see Annex I). It should also address the populations potentially at risk (where the product is likely to be used i.e. both labelled and off-labelled use), and outstanding safety questions which warrant further investigation to refine understanding of the risk-benefit balance during the post-authorisation period. In the RMP, the safety specification will form the basis of the pharmacovigilance plan, and the risk minimisation plan.

The safety specification consists of eight RMP modules of which RMP modules SI-SV, SVII and SVIII correspond to safety specification headings in ICH-E2E. RMP module SVI includes additional elements required to be submitted in the EU.

Module SI	Epidemiology of the indication(s) and target population(s)
Module SII	Non-clinical part of the safety specification
Module SIII	Clinical trial exposure
Module SIV	Populations not studied in clinical trials
Module SV	Post-authorisation experience
Module SVI	Additional EU requirements for the safety specification
Module SVII	Identified and potential risks
Module SVIII	Summary of the safety concerns

RMP modules SIII–SV form the "Limitations of the human safety database" part of the ICH-E2E safety specification and these, with the addition of RMP modules SI and SVII form the clinical part of the safety specification. RMP modules SVI and the ATMP version of SVII are EU specific although the topics may apply in any territory.

It is recommended that applicants/marketing authorisation holders follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development programme. Elements which might need to be incorporated include:

- quality aspects if relevant in relation to the safety and efficacy of the product;
- the disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches);
- innovative pharmaceutical forms; or
- use with a medical device.

V.B.8.1. RMP module SI “Epidemiology of the indications and target population”

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible, (because the epidemiology of the indication(s) may vary across regions), but the emphasis should be on the epidemiology in the EU of the proposed indication.

Information should be provided on the important co-morbidities in the target population. For example: if a medicinal product is intended for treating prostate cancer, the target population is likely to be men over the age of 50 years. Men over the age of 50 are also at risk of myocardial infarction. To identify whether a medicinal product might be increasing the risk of myocardial infarction, it is important to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not taking the medicinal product. Estimation of the risk in the target population, as compared with the same age/sex group in the general population may be particularly important if the disease itself increases the risk of a particular adverse event.

The RMP should include a statement of the intended purpose and impact of the product e.g. whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease.

V.B.8.2. RMP module SII “Non-clinical part of the safety specification”

This RMP module should present a summary of the important non-clinical safety findings, for example:

- toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
- general pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system);
- drug interactions;
- other toxicity-related information or data.

What constitutes an important safety finding will depend upon the medicinal product, the target population and experience with other similar compounds or therapies in the same class. Normally significant areas of toxicity (by target organ system), and the relevance of the findings to the use in humans, should be discussed. Also quality aspects if relevant to safety (e.g. important information on the active substance or its impurities, e.g. genotoxic impurities) should be discussed. If a product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity should be explicitly mentioned and the implications for use in this population discussed. Where the non-clinical safety finding could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.

For other special populations depending upon the indication and target population, consideration should be given to whether specific non-clinical data needs exist.

V.B.8.3. RMP module SIII “Clinical trial exposure”

In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g. tables/graphs. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time (patient-years, patient-months) exposed to the medicinal product.

This should be stratified for relevant categories and also by the type of trial (randomised blinded trial population only and all clinical trial populations.) Stratifications would normally include:

- age and gender;
- indication;
- dose;
- racial origin (see also V.B.8.4.).

Duration of exposure should be provided either graphically by plotting numbers of patients against time or in tabular format.

The exposure of special populations (pregnant women, breast-feeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms, immuno-compromised) should be provided as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the genetic polymorphism.

The categories above are only suggestions and tables/graphs should be tailored to the product. For example, indication may not be a relevant stratification for a medicinal product where only one indication has been studied, and route of administration, number of courses/immunisations or repeat administrations may be important categories to be added.

When presenting age data, categories should be chosen which are relevant to the target population. Broad artificial divisions which are not clinically relevant, such as <65 and >65, should be avoided. Paediatric data should be divided by categories (e.g. ICH-E11); similarly the data on elderly patients should be considered for stratification into categories such as 65-74, 75-84 and 85+, although the age strata should reflect that of the target population. For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate for the female population.

Unless clearly relevant, data should not be presented by individual trial but should be pooled. Totals should be provided for each table/graph as appropriate. Where patients have been enrolled in more than one trial (e.g. open label extension study following a trial) they should only be included once in the age/sex/ethnic origin tables. Where differences in the total numbers of patients arise between tables, the tables should be annotated to reflect the reasons for discrepancy.

When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables (as described above) representing pooled data across all indications.

V.B.8.4. RMP module SIV “Populations not studied in clinical trials”

RMP module SIV should discuss which sub-populations within the expected target population have not been studied or have only been studied to a limited degree in the clinical trial population. Limitations of the clinical trials should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population. This is particularly important when exclusion criteria are not proposed as contraindications for the drug. Lists of inclusion/exclusion criteria should not be provided by trial, but a summary of the effect of these in the overall development programme in relation to the target population should be provided. In discussing differences between target populations and those exposed in clinical trials it should be noted that some differences may arise through trial setting (e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria.

The implications, with respect to predicting the safety of the product in the marketplace, of any of these populations with limited or no research should be explicitly discussed. In addition, the limitations of the database with regard to the detection of adverse reactions due to:

- number of patients studied;
- cumulative exposure (e.g. specific organ toxicity);
- long term use (e.g. malignancy)

should be discussed. Where the missing information could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.

Populations to be considered for discussion should include (but might not be limited to):

- Paediatric population

Children (from birth to 18 years with consideration given to the different age categories as per ICH-E11, or, if justified, to other developmentally meaningful groups i.e. taking into account specific organ maturation). If paediatric development has been limited to certain age categories then the implications for other paediatric age groups should also be discussed.

- Elderly population

Implications for use in patients over the age of 65 should be discussed – with appropriate consideration given to use in the older end of the age spectrum. The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist. The cumulative effect of multiple impairments and multiple medications should be discussed. Consideration of whether particular laboratory screening should be performed routinely before use of the medicinal product(s) in the elderly should be discussed. In particular any adverse reactions which might be of special concern in the elderly e.g. dizziness or central nervous system effects should be explored.

- Pregnant or breast-feeding women

If the target population includes women of child-bearing age, the implications for pregnancy and/or breast-feeding should be discussed. If the medicinal product is not specifically for use during pregnancy, any pregnancies which have occurred during the developmental programme and their outcomes should be discussed. For products where pregnancy should be avoided for safety reasons, , the discussion on pregnancy should also include an analysis of the reasons why the contraceptive measures in place during the clinical trials failed and the implications for use in the less controlled conditions of everyday medical practice.

- Patients with hepatic impairment
- Patients with renal impairment
- Patients with other relevant co-morbidity (e.g. cardiovascular or immunocompromised including organ transplant patients)
- Patients with disease severity different from that studied in clinical trials

Any experience of use in patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity.

- Sub-populations carrying known and relevant genetic polymorphism

The extent of pharmacogenetic effects and the implications on genetic biomarker use in the target population should be discussed. Where a proposed drug indication constitutes patients with or without specific genetic markers, or the clinical development programme has been in patients with a specific mutation, the marketing authorisation holder should discuss the implications of this for the target population and explore whether use in patients with an unknown or different genotype could constitute a safety concern.

If a potentially clinically important genetic polymorphism has been identified but not fully studied in the clinical development programme, this should be considered as missing information and/or a potential risk. This should be reflected in the safety specification and pharmacovigilance plan. Whether it is included as a safety concern for the purposes of risk minimisation will depend upon the importance of the possible clinical implications.

- Patients of different racial and/or ethnic origins

Genetic variants can influence pharmacodynamics and pharmacokinetics, and subsequently affect the efficacy and/or safety of the administered drug. Inter-ethnic differences in drug efficacy and safety have been observed in different ethnic groups due to e.g. genetic polymorphisms.

One example of such inter-ethnic differences is the variation in frequency of the HLA-B*1502 allele. This allele is strongly associated with the occurrence of severe cutaneous adverse reactions to carbamazepine and has a prevalence of about 10% in some Asian populations, whilst the prevalence of the allele is negligible in those of European descent. This is why genomic testing is recommended for patients of some Asian origins when carbamazepine use is planned, while this testing will not make sense for a patient who is of European descent.

Major inter-ethnic differences in pharmacokinetics of drugs may also occur due to types and/or frequencies of gene variants coding for drug metabolising enzymes. The consequences of these inter-ethnic differences could be that the proportion of subjects with particular beneficial effects or adverse reactions varies, leading to different risk-benefit balances and specific recommendations in these ethnic populations.

Furthermore, efficacy in patients may be affected by racial origin. One example is that ACE inhibitors are less potent in black patients of African or Caribbean family origin than in white patients.

Therefore, information on racial origin may be relevant and valuable for evaluation of efficacy and safety and for preventing adverse reactions or improving benefits in the target population.

The experience of drug use in patients with different racial and/or ethnic origins should be discussed including the implications on efficacy and safety, based on pharmacokinetics and pharmacodynamics, in the target population. If it is likely that efficacy or safety may be affected by race or ethnicity, consideration should be given to including this either as a safety concern or as a topic for inclusion in RMP Part IV. Consideration should also be given as to whether post-authorisation efficacy and/or safety studies are necessary.

V.B.8.5. RMP module SV "Post-authorisation experience"

The purpose of this RMP module is to provide information on the number of patients exposed post authorisation; how the medicinal product has been used in practice and labelled and off-label use including use in the special populations mentioned in RMP module SIV. It should also include brief information on the number of patients included in completed observational studies conducted either to

elucidate a safety issue or for drug utilisation purposes. Details of significant actions taken to update information on the safety of the medicinal product should also be provided in this module.

V.B.8.5.1. RMP module SV section "Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons"

List any significant regulatory action (including those initiated by the marketing authorisation holder), in any market, taken in relation to a safety concern. Significant regulatory action would include: a restriction to the approved indication, a new contra-indication, a new or strengthened warning in section 4.4 of the SPC (or equivalent) or any action to suspend or revoke a marketing authorisation. This list should be cumulative, and specify the country, action taken and the date as appropriate. Roll-out in multiple countries of a new safety statement initiated by the MAH can be presented as one action.

When the RMP is updated, a brief description of the reasons leading to any significant actions since the last submission of the RMP should be provided. It may be appropriate to add comments if the regulatory action taken is not applicable to certain products/formulations as authorised in the EU.

V.B.8.5.2. RMP module SV section "Non-study post-authorisation exposure"

Where marketing of the medicinal product has occurred, the applicant/marketing authorisation holder should provide cumulative data on patients exposed post-marketing. Where possible, the information should be stratified by relevant variables. These may include age, sex, indication, dose and region (EU versus non EU). Depending upon the medicinal product, other variables may be relevant such as number of vaccination courses, route of administration or duration of treatment. If the data are available, EU use should be broken down into country or sales area.

When deciding which measure to use for exposure data, it is important to consider the way a medicinal product is used. Exposure data based on the number of kilogrammes of medicinal product sold divided by the average dose is only valid if the medicinal product is always used at one dose level for a fixed length of time, which is not the situation with most medicinal products. In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate and other measures should be used. For example, for medicinal products used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be more appropriate.

If the drug has different routes of administration, e.g. subcutaneous or oral, exposure data should be presented separately, where possible. Competent authorities may request additional stratification of exposure data, e.g. exposure in age groups or within different approved indications. However, if the drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, marketing authorisation holders should consider routinely providing such data where possible.

A more accurate breakdown of drug exposure based on market research should be provided where possible.

If a drug utilisation study has been performed, for reimbursement or other reasons, the results, as they reflect use in the real world setting, should be provided.

V.B.8.5.3. RMP module SV section "Post-authorisation use in populations not studied in clinical trials"

Where there are data on post-authorisation use in the special populations identified in RMP module SIV as having no or limited exposure, estimation of the numbers exposed and the method of calculation should be provided whether or not the usage is on- or off-label. For paediatric use, cross reference may be made to RMP section "Specific paediatric issues" in RMP module SVI (see V.B.8.6.6.). Information on the safety profile of the medicinal product in these special populations, as compared with the rest of the target population, should also be provided. In particular, any information regarding an increased or decreased benefit in a special population should be provided. Any special populations found to be at an increased or decreased risk in relation to a particular safety concern should be discussed under the specific risk in RMP module SVII but reference should be made in this section as to which risks and populations are affected.

V.B.8.5.4. RMP module SV section "Post-authorisation off-label use"

Post marketing, updates to the safety specification, should include information on EU off-label use; i.e. the intentional use, for a medical purpose, which is not in accordance with the authorised product information for a medicinal product. Off-label use includes use in non-authorised paediatric age categories. Unless specifically requested, it does not include use outside the EU in an indication authorised in that territory which is not authorised in the EU. EU use in clinical trials conducted as part of the marketing authorisation holder's development programme should be included only in RMP module SIII and not in this section.

Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. This includes drug utilisation studies which were requested by national competent authorities for purposes other than risk management. When off label use is a safety concern or a concern has been raised by the competent authorities regarding off-label use, marketing authorisation holders should attempt to quantify such use along with a description of the methods used to arrive at these figures.

V.B.8.5.5. RMP module SV section "Epidemiological study exposure"

Marketing authorisation holders should provide a listing of epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures. This listing should include studies undertaken by the marketing authorisation holder itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the MAH has been sent the results by a third party, should also be included. Information on the study title, study type (e.g. cohort, case control), population studied (including country and other relevant population descriptors), duration of study, number of persons in each category (e.g. cases, controls, exposure), disease as appropriate, person time (if appropriate) and study status (completed or on-going) should be provided. If a study has been published, a reference should be included in this RMP section, a synopsis should be included in RMP annex 5 and the publication provided in RMP annex 12.

V.B.8.6. RMP module SVI "Additional EU requirements for the safety specification"

Some safety topics were not included in ICH-E2E but are thought to be of particular interest due to either EU legislation or prior experience of a safety issue.

V.B.8.6.1. RMP module SVI section "Potential for harm from overdose"

Special attention should be given to medicinal products where there is an increased risk of harm from overdose, whether intentional or accidental. Examples include medicinal products where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the treated population (e.g. in depression). Where harm from overdose has occurred during clinical trials this should be explicitly mentioned. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern in RMP module SVIII and appropriate risk minimisation proposed in RMP part V.

V.B.8.6.2. RMP module SVI section "Potential for transmission of infectious agents"

The applicant/marketing authorisation holder should discuss the potential for the transmission of an infectious agent. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential for transmission of live virus should be discussed. For advanced therapy medicinal products a cross-reference to RMP module SVII (ATMP) may be made.

V.B.8.6.3. RMP module SVI section "Potential for misuse for illegal purposes"

The potential for misuse for illegal purposes should be considered. Misuse, as defined in GVP Module VI, refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. Misuse for illegal purposes has the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault. If appropriate, the means of limiting this, e.g. by the use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the risk minimisation plan.

V.B.8.6.4. RMP module SVI section "Potential for medication errors"

For the purposes of the RMP, medication error refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer. Medication errors are an important cause of morbidity and mortality and many could be prevented or mitigated. They fall broadly into 4 categories:

1. wrong medication;
2. wrong dose (including strength, form, concentration, amount);
3. wrong route of administration;
4. wrong patient

Applicants/marketing authorisation holders should consider routinely the likelihood of medication errors. In particular, they should assess, prior to marketing, common sources of medication errors. During the development phase and during the design of a medicinal product for marketing, the applicant needs to take into account potential reasons for medication error. The naming (taking into account the [Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed Through the Centralised Procedure](#)³), presentation (e.g. size, shape and colouring of the pharmaceutical form and packaging), instructions for use (e.g. regarding reconstitution, parenteral routes of administration, dose calculation) and labelling are among the items to be considered. In

³ See CPMP/328/98 latest version; available on EMA website <http://www.ema.europa.eu>.

addition, the Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use⁴ should be followed.

If a product has potential for serious harm when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is common practice to administer the product at the same time as other medicinal products given by the hazardous route. In this situation, medication errors should be included as a safety concern.

The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed. In addition, if there are other products containing the same active substance on the market with formulations which are not proven to be bioequivalent, measures to avoid medication error should be discussed and appropriate risk minimisation activities proposed.

When a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error. Where appropriate, medication error should be included as a safety concern and appropriate risk minimisation measures proposed to address the possibility of medication error due to visual impairment.

Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

Medication errors identified during product development including clinical trials should be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been taken into account in the final product design.

If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of medication errors, this topic should be discussed in the updated RMP and ways of limiting the errors proposed.

If the formulation or strength of a product is being changed, where appropriate, medication error should be included as a safety concern and the measures that the marketing authorisation holder will put in place to reduce confusion between old and new "product" should be discussed in the risk minimisation plan. Similarly, it may be appropriate to discuss risk minimisation activities in relation to changes to the presentation, pack size, route of administration or release characteristics of the medicinal product.

If the product is to be administered with a medical device (integrated or not), consideration should be given to any safety concerns which could represent a risk to the patient (medical device malfunction).

V.B.8.6.5. RMP module SVI section "Potential for off-label use"

The potential for off-label use should be discussed. Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information. This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas should also be considered where this is likely.

Where appropriate, use could be made of data on actual use versus authorised use in other markets and the implications for the authorisation in the EU discussed.

⁴ See ENTR/F/2/SF/jr (2009)D/89 Eudralex Volume 2C - Regulatory Guidance; available on <http://ec.europa.eu/health/documents/eudralex>.

V.B.8.6.6. RMP module SVI section "Specific paediatric issues"

This section deals with aspects of paediatric use not covered in RMP module SIV.

Issues identified in paediatric investigation plans

Any recommendations for long term follow up of safety or efficacy issues in relation to paediatric use which are mentioned in the paediatric investigation plan should be detailed here. This section should clarify if, and how, this had been taken into account in RMP module SVII. If the issue has been resolved following further development, or is no longer considered of sufficient impact to justify listing as a safety concern, this should be discussed and justified.

Proposals for specific long term paediatric studies should be considered at the time of application for a paediatric indication and if felt not to be necessary justification should be provided. If an indication in adults precedes an application for paediatric use, any registries established to provide data on use of the product in real medical practice should avoid age related exclusion criteria so that any potential off-label use in the paediatric population can be included.

In some circumstances, the safety concern identified in the paediatric investigation plan may be applicable to the whole population being treated. In these cases, consideration should be given as to whether some of the pharmacovigilance activities and/or risk minimisation activities from the paediatric investigation plan are appropriate for, and should be extended to cover, the whole population. For these safety concerns, this RMP section should also include details of how the specific paediatric aspects will be addressed and all paediatric investigation plan recommendations considered. Cross-reference may be made to RMP modules SIV and SVII and SVII.

Potential for paediatric off-label use

If the disease or disorder which is being treated or prevented is found in the paediatric population, and the product is not authorised in all paediatric age groups, the potential for off-label paediatric use in the non-authorised age groups should be discussed. If there are limited treatment options it should not be assumed that clinicians will adhere to the labelled indication so it is important that potential paediatric issues are discussed. Any actual use should be discussed in RMP module SV section "Non-study post-authorisation exposure" (see V.B.8.5.2.) and in RMP module SV section "Post-authorisation use in populations not studied in clinical trials" (see V.B.8.5.3.).

V.B.8.7. RMP module SVII "Identified and potential risks"

This RMP module provides information on the important identified and potential risks associated with use of the product. These should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

Because of the need for different additional categories of risks to be considered with advanced therapy medicinal products, a different version of RMP module SVII is available for products classified as advanced medicinal products. Only one version (either sections V.B.8.7.1 - V.B.8.7.5 or sections V.B.8.8.1 - V.B.8.8.3) of RMP module SVII should be provided in a RMP.

V.B.8.7.1. RMP module SVII section "Newly identified safety concerns"

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of the safety concern should be stated, whether it is an important identified or important potential risk

and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

V.B.8.7.2. RMP module SVII section "Recent study reports with implications for safety concerns"

Study reports (either interim or final, from whichever type of study), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate (e.g. RMP module SII; section V.B.8.7.3; V.B.8.7.4; V.B.8.7.5; RMP Module SVI and RMP Module SVIII).

V.B.8.7.3. RMP module SVII section "Details of important identified and potential risks from clinical development and post-authorisation experience"

This RMP section should provide more information on the important identified and potential risks. This RMP section should be concise and should not be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents of section 4.8 of the summary of product characteristics (SmPC).

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health (see also V.B.1). Normally, any risk which is clinically important and which is/is likely to be included in the contraindications or warnings and precautions section of the summary of product characteristics (SmPC) should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person's life, and which could lead to serious consequences if untreated should also be considered for inclusion, e.g. severe nausea and vomiting with chemotherapy.

For some products, disposal of the used product may constitute a safety concern, e.g. transdermal patches where there may be significant amounts of active substance remaining in the patch when it is discarded. There may also be occasions where there is an environmental concern over product disposal because of known harmful effects on the environment, e.g. substances which are particularly hazardous to aquatic life which should not be disposed of in landfill sites.

Presentation of risk data:

When the information is available, detailed risk data should include the following:

- frequency;
- public health impact (severity and seriousness/reversibility/outcomes);
- impact on the individual patient (effect on quality of life);
- risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (i.e. predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- potential mechanism;
- evidence source(s) and strength of the evidence.

The frequency of important identified risks should be expressed taking into account the source of the data. For a product already on the market, the reporting rate based on the number of spontaneously reported adverse events/adverse reactions (in the numerator) and the sales data (in the denominator) is very likely to underestimate the rate of occurrence of an adverse reaction in an exposed population and should be avoided. When an accurate frequency is needed for an important identified risk, this should always be based on systematic studies (e.g. clinical trials or epidemiological studies) in which both the number of patients exposed to the medicinal product and the number of patients who experienced the respective identified risk are known.

The denominator should be expressed using the appropriate measure: e.g. number of patients or in patient-time or equivalent units (courses of treatment, prescriptions, etc.) It should be stated clearly which frequency parameter is being used: e.g. incidence proportion (patient units in the denominator) or incidence rate (patient-time units in the denominator). Confidence intervals should be provided. When using patient-time, the underlying assumption is that the hazard function must be nearly constant over the follow-up time. Otherwise it should be split into relevant categories where the assumption of constancy holds. This may be particularly important if treatment duration is a risk factor. Where appropriate, the period of major risk should be identified. Identified risk incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess (relative incidence compared to a specified comparator group) should be given. Time to event data should be summarised using survival techniques. Cumulative hazard functions may also be used to represent the cumulative probability of occurrence of an adverse reaction in the presence of competing events.

For potential risks, the background incidence/prevalence in the target population(s) should be provided.

For most RMPs involving single products, risks which relate specifically to an indication or formulation can usually be handled as individual safety concerns, e.g. accidental intravenous administration could be a safety concern in a single product with both oral and subcutaneous forms.

For RMPs covering multiple products where there may be significant differences in the identified and potential risks for different products, it may be appropriate to categorise the risks to make it clearer which risks relate to which product. Headings which could be considered include:

- Risks relating to the active substance

This would include important identified or potential risks which are common to all formulations, routes of administration and target populations. It is likely that most risks will fall into this category for the majority of products.

- Risks related to a specific formulation or route of administration

Examples might include an RMP with two products: one a depot intramuscular formulation and the other an oral formulation. Additional concerns relating to accidental intravenous administration clearly would not be applicable to the oral product.

- Risks relating to a specific target population

The paediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a product intended solely for adult patients.

- Risks associated with switch to non-prescription status.

Division of identified and potential risks using headings should only be considered when the risks clearly do not apply to some products and lack of separation could cause confusion.

V.B.8.7.4. RMP module SVII section "Identified and potential interactions including food-drug and drug-drug interactions"

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatments for the condition, but also in relation to commonly used medications in the target population. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed. Interactions which are important clinically should be included as a safety concern in RMP module SVIII "Summary of the safety concerns."

V.B.8.7.5. RMP module SVII section "Pharmacological class effects"

Important risks which have not been included in RMP module SVII "Details of important identified and potential risks from clinical development and post-authorisation experience" (above) but which are believed to be common to the pharmacological class should be discussed here. The discussion should include the mechanism, the impact (severity and duration), frequency seen with other members of the same or similar pharmacological class.

For risks which have been included in the RMP section SVII "Details of important and identified and potential risks from clinical development and post-authorisation experience" above, all that is required in this RMP section are the frequencies seen with the medicinal product compared with those seen with other products in the same or similar pharmacological class.

If there is evidence that a risk, which is common to other members of the pharmacological class, is not thought to be a safety concern with the concerned medicinal product, details, and the evidence supporting this, should be provided and discussed.

V.B.8.8. RMP module SVII "Identified and potential risks (ATMP version)"

Advanced therapy medicinal products (ATMPs) because of their nature may have specific risks that are usually not applicable to other non-advanced therapy medicinal products (see [Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products](#)⁵). For this reason, for ATMPs, this ATMP specific version of RMP module replaces the standard RMP module SVII.

Although not all of the risks listed in section [V.B.8.8.3](#) are unique to ATMPs or applicable to all ATMPs, they represent the most relevant ones which need to be considered.

V.B.8.8.1. RMP module SVII section "Newly identified safety concerns (ATMP)"

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of the safety concern should be stated, whether it is an important identified or important potential risk and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

⁵ EMEA/149995/2008; available on EMA website <http://www.ema.europa.eu>

V.B.8.8.2. RMP module SVII section "Recent study reports with implications for safety concerns (ATMP)"

Study reports (either interim or final), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate (e.g. RMP module SII; section V.B.8.8.3; RMP Module SVI and RMP Module SVII).I

V.B.8.8.3. RMP module SVII section "Details of important identified and potential risks (ATMP)"

This section should provide more information on the most important identified and potential risks. This section should be selective and should not be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents of section 4.8 of the summary of product characteristics (SmPC).

What constitutes an important risk will depend upon several factors including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and is/is likely to be included in the warnings and precautions section of the summary of product characteristics should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of either the patient or donor, affect the quality of life, and which could lead to serious consequences if untreated should also be considered for inclusion. The additional risks specific to ATMPs which should be considered for discussion include:

- risks to living donors, for instance:
 - risks to living donors related to their conditioning prior to procurement (e.g. immunosuppression, cytotoxic agents, growth factors);
 - risks to living donors related to surgical/medical procedures used during or following procurement, irrespective of whether the tissue was collected or not;
- risks to patients related to quality characteristics of the product, in particular:
 - species of origin and characteristics of cells (and related body fluids, biomaterials, biomolecules) that are used during manufacturing, and the safety testing performed;
 - characteristics of vectors for gene therapy medicinal products;
 - biologically active substances used in manufacturing (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
 - quality assurance and characteristics of the finished product in terms of defined composition, stability, biological activity, and purity with reference to non-physiologic proteins and fragments thereof;
 - risk related to transmissible diseases (e.g. viral, bacterial, parasitical infections and infestations, but also malignant disease);
- risks to patients related to the storage and distribution of the product, for instance:
 - risks related to preservation, freezing and thawing;
 - risks of breaking the cold chain or other type of controlled temperature conditions;
 - risks related to stability of the product;

- risks to patients related to administration procedures, for instance:
 - biologically active substances used in preparation of the product prior to administration (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
 - risks related to conditioning of the patient;
 - risks of related medical or surgical procedures (e.g. anaesthesia, infusion, transfusion, implantation, transplantation or other application method);
 - risks related to clinical follow-up (e.g. immunosuppression as co-medication or as necessary for treatment of complications, diagnostic procedures, hospitalisation);
 - risks related to mistakes or violations of the standard procedures for administration of the product (e.g. different administration procedures used by different healthcare establishments/healthcare professionals resulting in differing results);
- risks related to interaction of the product and the patient, for instance:
 - unwanted immunogenicity and its consequences (including e.g. anaphylaxis, graft versus host disease, graft rejection, hypersensitivity reactions, immune deficiencies);
 - risks related to both intended and unintended genetic modification of the patient's cells (apoptosis, change of function, alteration of growth and/or differentiation, malignancy);
 - early and late consequences of homing, grafting, differentiation, migration and proliferation;
 - risks related to infection with vectors used in gene therapy medicinal products (type of vector, target cells, persistence, potential for latency and reactivation, potential for integration of genetic material into the host genome, prolonged expression of the transgene, altered expression of the host's genes);
- risks related to scaffolds, matrices and biomaterials (e.g. biodegradation, mechanical factors);
- risks related to persistence of the product in the patient, e.g.:
 - availability of rescue procedures or antidotes and their risks;
 - late complications, particularly malignancies and auto-immunity;
 - considerations on the potential impact of previous, concomitant, or future therapies typical for the diagnosis or treatment of the respective disease on the product, or vice versa impact of the product on those other therapies (e.g. an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction);
- risks related to re-administration, for instance:
 - immune reactions - anaphylaxis, neutralising antibodies;
 - risks related to repeated surgical or administration procedures;
- risks to close contacts, for instance:
 - based on the environmental risk assessment, virus shedding and its consequences;
- specific parent-child risks, for instance:
 - risk of germ line integration of transgene, or other genetic transformation of the germ line;
 - foetal transmission (of e.g. vectors, biologically active substances, cells, infectious agents);

- trans-mammary exposure of children in breast-feeding women (to e.g. vectors, biologically active substances, cells, infectious agents).

V.B.8.9. RMP module SVIII “Summary of the safety concerns”

At the end of the RMP part “Safety specification” a summary should be provided of the safety concerns.

A safety concern is:

- an important identified risk;
- an important potential risk; or
- missing information (see Annex I).

It is noted that the ICH definition of safety concern is: an important identified risk, important potential risk or important missing information, i.e. includes the qualifier “important” in relation to missing information (see Annex IV, ICH-E2C(R2) Guideline). The ICH-E2E Guideline (see Annex IV) uses the terms safety issue and safety concern interchangeably with the same definition for safety concern as defined in the ICH-E2C(R2) Guideline.

The change of the EU term, to name this concept “missing information” rather than “important missing information”, is to be clear that in the EU a marketing authorisation cannot be granted if there are unacceptable gaps in knowledge, in accordance with Article 12 of REG (EC) No 726/2004 a marketing authorisation shall be refused if the quality, safety or efficacy are not properly or sufficiently demonstrated.

For RMPs covering multiple products where there may be significant differences in the important identified and important potential risks for different products, similar to the presentation of risks in RMP module SVII, it may be appropriate to subdivide the summary of safety concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

- safety concerns relating to the active substance;
- safety concerns related to a specific formulation or route of administration;
- safety concerns relating to the target population;
- risks associated with switch to non-prescription status.

Division of safety concerns by headings should only be considered when the risks clearly do not apply to some products and inclusion as a single list could cause confusion.

V.B.9. RMP Part III “Pharmacovigilance plan”

The purpose of the pharmacovigilance plan is to discuss how the applicant/marketing authorisation holder plans to identify and/or characterise the risks identified in the safety specification. It provides a structured plan for:

- the identification of new safety concerns;
- further characterisation of known safety concerns including elucidation of risk factors;
- the investigation of whether a potential safety concern is real or not;
- how missing information will be sought.

It does NOT include actions intended to reduce, prevent or mitigate risks

The pharmacovigilance plan should be based on the safety concerns summarised in RMP module SVIII of the safety specification. Early discussions between competent authorities and the marketing authorisation holder or applicant are recommended to identify whether, and which, additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and therefore signal detection, which is part of routine pharmacovigilance, will be an important element in identifying new risks for all products.

Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities. For each safety concern, the applicant/marketing authorisation holder should list their planned pharmacovigilance activities for that concern. Pharmacovigilance plans should be proportionate to the risks of the product. If routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies) "routine pharmacovigilance" should be entered against the safety concern.

V.B.9.1. RMP part III section "Routine pharmacovigilance activities"

Routine pharmacovigilance is the set of activities required to fulfil the legal requirements for pharmacovigilance contained within Directive 2001/83/EC and Regulation (EC) No 726/2004. The Pharmacovigilance System Master File (see [Module II](#)) contains details of the system and processes each marketing authorisation applicant/holder has in place to achieve this. These details are not required to be submitted in the RMP.

In certain situations, the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee for Medicinal Products for Human Use (CHMP) or the Coordination Group for Mutual recognition and Decentralised Procedures – Human (CMDh) may make recommendations for specific activities related to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions which differ from the normal requirements for routine pharmacovigilance (see [Module I](#)). If these recommendations include recording of tests (including in a structured format) which would form part of normal clinical practice for a patient experiencing the adverse reaction then this requirement would still be considered as routine. The routine pharmacovigilance section of the pharmacovigilance plan should be used in these circumstances to explain how the applicant will modify its routine pharmacovigilance activities to fulfil any special PRAC, CHMP or CMDh recommendations on routine pharmacovigilance.

However, if the recommendation includes the submission of tissue or blood samples to a specific laboratory (e.g. for antibody testing) which is outside "normal" clinical practice, then this would constitute an additional PhV activity.

Specific adverse reaction follow-up questionnaires

Where an applicant/marketing authorisation holder is requested, or plans to use, specific questionnaires to obtain structured information on reported adverse reactions of special interest, copies of these forms should be provided in RMP annex 7 and will be made available upon request. Applicants/marketing authorisation holders are encouraged to use the same or similar questionnaires for the same adverse event to decrease the burden on healthcare professionals.

Use of specific questionnaires as a follow-up to a reported suspected adverse reaction is considered to be routine pharmacovigilance.

V.B.9.2. RMP part III section “Additional pharmacovigilance activities”

Additional Pharmacovigilance activities may be non-clinical studies, clinical trials or non- interventional studies. A safety concern may have no, or a number of, additional pharmacovigilance activities associated with it depending upon its nature, the degree to which it has already been characterised, and the feasibility of studying it. Applicants/marketing authorisation holders should consider the situations when additional pharmacovigilance activities are needed. For example, a medicinal product intended for chronic use may only have relatively short term follow up data at the time of authorisation. Long term follow-up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long term effects of the medicinal product. A medicinal product, where there is conflicting pre-clinical data, e.g. carcinogenicity in only one species, may also require long term follow-up of a cohort of patients to confirm that there is not an increased risk of cancer in human use. Another example, when additional pharmacovigilance activities should be considered, is when a potential risk with an individual medicinal product has a significant background incidence in the target population(s), leading to difficulties in distinguishing between the effects of the medicinal product and the “normal” incidence. When any doubt exists about the need for additional pharmacovigilance activities, consultation with a competent authority should be considered.

The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicinal product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicinal product used in the palliative treatment of metastatic cancer.

Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification whether the studies are to identify and characterise risks, or to assess the effectiveness of risk minimisation activities. The applicant/marketing authorisation holder should include all studies designed to address the safety concern or measure the effectiveness of risk minimisation measures. This includes all post-authorisation safety studies which are initiated, managed or financed by marketing authorisation holders, voluntarily, or pursuant to obligations imposed by a competent authority [REG Art 10, Art 10a(1)], DIR Art 21a, Art 22a(1), Art 22c]. Studies requested by other regulatory authorities (including those outside of the EEA) to investigate a specific safety concern should also be included. If a marketing authorisation applicant/holder has a marketing partner, studies designed to address a particular safety concern which are initiated, managed or financed by that partner should be included in the pharmacovigilance plan, if possible.

If, when reviewing a study protocol, a study is thought not to have as its primary focus one of the objectives of a PASS (as described in Module VIII), or a PAES, or the study is judged to be unlikely to achieve its stated scientific purpose, the applicant/marketing authorisation holder will be required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP.

Pharmacoepidemiology studies included in the pharmacovigilance plan should be designed and conducted according to the respective legislation in place and recommendations in the [Guidelines for](#)

Good Pharmacoepidemiology Practices (GPP)⁶ and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology⁷. For studies involving children, the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population⁸ should be consulted. It is highly recommended that expert advice is sought on the design and conduct of any studies – whether by the scientific advice procedure or by consulting known experts in the appropriate field. The responsibility for the scientific value of study protocols remains with applicants or marketing authorisation holders, even if they have been previously discussed with competent authorities.

Further guidance on the conduct of post-authorisation safety studies (PASS) is given in **Module VIII**.

For some safety concerns, additional pharmacovigilance activities other than pharmacoepidemiology studies may be required, e.g. pharmacokinetic studies, clinical trials or further pre-clinical work. The appropriate guidelines and legislation should be followed in the conduct of these studies.

Protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until completion of the study and submission to the competent authorities of the final study report. Changes to the protocol which do not affect milestones or due dates are not considered to be updates to the RMP (see also **Module VIII**).

For studies conducted as an obligation, the marketing authorisation holder shall submit the study protocol, in English except for studies to be conducted in only one Member State that requests the study [DIR Art 22a]. For other studies, if the study protocol or the study report is written in another language, the marketing authorisation should facilitate access to study information by including an English translation of the title, the abstract of the study protocol and the abstract of the final study report (see **Module VIII**).

Synopses of study reports from additional pharmacovigilance activities should be included in RMP annex 9. The impact of the new data on the risk-benefit balance of the medicinal product should be carefully assessed and the safety specification, pharmacovigilance plan and risk minimisation measures updated accordingly.

V.B.9.2.1. Particular situations with post authorisation safety studies

This section should be read in conjunction with **Module VIII** on post-authorisation safety studies.

a. Studies to measure the effectiveness of risk minimisation measures

Post-authorisation safety studies (PASS) include in their definition studies which measure the effectiveness of risk management measures. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan. Further guidance on measuring the effectiveness of risk minimisation measures can be found in **Module XVI**.

b. Drug utilisation studies

Drug utilisation studies are sometimes requested by national competent authorities to monitor drug usage in their country, often in relation to reimbursement discussions. However, although they may not be initiated to collect safety data, they can provide useful information on whether risk minimisation

⁶ International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2005; 14 (8): 589-595; available on the ISPE website http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

⁷ ENCePP Guide on Methodological Standards in Pharmacoepidemiology" EMA/95098/2010; available on <http://www.encepp.eu>.

⁸ EMEA/CHMP/PhVWP/235910/2005; available on http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000087.jsp&mid=WC0b01ac0580025b90&jenabled=true.

activities are effective and on the demographics of target populations. Ideally, requests for drug utilisation studies by national competent authorities in one or more EU countries should be identified to the Rapporteur/Reference Member State pre-opinion and included in the pharmacovigilance plan. However, these studies are sometimes requested post-authorisation by authorities not involved in medicinal product licensing. In these circumstances, the studies should be included in the next update to the RMP.

c. Joint studies

If safety concerns apply to more than one medicinal product, the national competent authority or the Agency shall, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [DIR Art 22a(1), REG Art 10a(1)]. The conduct of a joint study may also be appropriate where there are limited patients (rare diseases) or the adverse reaction is rare. The national competent authority or the Agency should facilitate the agreement of the concerned marketing authorisation holders in developing a single protocol for the study and conducting the study. Where the PRAC agrees to impose the same PASS on more than one marketing authorisation holder and the concerned marketing authorisation holders have failed to agree a common protocol within a reasonable period of time, as determined by the PRAC, the national competent authority or the Agency, with input from the PRAC, may define either a common core protocol or key elements within a protocol which the concerned marketing authorisation holders will have to implement within a timescale laid down within the request. Hence, the study would become a condition of the marketing authorisation and be reflected in the RMP. In some circumstances, the encouragement to do joint studies may relate to a single active substance where there are multiple marketing authorisation holders for the same active substance.

d. Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry).

Registries should ideally include a comparator group so a disease registry will usually be more suitable than a registry confined to a specific product. However, if, an applicant/marketing authorisation holder institutes a registry as part of an agreed RMP, the protocol for the registry will allow all patients who are prescribed the active substance or who have the same disease, as appropriate, to be entered in the registry. Entry to the registry should not be conditional on being prescribed a product with a particular invented name or marketing authorisation holder unless there are clear scientific reasons for this. The same applies to similar biological products.

Unless there are over-riding public health or scientific concerns which lead to mandatory inclusion in a registry, refusal to enter a registry should not normally be a reason for refusing access to a medicine.

V.B.9.3. RMP part III section “Action plans for safety concerns with additional pharmacovigilance requirements”

For safety concerns with additional pharmacovigilance activities only, the action plan for each safety concern should be presented according to the following structure:

- safety concern;
- proposed action(s);

- individual objectives of proposed action(s) (i.e. what aspects of the safety concern they are intended to characterise); and

for each action:

- details of individual action;
 - steps; and
 - milestones (including expected dates).

As well as listing any additional pharmacovigilance activities under “proposed actions,” protocols (draft or otherwise) for any formal studies should be provided in RMP annex 6. Marketing authorisation applicants/holders should also follow the requirements detailed in Module VIII, where appropriate. It is recommended that the ENCePP Guide on Methodological Standards in Pharmacoepidemiology⁹ including the ENCePP Checklist for Study Protocols¹⁰, should be referred to when considering epidemiological protocol design.

V.B.9.4. RMP part III section “Summary table of additional pharmacovigilance activities”

The pharmacovigilance plan describes pharmacovigilance activities designed to identify and characterise risks associated with the use of a medicinal product. Some may be imposed as conditions of the marketing authorisation (MA) either because they are key to the benefit-risk of the product, or because they are specific obligations in the context of a MA under exceptional circumstances. If the obligation is a non-interventional PASS, it will be subject to the supervision as described in Art 107 (m)-(q) and the format and content as specified in the EC implementing measures.

The pharmacovigilance plan also includes studies that are conducted or financed by the marketing authorisation holder to address particular safety concerns and so includes studies which are not obligations in the above sense. These studies may be on-going or planned, may have been requested by another regulatory authority, may have been specifically requested by the CHMP or may have been suggested by the marketing authorisation applicant/holder and agreed with the CHMP as forming part of the pharmacovigilance plan. They may also be conducted to evaluate the effectiveness of risk minimisation activities.

Finally, the Pharmacovigilance Plan also has a role in providing an overview of studies which, although not part of the formal agreed plan to identify and characterise specific safety concerns, the Rapporteur, Reference Member State or national competent authority needs to be aware of. These studies are typically requested post-authorisation by a national competent authority for reimbursement reasons e.g. drug utilisation studies.

The summary table of the pharmacovigilance plan should provide clarity to all stakeholders as to which category an activity in the pharmacovigilance plan falls under, i.e.:

1. Imposed obligations in the meaning of Art. 10/10a and 21a/22a included as a condition of the MA;
2. Specific Obligations in the framework of a MA under exceptional circumstances. These studies will also be reflected in Annex II to the marketing authorisation (or national equivalent);
3. Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities;

⁹ ENCePP Guide on Methodological Standards in Pharmacoepidemiology” EMA/95098/2010; available on <http://www.encepp.eu>.

¹⁰ ENCePP Checklist for Study Protocols”, EMEA/540136/2009; available on <http://www.encepp.eu>.

4. Other studies conducted by MAH which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimisation activities.

Table V.2: Attributes of different PhV activities

	Type of activity	In Annex II of Opinion (CAPs only)	Category in Summary table of PhV activities	Status	Supervised under Article 107m	Supervised under Article 107 n-q
Imposed PASS	"Interventional"*	X	1	Mandatory and subject to penalties		
	Non-interventional	X	1	Mandatory and subject to penalties	X	X
Specific obligation	"Interventional"*	X	2	Mandatory and subject to penalties		
	Non-interventional	X	2	Mandatory and subject to penalties	X	X
Required	"interventional"*		3	Legally enforceable		
	Non-interventional		3	Legally enforceable	X	
Stated	"interventional"*		4	Not enforced		
	Non-interventional		4	Not enforced	X	

*Clinical interventional studies are subject to the requirements of Directive 2001/20/EC. Non clinical interventional studies are subject to the legal and ethical requirements related to the protection of laboratory animals, and Good Laboratory Practice as appropriate.

For activities in categories 1-3, the following summary table should be used:

Description of Activity	Milestones <i>(may be several per activity)</i>	Due Date <i>(may be several per activity)</i>

For activities in category 4 the following summary table should be used:

Description of Activity	Expected date when results will be available

V.B.10. RMP part IV “Plans for post-authorisation efficacy studies”

Efficacy, as assessed at the time of authorisation, is based on data from clinical trials which, by their nature, are of relatively limited duration (e.g. usually between 6 months to 3 years). The benefit (efficacy of the medicine) risk balance must be positive for a medicine to be authorised. Whereas it is recognised that many risks will be identified post authorisation, there is an implicit assumption that efficacy remains relatively constant over time. This may not always be valid.

For most medicines there will not be a need for post-authorisation efficacy studies. However, there may be circumstances where efficacy may vary over time and also patients in whom this assumption of constant efficacy may not be true and where longer term efficacy data post authorisation is necessary.

The regulations on paediatric medicinal products (Regulation (EC) No 1901/2006)¹¹, and advanced therapy medicinal products (Regulation (EC) No 1394/2007)¹² provide the legal basis and specify the potential need for long term follow-up of efficacy as part of post-authorisation surveillance for certain medicinal products namely:

- applications for a marketing authorisation that include a paediatric indication;
- applications to add a paediatric indication to an existing marketing authorisation;
- application for a paediatric use marketing authorisation;
- advanced therapy medicinal products.

In addition, Article 10a(1) of Regulation (EC) No 726/2004 and Article 21a(f) and Article 22a(1) of Directive 2001/83/EC, provide the legal basis for requiring post-authorisation efficacy studies for products where there are concerns about efficacy which can only be resolved after the product has been marketed, or when knowledge about the disease or the clinical methodology used to investigate efficacy indicate that previous efficacy evaluations may need significant revision.

The requirement for efficacy studies post authorisation refers solely to the current indication(s) and not to studies investigating additional indications.

V.B.10.1. RMP part IV section “Summary of existing efficacy data”

As background to any proposed post-authorisation efficacy studies, and to provide context for the summary of the RMP, there should be a summary of the efficacy of the product and the studies and endpoints on which it was based. Where the RMP covers more than one medicinal product, the

¹¹ Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use

¹² Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products

information should be provided by medicinal product to permit easy extraction for the summary of the RMP module. Similarly medicinal products with more than one indication should have a separate summary of efficacy for each indication.

The summary of efficacy (one page maximum per indication/population) should be in lay language and the following should be considered for inclusion:

- current (gold) standards of treatment;
- where the medicinal product fits in the therapeutic armamentarium (i.e. 1st line, relapse, etc.);
- a brief statement of the standard against which the medicine was judged;
- number of patients in pivotal studies and treatment regimes;
- results in lay language.

The following areas should be discussed briefly and the need for further studies post authorisation evaluated:

- the robustness of the endpoints on which the efficacy evaluation is based;
- applicability of the efficacy data to all patients in the target population;
- factors which might affect the efficacy of the product in everyday medical practice;
- variability in benefits of treatment for sub populations.

For updates to the RMP, any subsequent data which impacts on efficacy should be mentioned and its impact on the benefits of the medicinal product discussed.

V.B.10.2 Tables of post-authorisation efficacy studies

A summary table showing an overview of the planned studies together with timelines and milestones should be provided here with the (draft) protocols for these studies included in RMP annex 8.

Efficacy studies which are specific obligations and/or conditions of the marketing authorisation should also be included in this part of the RMP.

It should be noted that the Commission may adopt a delegated act on the situations where efficacy studies may be required and the Agency shall adopt scientific guidance on post-authorisation efficacy studies.

Efficacy studies which are specific obligations and/or conditions of the MA:

Description of Study	Milestones <i>(may be several Per activity)</i>	Due Date <i>(may be several Per activity)</i>

Other efficacy/effectiveness studies:

Description of Study	Milestones <i>(may be several Per activity)</i>	Due Date <i>(may be several Per activity)</i>

V.B.11. RMP Part V “Risk minimisation measures”

On the basis of the safety specification, a marketing authorisation applicant/holder should assess what risk minimisation activities are needed for each safety concern. The risk minimisation plan should provide details of the risk minimisation measures which will be taken to reduce the risks associated with individual safety concerns. It is not possible to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis and will depend upon the severity of the risk, the healthcare setting, the indication, the pharmaceutical form and the target population. A safety concern may be addressed using more than one risk minimisation measure.

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product. Examples when multiple risk minimisation plans could be considered include:

- an active substance where there are products with both prescription only and non-prescription legal status;
- medicinal products where there are major risks, and the indications cross areas of medical expertise. In the latter case, there could be diverse educational needs for different specialists since the areas of specialised knowledge will be distinct. For example an active substance which causes important QT prolongation would most likely not need educational material explaining the implications of this and the interactions with other products if the product were intended solely for use by cardiologists in a hospital setting but might need educational material if intended for use in general practice or orthopaedic surgery where it is unlikely that prescribers will have this specialist knowledge;
- active substances where there are major risks which differ according to the target population.

Risk minimisation activities may consist of routine risk minimisation (e.g. measures associated with locally authorised product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communications/educational materials/controlled distribution systems). All risk minimisation measures should have a clearly identifiable objective.

All risk minimisation measures should be reviewed at regular intervals and their effectiveness assessed (see [V.B.11.4.](#)).

Additional risk minimisation measures and the assessment of the effectiveness of risk minimisation measures in general is discussed in more detail in [Module XVI.](#)

V.B.11.1. RMP part V section “Routine risk minimisation”

Routine risk minimisation activities are those which apply to every medicinal product. These relate to:

- the summary of product characteristics;
- the labelling;
- the package leaflet;
- the pack size(s);
- the legal status of the product.

The summary of product characteristics (SmPC) and the package leaflet are important tools for risk minimisation as they constitute a controlled and standardised format for informing healthcare practitioners and patients about the medicinal product. The **Guideline on Summary of Product Characteristics**¹³ provides guidance on how information should be presented. As discussed in V.B.8.6.4., the design of the packaging, and even the formulation itself, may play an important role in preventing medication error.

a. Pack size

Since every pack size is specifically authorised for a medicinal product, planning the number of “dosage units” within each pack, and the range of pack sizes available can be considered a form of routine risk management activity. In theory, controlling the number of “dosage units” should mean that patients will need to see a healthcare professional at defined intervals: increasing the opportunity for testing and reducing the length of time a patient is without review. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered.

A small pack size can also be useful, especially if overdose is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled.

b. Legal status

All medicinal products in the EU have a legal status. Controlling the conditions under which a medicinal product may be made available can reduce the risks associated with its use or misuse. This can be achieved by controlling the conditions under which a medicinal product may be prescribed, or the conditions under which a patient may receive a medicinal product.

When a marketing authorisation is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which a medicinal product may be made available to patients. The conditions under which a medicinal product is made available is commonly referred to as the “legal status” of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medicinal prescription. It may also restrict where the medicinal product can be administered (e.g. in a hospital, but see below) or by whom it may be prescribed (e.g. specialist).

For medicinal products only available on prescription, additional conditions may be imposed by classifying medicinal products into those available only upon either a restricted medical prescription or a special medical prescription.

¹³ http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

Restricted medical prescription

This may be used to control who may initiate treatment, prescribe the medicinal product and the setting in which the medicine can be given or used. According to EU legislation, when considering classification of a medicinal product as subject to restricted medical prescription, the following factors shall be taken into account:

- the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment;
- the medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere; or
- the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment [DIR Art 71(3)].

In the case of an application for a marketing authorisation submitted in accordance with the centralised procedure, the CHMP is responsible for recommending the legal status to the Commission. Although the use of legal status is not an activity that can be used directly by a marketing authorisation applicant for the purposes of risk reduction, the marketing authorisation applicant could request the competent authority to consider a particular legal status and this is indicated in the SmPC.

However, the definition of what constitutes a specialist is not uniform throughout the Member States so, in practice, the term "specialist" is usually phrased in section 4.2 of the summary of product characteristics (SmPC) as: "treatment by a physician experienced in the treatment of <the disease>". Although restricting to use in a hospital environment may in practice ensure that the medicinal product is always prescribed by a specialist, this needs to be balanced against the inconvenience to patients if they need to attend a hospital for every prescription. Care also needs to be taken when considering where a medicinal product can be safely administered. For example the term "clinic" has different connotations depending upon the country. For this reason, the type of equipment needed should be specified rather than a location: e.g. "use in a setting where resuscitation equipment is available."

Special medical prescription

For classification as subject to special medical prescription, the following factors shall be taken into account:

- the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971; or
- the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes; or
- the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the previous indent as a precautionary measure [DIR Art 71(2)].

Categorisation at Member State level

There is the possibility of implementing further sub-categories at Member State level which permits the Member States to tailor the broad classifications described above to their national situation. The

definitions and therefore also the implementation varies in those Member States where the sub-categories exist.

The majority of safety concerns may be adequately addressed by routine risk minimisation activities. However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary.

V.B.11.2. RMP part V section “Additional risk minimisation activities”

Additional risk minimisation activities are those risk minimisation measures which are not the routine risk minimisation activities listed above. Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided.

Many additional risk minimisation tools are based on communication which aims to augment the information in the summary of product characteristics (SmPC) and the package leaflet. Any communication material should be clearly focused on the risk minimisation goals, and should not be confused or combined with promotional material for marketing campaigns. Further description and guidance on the use of additional risk minimisation activities is provided in **Module XVI**.

It is essential that appropriate specialists/ experts are involved when developing risk minimisation activities. Marketing authorisation applicants/ holders are also encouraged to discuss risk minimisation plans with the competent authorities as early as is feasible when it is likely that specific risk minimisation activities will need to be adapted to the different health care systems in place in the different Member States. For very complex risk minimisation measures, it may be appropriate to contact competent authorities, in the countries where it is planned to market the product, either prior to submitting risk minimisation proposals or during the course of the evaluation procedure. Where possible and appropriate, proposed risk minimisation activities should be discussed with patients and healthcare professionals if it is likely that risk minimisation activities will be directed towards them.

The Pharmacovigilance Risk Assessment Committee (PRAC) is the body mandated to review RMPs and make recommendations on their content and on the suitability of proposed pharmacovigilance activities and risk minimisation measures. For centrally authorised products, only additional risk minimisation measures which are recommended by the PRAC and subsequently agreed by the CHMP will be allowed in the risk minimisation plan and any other activities considered as not essential for the safe and effective use of the product will need to be removed and an updated RMP submitted before the CHMP Opinion. Additional risk minimisation activities will become, once agreed by the European Commission, conditions of the marketing authorisation and the key elements will be detailed in annex II to the Commission Decision and, exceptionally if applicable, a Commission Decision in accordance with the annex 127a may be addressed to the Member States for implementation of certain of these conditions.. Where appropriate, full details of additional risk minimisation activities (including mock ups) should be provided in RMP annexes 10 and 11.

Educational material

Any educational material should be non-promotional. It is recommended that communication experts, patients and healthcare professionals are consulted on the design and wording of educational material and that, where appropriate, it is piloted before releasing for use.

For centrally authorised products, the CHMP will agree the key elements of what should be included in the educational material and these key elements will become, once agreed by the European

Commission, a condition of the marketing authorisation. The final version of the educational material will need to be approved by the national competent authority for the territory in which it will be used who will check that the material contains the key elements in an appropriate design and format and is not promotional.

For public health reasons, applicants/marketing authorisation holders for the same active substance may be required by the competent authority to have educational material with as similar as possible layout, content, colour and format to avoid patient confusion. This requirement may also be extended to other patient material such as patient alert cards and patient monitoring cards. For this reason, marketing authorisation applicants/holder are strongly recommended to avoid the use of company logos or other trademarked or patented material in educational material.

Further extensive guidance on additional risk minimisation measures is provided in [Module XVI](#).

V.B.11.3. Format of risk minimisation plan(s)

Each safety concern identified in the summary of the safety specification should be addressed. If no risk minimisation activity is proposed then "none proposed" should be entered against the objective.

For each safety concern, the following information should be provided:

- objectives of the risk minimisation activities
- routine risk minimisation activities;
- additional risk minimisation activities (if any), individual objectives and justification of why needed;
- how the effectiveness of each (or all) risk minimisation activities will be evaluated in terms of attainment of their stated objectives;
- what the target is for risk minimisation, i.e. what are the criteria for judging success;
- milestones for evaluation and reporting.

For routine risk minimisation activities, the proposed text in the summary of product characteristics (SmPC), or a précis, should be provided along with details of any other routine risk minimisation activities proposed for that safety concern. If the medicinal product has two or more marketing authorisations (i.e. in different Member States) which have different SmPC text, it may be appropriate to comment on the differences in the text between Member States.

V.B.11.4. RMP part V section "Evaluation of the effectiveness of risk minimisation activities"

Risk minimisation measures are public health interventions intended to prevent or reduce the probability of the occurrence of adverse reactions associated with exposure to a medicinal product, or to reduce their severity/impact on the patient should the adverse reactions occur. The terms "risk minimisation measures and risk minimisation activities are used virtually synonymously in GVP. The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall risk-benefit balance is optimised.

When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable. Such information may be presented by region, if applicable/relevant. Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities should be included when available. As part of this critical

evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then alternative activities need to be put in place. The marketing authorisation holder should always comment on whether additional or different risk minimisation activities are needed for each safety concern.

In certain cases it may be judged that risk minimisation cannot control the risks to the extent possible to ensure a positive risk-benefit balance and that the medicinal product needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks.

More extensive guidance on monitoring the effectiveness of risk minimisation activities is included in **Module XVI**.

V.B.11.5. RMP part V section "Summary of risk minimisation measures"

A table summarising the routine and additional risk minimisation activities by safety concern should be provided. This table will be used in the European Public Assessment Report (EPAR).

V.B.12. RMP part VI "Summary of activities in the risk management plan by medicinal product"

A summary of the RMP for each medicinal product shall be made publically available [REG Art 23(3), Art 26(c), DIR Art 106(c) IR Art 31(2)]. The summary must include key elements of the RMP with a specific focus on risk minimisation activities. With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information [IR Art 31(1)].

It is difficult for one summary to satisfy the needs of all stakeholders and there may be a need for a summary of the RMP to be provided for different stakeholders in varying formats. For products authorised under the centralised procedure, the Agency currently publishes a full scientific assessment of the dossier in the format of a European Public Assessment Report (EPAR). This contains some information on the RMP in an abbreviated tabular format since much of the relevant safety and efficacy data is contained elsewhere within the EPAR. The Agency also publishes a brief summary of the EPAR written in lay language (i.e. the EPAR summary).

Based on the information contained in part VI of the RMP, the Agency, in consultation with the national competent authorities, have agreed three possible formats for the public summary of the RMP. These take the form of the two documents described above (EPAR summary and information in the CHMP assessment report in an abbreviated tabular format) and a more detailed summary of the RMP which is published as a stand-alone document. There will be a stepwise implementation. Which format is used for a particular medicine will depend upon the Member State and the type of product. The Agency is piloting the publication of the detailed summary for centrally authorised products in addition to the two documents described above.

The elements needed to fulfil these three documents are contained within Part VI of the RMP: "the summary of the RMP" and are described in Sections **V.B.12.1 to V.B.12.8.** This shall be provided for all medicinal products which have a RMP regardless of whether they are centrally or nationally authorised.

The summary of the RMP shall be written by the MAA/MAH and will be evaluated during the assessment of the RMP. The final format of the Summary and processes for its production and publication are still subject to discussion. Further details will be published on the Agency website and those of national competent authorities (as appropriate) as soon as these are available.

V.B.12.1. RMP part VI section “format and content of the summary of the RMP”

This is a scientific summary, written for the lay reader to fulfil the requirements in the legislation. In situations where the RMP covers more than one product, a separate RMP part VI should be prepared for each product. To present a balanced picture, the risks discussed in the RMP should be put into context with a very concise and focussed description of the benefits of the medicinal product. Technical terms, scientific abbreviations or acronyms should be avoided or explained in full if deemed necessary.

The summary of the RMP part VI should contain the following information based on RMP modules SI, SVIII and RMP parts IV and V:

- Overview of disease epidemiology;
- Summary of treatment benefits;
- Unknowns relating to treatment benefits;
- Summary of safety concerns:
 - Important identified risks;
 - Important potential risks;
 - Missing information;
- Summary of risk minimisation activities by safety concern;
- Planned post authorisation development plan;
- Studies which are a condition of the marketing authorisation (see [V.B.9.4.](#) and [V.B.10.2.](#));
- Major Changes to the Risk Management Plan over time.

The information provided in each section should be brief, focussed and in accordance with the word limits in the templates.

V.B.12.2. RMP part VI section “Overview of disease epidemiology”

The applicant/marketing authorisation holder should summarise the epidemiology of the disease/condition the medicinal product is intended to treat or prevent (as presented in RMP module SI) in a non-alarmist manner and in language appropriate to the target population. If the product is used in a range of disease severity, this fact should be emphasised and discussed. Sensitivity should be used when presenting the morbidity and mortality of the disease whilst retaining factual accuracy. If success of treatment is measured using survival figures, appropriate emphasis should be given to the fact that, by definition, survival (e.g. 5 year survival) figures relate to historical treatment.

If the product is a diagnostic, product used for anaesthesia or similar usage not associated with a particular disease/condition then this section of the overview may be omitted.

V.B.12.3. RMP part VI section “Summary of treatment benefits ”

This should consist of very concise high level key messages concerning the results of the pivotal trials and any important supplementary evidence and should adhere to the word limits in the template.

V.B.12.4. RMP part VI section “Unknowns relating to treatment benefits”

This should discuss the applicability of efficacy to all patients in the target population. It should describe very briefly any relevant parts of the target population where experience is limited and

whether efficacy is expected to be different in these people, e.g. factors such as age, sex, race and organ impairment.

V.B.12.5. RMP part VI section “Summary of safety concerns”

This section should briefly describe the safety concerns in suitable language for the general public. It should include the frequency and severity of the safety concern for the important identified risks and their preventability.

Risk	What is known	Preventability
Risk 1		
Risk 2 etc.		

For important potential risks the reasons why the reason why it is thought to be a potential risk (e.g. toxicology in animal study, known effect in other members of the pharmaceutical class) should be explained together with the uncertainties, e.g. “occurs in other medicinal products in the same class but was not seen in the clinical trials for this medicinal product which studied 3,761 people”.

Risk	What is known
Risk 1	
Risk 2 etc.	

For missing information it should be stated (using the above format as well) that there is no, or insufficient, information regarding the safety concern, the possible relevance to the target population should be highlighted as well as the associated recommendations, e.g. contraindication, use with caution.

V.B.12.6. RMP part VI section "Summary of risk minimisation activities by safety concern"

Details of routine risk minimisation measures will be provided in the published summary by a link to the product information.

For each safety concern which has additional risk minimisation measures, brief details of the measures for that concern should be provided. The objective and rationale for each measure should be stated along with the proposed actions e.g.:

These additional risk minimisation measures are for the following risks:

Blood clots (Thromboembolic events)

Healthcare Professional and patient education

Objective and rationale
Patients and HCPs to understand the risk of occurrence of thromboembolic events and the appropriate management of this risk.

Proposed actions

- HCP educational materials to be provided to prescribing physicians and pharmacists warning about these risks and measures to take
- Patient booklet will inform patients what the symptoms of thromboembolic events are and the importance of seeking medical help immediately
- Direct HCP communication prior to launch ('Dear HCP' letter).

Where there are safety concerns specific to a particular indication or population, or where an ATMP is involved it may be appropriate to structure the risks by the headings suggested in module SVII.

V.B.12.7. RMP part VI section "Planned post-authorisation development plan"

Data should be presented in the form of a table showing the planned activities in terms of efficacy studies and the further investigation of safety concerns. This table would combine the data from sections V.B.9.4. and V.B.10.2.. Each row of the table should include the name of the study, objectives for the study, the safety concern or efficacy issue being addressed, the status and planned date for submission of the results.

List of studies in post authorisation development plan

Study	Objectives	Safety concerns/efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study 1				
Study 2 etc				

Studies which are a condition of the marketing authorisation

Statement on which studies in the above table are conditions of the MA e.g. "None of the above studies is a condition of the marketing authorisation."

V.B.12.8. RMP part VI section "Summary of changes to the risk management plan over time"

This table should provide a listing of all significant changes to the RMP in chronological order. This should include, for example, the date and version number of the RMP when new safety concerns were added or existing ones removed or changed, dates and version of the RMP when new studies were added or finished, and a brief summary of changes to risk minimisation activities and the associated dates these changes were agreed. Since changes to risk minimisation activities involve a variation, the date used for changes to risk minimisation activities should be that of the decision, whether by the European Commission or a national competent authority. The date for safety concerns and studies should be the date of the RMP in which they are first added.

V.B.13. RMP part VII "Annexes to the risk management"

The RMP should contain the annexes listed below. Annexes 1-3, 10 and 11 should be provided for each medicinal product within the RMP. If no information is available for a given annex this should be stated. If a single study is addressing issues in both parts III and IV of the RMP, it should be included in RMP annex 6 with a cross reference in RMP annex 8.

RMP annex 1: Interface between RMP and Eudravigilance/EPITT (electronic only)

See <http://eudravigilance.ema.europa.eu/human/EURiskManagementPlans.asp>.

RMP annex 2: Current (or proposed if product is not authorised) local (centralised/mutual recognition/decentralised/national) summary of product characteristics (SmPC) and package leaflet. If multiple versions are included, they should show in which Member State(s) they are applicable. If available, a core SmPC should be provided with an overview of the changes applicable to the SmPC in each Member State.

RMP annex 3: worldwide marketing authorisation status by country (including EEA). This should include:

- current licence status (approved/refused/ under review/ suspended/expired/withdrawn);
- date(s) of approval/refusal/suspension/expiration/withdrawal;
- date(s) marketed/withdrawn from market;
- trade name(s);
- any explanatory comments.

RMP annex 4: Synopsis of on-going and completed clinical trial programme.

RMP annex 5: Synopsis of on-going and completed pharmacoepidemiological study programme.

RMP annex 6: Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III.

RMP annex 7: Specific adverse event follow-up forms.

- RMP annex 8: Protocols for proposed and on-going studies in RMP part IV.
- RMP annex 9: Synopsis of newly available study reports for RMP parts III-IV.
- RMP annex 10: Details of proposed additional risk minimisation activities (if applicable).
- RMP annex 11: Mock up examples in English (or the National language if the product is only authorised in a single Member State) of the material provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a requirement of national authorisations including those using the mutual recognition or decentralised procedure as applicable.
- RMP annex 12: Other supporting data (including referenced material).

V.B.14. The relationship between the risk management plan and the periodic safety update report

The primary post-authorisation pharmacovigilance documents will be the RMP and the periodic safety update report (PSUR). Although there is some overlap between the documents, the main objectives of the two are different and the situations when they are required are not always the same. Regarding objectives, the main purpose of the PSUR is integrated, post-authorisation risk benefit assessment whilst that of the RMP is pre-and post-authorisation risk-benefit management and planning. As such the two documents are complementary. Regarding submission, whereas for many medicinal products, both documents will need to be submitted, for other medicinal products only one will be required depending upon where the product is in its lifecycle. For this reason both documents need to be “stand-alone” but it is anticipated that certain modules may be common to prevent duplication of effort.

The PSUR examines the overall safety profile as part of an integrated benefit-risk evaluation of the medicinal product at set time periods and as such will consider the overall risk-benefit balance of the medicinal product (and a much wider range of (suspected) adverse reactions). It is anticipated that only a small proportion of these would be classified as important identified or important potential risks and become a safety concern discussed within the RMP. Deciding to add an adverse reaction to section 4.8 of the summary of product characteristics (SmPC) is not a sufficient cause per se to include it as a safety concern in the RMP (see [V.B.8.7.2.](#)).

When a PSUR and a RMP are to be submitted together, the RMP should reflect the conclusions of the accompanying PSUR. For example if a new signal is discussed in the PSUR and the PSUR concludes that this is an important identified or important potential risk, this risk should be included as a safety concern in the updated RMP submitted with the PSUR. The pharmacovigilance plan and the risk minimisation plan should be updated to reflect the marketing authorisation holder’s proposals to further investigate the safety concern and minimise the risk.

V.B.14.1. Common modules between periodic safety update report and risk management plan

The proposed PSUR and RMP modular format is intended to minimise duplication by enabling common (sections of) modules to be utilised interchangeably across both reports. Common (sections of) modules are identified in the following table.

Table V.3: Common sections between RMP and PSUR (may not be in identical format)

RMP section	PSUR section
Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”	Section 3 – “Actions taken in the reporting interval for safety reasons”
Part II, module SV – “Post-authorisation experience”, section “Non-study post-authorisation exposure”	Sub-section 5.2 – “Cumulative and interval patient exposure from marketing experience”
Part II, Module SVII – “Identified and potential risks”	Sub-section 16.4 – “Characterisation of risks”
Part II, module SVIII – “Summary of the safety concerns” (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)	Sub-section 16.1 – “Summary of safety concerns”
Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”	Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”

V.B.15. Principles for assessment of risk management plans

The principle points which need to be considered when preparing or reviewing a risk management plan for a medicinal product are:

a. Safety specification

- Have all appropriate parts of the safety specification been included?
- Have all appropriate data been reviewed when compiling the safety specification, i.e. are there important (outstanding) issues from other sections of the dossier which have not been discussed in the safety specification?
- If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
- What are the limitations of the safety database and what reassurance does it provide regarding the safety profile of the medicinal product?
- Are there specific risks in addition to those addressed under ICH-E2E, e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error, etc.?
- Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and missing information) with the product?
- If a generic or hybrid application, have all safety concerns from the reference medicinal product been included in the safety specification?
- Does its place in the therapeutic armamentarium as described concur with the intended indication and current medical practice?

b. Pharmacovigilance plan

- Are all safety concerns from the safety specification covered in the pharmacovigilance plan?

- Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?
- Are the activities in the pharmacovigilance plan clearly defined and described and suitable for identifying or characterising risks or providing missing information?
- Are the safety studies which have been imposed by a competent authority as conditions clearly identified?
- If medication error is a safety concern, does the RMP include appropriate proposals to monitor these?
- Are the proposed additional studies necessary and/or useful?
- When draft protocols are provided, are the proposed studies in the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?
- Are appropriate timelines and milestones defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?

c. Plans for post-authorisation studies on efficacy

- Does the description of the efficacy of the product and what studies and endpoints it was based on conform with the contents of the dossier?
- Do all proposed studies have a valid scientific question as their primary aim and are any designed to increase use of the product)?

d. Risk minimisation measures

- Does the product information adequately reflect all important identified risks and missing information?
- Are any potential risks sufficiently relevant to the safe and effective use of the product that information about them should be included in the product information?
- Is the proposed wording about the risks and location in the product information appropriate and in line with relevant guidelines (e.g. SmPC guideline)?
- Has the marketing authorisation holder considered ways to reduce medication errors?
- Has this been translated into appropriate product information (including device design where appropriate) and pack design?
- Are proposed risk minimisation activities appropriate and adequate?
- Have additional risk minimisation activities been suggested and if so, are they risk proportionate and adequately justified?
- Are the methodologies for measuring and assessing the effectiveness of risk minimisation activities well described and appropriate?
- Have criteria for evaluating the success of additional risk minimisation activities been defined a priori?

e. Summary of the Risk Management Plan

- Is it a true representation of the RMP?

- Have the facts been presented appropriately
- Are the content, format and language suitable for the intended audience?
- Have all required formats been provided?

f. When an update is being assessed

- Have new data been incorporated into the safety specification?
- Have appropriate changes been made to the pharmacovigilance plan (if necessary in the light of new data)?
- Is there an evaluation of the effectiveness of risk minimisation measures?
- Have appropriate changes to risk minimisation measures been proposed if necessary?
- Does the new data suggest that a formal evaluation of the risk-benefit balance (if not already done in a PSUR) is needed?

V.B.16. Quality systems and record management

Although many experts may be involved in writing the RMP, the final responsibility for its quality, accuracy and scientific integrity lies with the marketing authorisation applicant/holder. As such the qualified person responsible for pharmacovigilance in the EU (QPPV) should be aware of, and have sufficient authority over the content. The marketing authorisation holder is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in **Module I**. The marketing authorisation holder should maintain records of when RMPs were submitted to EU competent authorities and the significant changes between each version of the RMP. These records, the RMPs and any documents relating to information within the RMP may be subject to audit and inspection by appropriately qualified pharmacovigilance inspectors.

V.C. Operation of the EU network

Risk management in the EU has historically focused upon the risk reduction approach. In the EU, the legislation uses the terms “risk management system” and “risk management plan.” The chapter on risk management systems for medicinal products for human use in Volume 9A, which this guidance replaces, was based solely on managing risks. However, when considering how to maximise, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit.

V.C.1. Legal basis for the implementation of risk management within the EU

Directive 2001/83/EC and Regulation (EC) No 726/2004 as amended contain many requirements in relation to pharmacovigilance and in particular risk management. The following articles provide the main references in relation to the legal basis for risk management but additional articles may also be relevant:

Directive 2001/83/EC

Article 8 (3), Article 21a, Article 22a, Article 22c, Article 104, Article 106(c), Article 127a

Commission Implementing Regulation (EU) No. 520/512

Article 30, Article 31, Article 32, Articles 33, Annex 1

Regulation (EC) No 726/2004

Article 6, Article 9(4), Article 10a, Articles 23(3), Article 26(c)

Regulation (EC) No 1901/2006

Article 34

Regulation (EC) No 1394/2007

Article 14

V.C.2. Risk management in the EU

As stated above, the overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. Therefore, although the legal provisions primarily relate to risks, public health will be better served by looking at both benefits and risks. Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 and Directive 2010/84/EU amending Directive 2001/83/EC, which apply from July 2012, include provisions for post-authorisation efficacy studies, in addition to post-authorisation safety studies, to be a condition of the marketing authorisation in certain circumstances.

The requirements in the Directive and Regulation are linked to medicinal products. However, to prevent duplication of planning and resource utilisation, the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC provides the possibility for risk management plans to be substance specific. For an individual marketing authorisation holder and applicant, all products containing the same active substance should be included in one RMP [IR Art 30(2)] unless separate presentations are requested by the competent authority or agreed by the same at the request of the applicant/marketing authorisation holder. If the marketing authorisation holder has products in the same substance class authorised under different authorisation routes (i.e. centralised, decentralised), the competent authorities should be notified of this fact and the need for separate RMPs discussed with them. Pragmatic and practical considerations should determine the need for united or separated RMPs.

V.C.3. Situations when a risk management plan should be submitted

An RMP or an update, as applicable, may need to be submitted at any time during a product's life-cycle, i.e. during both the pre- and post-authorisation phases.

Article 8(3)(iaa) requires that for all new marketing applications: the risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned shall be submitted, together with a summary thereof.

Situations, in addition, where a RMP or RMP update will normally be expected include:

- with an application involving a significant change to an existing marketing authorisation:
 - new dosage form;
 - new route of administration;
 - new manufacturing process of a biotechnologically-derived product;
 - paediatric indication;
 - other significant change in indication;

A significant change in indication is a change of authorised indication(s) of a medicinal product where the new treatment target population differs materially from the one for which the medicinal product was previously authorised. This includes (but is not limited to): a new disease area, a new age group (e.g. paediatric indication) or a move from severe disease to a less severely affected population. It may also include a move from 2nd line or other therapy or for an oncology product a change to the concomitant medication specified in the indication.

- at the request of the Agency or national competent authority when there is a concern about a risk affecting the risk-benefit balance;
- with a submission of final study results impacting the RMP;
- with a PSUR for single centrally authorised medicinal product, when the changes to the RMP are a direct result of data presented in the PSUR.

The need for a RMP or an update to the RMP should be discussed with the Agency or national competent authority, as appropriate, well in advance of the submission of an application involving a significant change to an existing marketing authorisation.

An updated RMP should always be submitted if there is a significant change to the risk-benefit balance of one or more medicinal products included in the RMP.

V.C.3.1. Requirements in specific situations

Normally all parts of an RMP should be submitted. However, in certain circumstances as detailed below, in line with the concept of proportionality, certain parts or modules may be omitted (see Figure V.3) unless otherwise requested by the competent authority. However, any safety concerns identified in a reference medicinal product in a module which is omitted from the risk management plan of a generic should be included in RMP module SVIII unless clearly no longer relevant.

a. New applications involving generic medicinal products

For new applications under Article 10(1) of Directive 2001/83/EC, RMP modules SI – SVII may be omitted. RMP module SVIII should be based on the safety concerns of the reference medicinal product unless the generic differs significantly in properties which could relate to safety, or unless requested otherwise by the Agency or national competent authority. Provided the reference medicinal product does not have any additional pharmacovigilance activities or efficacy studies imposed as a condition of the marketing authorisation, RMP parts III and IV may be omitted. Part VI should be based on an appropriately modified version of the public summary of the reference medicinal product.

Further guidance will be provided for situations where the reference medicinal product does not have a RMP.

For updates to the RMP, RMP module SV should be included.

b. New applications under Article 10c "informed consent"

For new applications under Article 10c of Directive 2001/83/EC, the RMP should be the same as the RMP of the cross-referred medicinal product. A RMP will still be required even if the cross-referred product does not have a RMP.

c. New applications involving hybrid or fixed combination medicinal products

For new applications under Article 10(3) or Article 10b of Directive 2001/83/EC, only the data on the fixed combination or data relating to the differences compared with the reference medicinal product need be supplied for RMP modules SII and SIII.

d. New applications under Article 10a "well established medicinal use"

For new applications under Article 10a of Directive 2001/83/EC, RMP modules SII - SIV may be omitted.

e. New applications for a product with new indications where the marketing authorisation applicant already has products with the same active substance authorised for 10 years

When an application for a new medicinal product, is for the same active substance for which the marketing authorisation applicant already has one or more existing authorised and marketed product(s) and

1. the provisions of "well established medicinal use" cannot be met; and
2. the marketing authorisation applicant does not have a risk management plan for any product containing the active substance; and
3. the currently authorised products were placed on the market in the EU 10 or more years prior to the application.

Clinical trial data relating to the already authorised product(s) may be omitted from RMP module SIII and RMP module SIV should be written only in reference to the target population(s) of the new application unless requested otherwise by the competent authority. However, data from experience of the use of the already authorised medicinal products in the special populations which are the subject of RMP module SIV may be included.

Figure V.3. Requirements for new marketing applications

Type of new application	Part I	Part II-Module SI	Part II-Module SII	Part II-Module SIII	Part II-Module SIV	Part II-Module SV	Part II-Module SVI	Part II-Module SVII	Part II-Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓								✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
"Well established use"	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
"Same active substance"	✓	✓	*	*	*	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Application under Article 10(c) of Directive 2001/83/EC

^ May be omitted under certain circumstances

* Modified requirement

f. Initial risk management plan for medicinal products on the market in the EU for 10 years

Unless otherwise requested by the Agency or competent authority, marketing authorisation holders required to submit an initial RMP for a marketed product may omit modules SIII and SIV provided the following conditions are met:

1. the product was placed on the market 10 or more years before the requirement for an RMP is established; and
2. the requirement for an RMP is not due to an application for a significant change to an existing marketing authorisation.

If condition 2 cannot be met, clinical trial data relating to this change should be supplied in RMP module SIII but RMP module SIV may be omitted. Discussion of the existing post-authorisation data and its applicability to the target population should be extensively discussed in RMP module SV.

V.C.4. Submission of the risk management plan

Currently, for centrally authorised products, the RMP is submitted as PDF files within the eCTD submission. Following a Commission Decision where the procedure has involved the submission of an RMP, marketing authorisation holders submit the RMP annex I in XML format within a specified timescale. RMP annex I provides the key information regarding the RMP in a structured electronic format which, following validation at the Agency, is uploaded into an Agency database which is accessible and searchable by the Agency and national competent authorities. The system for nationally authorised products varies by Member State.

The Agency is charged with setting up and maintaining a repository for PSURs in collaboration with competent authorities in Member States and the European Commission (see **Module VII**). It is anticipated that this will contain an RMP module. In the interim period, details of submission requirements and the electronic format will be provided on the Agency and Member State websites as appropriate.

The initial RMP should be submitted as part of the initial marketing authorisation, or if required, for those products that do not have an RMP, through the appropriate post-authorisation procedure.

Post-authorisation, submission of a new or updated RMP outside of another regulatory procedure constitutes a variation in accordance with the **Guidelines on Variations**¹⁴. For detailed guidance on relevant variation categories and their classification, please also refer to the Agency's **Practical Questions and Answers** to support the implementation of the **Guidelines on Variations** in the centralised procedure.

V.C.5. Updates to the risk management plan

If an RMP has previously been submitted by the applicant/marketing authorisation holder for the active substance, any following submissions shall be in the form of an update unless requested otherwise. Each submission of the RMP shall have a distinct version number and shall be dated. This applies whether the entire RMP or only a part or module is being submitted [IR Art 32(2)]. When technically

¹⁴ Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.

feasible, clean and track change versions should be submitted along with a cover letter detailing the changes since the last submitted version.

There will no longer be scheduled "routine" updates to the RMP. In exceptional cases, when justified by risk, the competent authority may still specify a date for submission of the next RMP as a condition of the marketing authorisation.

It is the responsibility of the marketing authorisation holder to monitor the safety profile of the product(s) and to update and submit the RMP if there is a significant change to the risk-benefit balance of one or more medicinal products included in the RMP. A significant change would, in particular, usually include extension of indications, clinically important changes to the product information, reaching an important pharmacovigilance milestone and also certain new strengths and formulations.

An updated RMP should now be submitted:

- at the request of the Agency or a national competent authority;
- whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the risk-benefit balance or as a result of an important pharmacovigilance or risk minimisation milestone being reached.

If, when preparing a PSUR, there is a need for consequential changes to the RMP as a result of new safety concerns, or other data, then an updated RMP should be submitted at the same time. In this case no stand-alone RMP variation is necessary.

Should only the timing for submission of both documents coincide, but the changes are not related to each other, the RMP submission should be handled as a stand-alone variation.

However, in the context of a PSUR EU single assessment (PSUSA), as an interim measure, submission of RMP updates cannot be accepted together with the PSURs of medicinal products (centrally and/or nationally authorised). Marketing authorisation holders should take the opportunity of another upcoming procedure to update their RMP. Alternatively marketing authorisation holders should submit a separate variation to update their RMP. (See also [Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure¹⁵](#)).

For nationally authorised medicinal products, RMP updates should be submitted to the national competent authority for assessment.

When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable (see [V.B.11.4.](#)).

V.C.5.1. Updates to the risk management plan submitted during a procedure

A medicinal product can only have one "current" version of a RMP. If a medicinal product has more than one procedure in process at the same time which requires submission of a RMP, ideally a combined RMP should be submitted with appropriate separation of data in RMP module SIII. In certain circumstances, when this is not possible or practical, there may be more than one version of the RMP under evaluation at a time.

If several updates to the RMP are submitted during the course of a procedure, the version considered as the "current" RMP for future updates and track changes purposes, shall be the last one submitted

¹⁵

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000104.jsp&mid=WC0b01ac0580025b88

before the Opinion. For example, in the final weeks before the Opinion, the RMP may be updated several times to reflect on-going PRAC and CHMP discussions, e.g. changed indications, changes in SmPC wording which affect risk minimisation.

Following the finalisation of the procedure, the final version of the RMP should be provided in eCTD. For centrally authorised procedures, the final RMP agreed at the time of the CHMP Opinion should also be provided as a word document within 15 days of the Opinion. The RMP should reflect the outcome of the procedure – i.e. removal of all references and data which were subject to a negative Opinion. The exception to this requirement is that populations studied in clinical trials related to a negative Opinion may be included in suitably annotated exposure data in RMP module SIII.

Unless requested otherwise, for RMPs updated during (after the start) of a procedure, track changes should show changes since the start of the procedure whilst the cover letter should show changes since the last version was submitted.

V.C.6. Procedure for the assessment of the risk management plan within the EU

Within the EU, the regulatory oversight of RMPs for products authorised either centrally or in more than one Member State lies with the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC appoints a PRAC rapporteur for an individual RMP who works closely with the (Co-)Rapporteur(s) appointed by the CHMP or with the Reference Member State. Further guidance on the details of the process will be added later.

The EMA may, on a case-by-case basis, consult with healthcare professionals and patients during the assessment of RMPs to gather their input on proposed risk minimisation measures.

V.C.7. Implementation of additional risk minimisation activities for centrally authorised products

Centrally authorised products have one marketing authorisation for the whole of the EU. However, individual Member States may have very different health systems and medical practice may differ between Member States so the conditions and restrictions in the marketing authorisation may be implemented in different ways depending upon national customs. For this reason there will be two Commission Decisions – one addressed to the marketing authorisation holder describing the key elements of any conditions and/or restrictions that the marketing authorisation holder must implement, and one addressed to the Member States giving the Member States the responsibility for ensuring that the key elements described in the conditions and/or restrictions are implemented by the marketing authorisation holder in their territory. How these key elements are implemented in each Member State is a matter for discussion and agreement between the national competent authority and the marketing authorisation holder. For centrally authorised products which are likely to require major risk minimisation activities, marketing authorisation holders are encouraged to discuss the feasibility of how they might be implemented with individual national competent authorities during the building of the risk minimisation plan.

For products with additional risk minimisation activities, it is the responsibility of the marketing authorisation holder and national competent authority to ensure that all conditions or restrictions with regard to the safe use of the product are complied with prior to the launch of the product in a particular territory.

Marketing authorisation holders are responsible for ensuring compliance with the conditions of the marketing authorisation for their product wherever it is used within the European Economic Area (EEA).

National competent authorities should also ensure that any conditions or restrictions with regard to the safe and effective use of a centrally authorised product are applied within their territory regardless of the source of the product.

V.C.8. Transparency

The Agency and Member States shall make publically available public assessment reports and summaries of risk management plans [REG Art 26(1), DIR Art 106].

For centrally authorised products the Agency will:

- make public a summary of the RMP;
- include tables relating to the RMP in the European Public Assessment Report (EPAR) including the product information and any conditions of the marketing authorisation.

To promote public health, the Agency will make available (either on request or via its web portal):

- any questionnaires included in RMPs for centrally authorised products which are used to collect information on specified adverse reactions;
- details, which may include copies, of educational material or other additional risk minimisation activities required as a condition of the marketing authorisation;
- details of disease or substance registries requested as part of the pharmacovigilance plan for centrally authorised products.

The national competent authorities will provide details of how they intend to implement Article 106 of Directive 2001/83/EC.

Appendix J: Management and Reporting of Adverse Reactions to Medicinal Products

8 September 2014
EMA/873138/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1)

Date for coming into effect of first version	2 July 2012
Draft Revision 1* finalised by the Agency in collaboration with Member States	28 May 2013
Draft Revision 1 agreed by ERMS FG	29 May 2013
Draft Revision 1 adopted by Executive Director	6 June 2013
Released for public consultation	7 June 2013
End of consultation (deadline for comments)	5 August 2013
Revised draft Revision 1 finalised by the Agency in collaboration with Member States	16 July 2014
Revised draft Revision 1 agreed by ERMS FG	31 August 2014
Revised draft Revision 1 adopted by Executive Director as final	8 September 2014
Date for coming into effect of Revision 1 <u>Note:</u> New requirements for non-interventional post-authorisation studies will become mandatory for any new study started after 1 January 2015. Implementation for new or ongoing studies started before that date is optional.	16 September 2014

* Note: Revision 1 contains the following:

- Revisions in VI.A.2.1.1. (Causality), VI.A.2.4. (Seriousness), VI.B.1.2. (Solicited reports), VI.B.3. (Follow-up of reports), VI.B.6.3. (Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure), VI.C.1. (Reporting rules for clinical trials and post-authorisation studies in the EU), VI.C.2.2.2. (Solicited reports), VI.C.6.2.3.7. (Reports of suspected adverse reactions originating from organised data collection systems and other systems);
- Clarifications on the clock start for the reporting of valid ICSRs in VI.B.7.;
- Clarifications on the handling of ICSRs when reported in an official language in VI.C.6.2.2.9.;
- Replacements of tables highlighting interim arrangements applicable to marketing authorisation holders in VI.App.3.1.1.;
- Correction in VI.C.2.2.9. (Period during a public health emergency).

See websites for contact details



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VI.A. Introduction

VI.A.1. Scope

This Module of GVP addresses the legal requirements detailed in Title IX of Directive 2001/83/EC [DIR] and chapter 3 of Regulation (EC) No 726/2004 [REG], which are applicable to competent authorities in Member States, marketing authorisation holders and the Agency as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU). Recommendations regarding the reporting of emerging safety issues or of suspected adverse reactions occurring in special situations are also presented in this Module. The requirements provided in chapters IV, V and IX of the Commission Implementing Regulation (EU) No 520/2012 [IR] shall be applied in this Module.

The guidance provided in this Module does not address the collection, management and reporting of events or patterns of use, which do not result in suspected adverse reactions (e.g. asymptomatic overdose, abuse, off-label use, misuse or medication error) or which do not require to be reported as individual case safety report or as emerging safety issues. This information may however need to be collected and presented in periodic safety update reports for the interpretation of safety data or for the benefit risk evaluation of medicinal products. In this aspect, guidance provided in [Module VII](#) applies.

All applicable legal requirements detailed in this Module are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

VI.A.2. Terminology

The definitions provided in Article 1 of Directive 2001/83/EC shall be applied for the purpose of this Module; of particular relevance are those provided in this Section. Some general principles presented in the ICH-E2A and ICH-E2D guidelines (see [GVP Annex IV](#)) should also be adhered to; they are included as well in this Section (see [GVP Annex I](#) for all definitions applicable to GVP).

VI.A.2.1. Adverse reaction

An adverse reaction is a response to a medicinal product which is noxious and unintended [DIR Art 1]. This includes adverse reactions which arise from:

- the use of a medicinal product within the terms of the marketing authorisation;
- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- occupational exposure.

VI.A.2.1.1. Causality

In accordance with ICH-E2A (see [GVP Annex IV](#)), the definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, as detailed in ICH-E2D (see [GVP Annex IV](#)), if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore all

spontaneous reports notified by healthcare professionals¹ or consumers² are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.

VI.A.2.1.2. Overdose, off-label use, misuse, abuse, occupational exposure

a. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

b. Off-label use

This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.

c. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.

d. Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects [DIR Art 1].

e. Occupational exposure

This refers to the exposure to a medicinal product (as defined in [DIR Art 1]), as a result of one's professional or non-professional occupation.

VI.A.2.2. Medicinal product

A medicinal product is characterised by any substance or combination of substances,

- presented as having properties for treating or preventing disease in human beings; or
- which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [DIR Art 1].

In accordance with Article 107 of Directive 2001/83/EC, the scope of this module is not only applicable to medicinal products authorised in the EU but also to any such medicinal products commercialised outside the EU by the same marketing authorisation holder (see [VI.C.2.2.](#)). Given that a medicinal product is authorised with a defined composition, all the adverse reactions suspected to be related to any of the active substances being part of a medicinal product authorised in the EU should be managed in accordance with the requirements presented in this module. This is valid independently of the strengths, pharmaceutical forms, routes of administration, presentations, authorised indications, or trade names of the medicinal product.

The guidance provided in this Module also applies, subject to amendments where appropriate, to medicinal products supplied in the context of compassionate use (see [VI.C.1.2.2.](#)) as defined in Article

¹ See [VI.A.2.3.](#) for definition of primary source

83(2) of Regulation (EC) No 726/2004. As the case may be, this guidance may also apply to named patient use as defined under Article 5(1) of Directive 2001/83/EC.

VI.A.2.3. Primary source

The primary source of the information on a suspected adverse reaction(s) is the person who reports the facts. Several primary sources, such as healthcare professionals and/or a consumer, may provide information on the same case. In this situation, all the primary sources' details, including the qualifications, should be provided in the case report, with the "Primary source(s)" section repeated as necessary in line with ICH-E2B(R2) (see GVP Annex IV)².

In accordance with the ICH-E2D (see GVP Annex IV),

- a healthcare professional is defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations;
- a consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, relative of a patient or carer.

Medical documentations (e.g. laboratory or other test data) provided by a consumer that support the occurrence of the suspected adverse reaction, or which indicate that an identifiable healthcare professional suspects a reasonable possibility of causal relationship between a medicinal product and the reported adverse event, are sufficient to consider the spontaneous report as confirmed by a healthcare professional.

If a consumer initially reports more than one reaction and at least one receives medical confirmation, the whole report should be documented as a spontaneous report confirmed by a healthcare professional and be reported accordingly. Similarly, if a report is submitted by a medically qualified patient, friend, relative of the patient or carer, the case should also be considered as a spontaneous report confirmed by a healthcare professional.

VI.A.2.4. Seriousness

As described in ICH-E2A (see GVP Annex IV), a serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

The characteristics/consequences should be considered at the time of the reaction to determine the seriousness of a case. For example, life-threatening refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical judgement should be exercised in deciding whether other situations should be considered as serious reactions. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered as serious³. The EudraVigilance Expert Working Group has co-ordinated the development of an important medical event (IME) terms list based on the Medical Dictionary for Regulatory Activities (MedDRA) (see GVP Annex IV). This IME list aims to facilitate the classification of suspected adverse reactions, the analysis of aggregated data and the assessment of the individual case safety reports (ICSRs) in the framework of the day-to-day pharmacovigilance activities. The IME list is intended for

² See VI.C.6 as regards the electronic reporting of ICSRs in the EU.

³ Examples are provided in section II.B of ICH-E2A (see GVP Annex IV).

guidance purposes only and is available on the EudraVigilance web site⁴ to stakeholders who wish to use it for their pharmacovigilance activities. It is regularly updated in line with the latest version of MedDRA.

VI.A.2.5. Individual case safety report (ICSR)

This refers to the format and content for the reporting of one or several suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspect medicinal product.

VI.B. Structures and processes

Section B of this Module highlights the general principles in relation to the collection, recording and reporting of reports of suspected adverse reactions associated with medicinal products for human use, which are applicable to competent authorities and marketing authorisation holders. The definitions and recommendations provided in [VI.A](#) should be followed. EU requirements are presented in [VI.C](#).

VI.B.1. Collection of reports

Competent authorities and marketing authorisation holders should take appropriate measures in order to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from unsolicited or solicited sources.

For this purpose, a pharmacovigilance system should be developed to allow the acquisition of sufficient information for the scientific evaluation of those reports.

The system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment.

All notifications that contain pharmacovigilance data should be recorded and archived in compliance with the applicable data protection requirements (see [VI.C.6.2.2.8](#) for EU requirements).

The system should also be structured in a way that allows for reports of suspected adverse reactions to be validated (see [VI.B.2](#)) in a timely manner and exchanged between competent authorities and marketing authorisation holders within the legal reporting time frame (see [VI.B.7.1](#)).

In accordance with the ICH-E2D (see [GVP Annex IV](#)), two types of safety reports are distinguished in the post-authorisation phase; reports originating from unsolicited sources and those reported as solicited.

VI.B.1.1. Unsolicited reports

VI.B.1.1.1. Spontaneous reports

A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. Regional Pharmacovigilance Centre, Poison Control Centre) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection systems where adverse events reporting is actively sought, as defined in [VI.B.1.2](#).

⁴ <http://eudravigilance.ema.europa.eu/human/textforIME.asp>.

Stimulated reporting that occurs consequent to a direct healthcare professional communication (see [Module XV](#)), publication in the press, questioning of healthcare professionals by company representatives, communication from patients' organisations to their members, or class action lawsuits should be considered spontaneous reports.

Unsolicited consumer adverse reactions reports should be handled as spontaneous reports irrespective of any subsequent "medical confirmation".

The reporting modalities and applicable time frames for spontaneous reports are described in [VI.B.7.](#) and [VI.B.8.](#)

VI.B.1.1.2. Literature reports

The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorisation holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. The marketing authorisation holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties⁵. In addition, marketing authorisation holders should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the company safety department as appropriate.

Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by marketing authorisation holders to identify and record ICSRs originating from spontaneous reports or non-interventional post-authorisation studies.

If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be considered by the concerned marketing authorisation holder(s).

Valid ICSRs should be reported according to the modalities detailed in [VI.B.7.](#) and [VI.B.8.](#)

One case should be created for each single patient identifiable based on characteristics provided in [VI.B.2.](#) Relevant medical information should be provided and the publication author(s) should be considered as the primary source(s).

EU specific requirements, as regards medicinal products and scientific and medical publications, which are not monitored by the Agency and for which valid ICSRs shall be reported by marketing authorisation holders, are provided in [VI.C.2.2.3.](#)

VI.B.1.1.3. Reports from other sources

If a marketing authorisation holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be handled as a spontaneous report. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR. The same reporting time frames should be applied as for other spontaneous reports.

⁵ See [VI. Appendix 2.](#) for the detailed guidance on the monitoring of medical and scientific literature.

VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media

Marketing authorisation holders should regularly screen internet or digital media⁶ under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the marketing authorisation holder⁷. The frequency of the screening should allow for potential valid ICSRs to be reported to the competent authorities within the appropriate reporting timeframe based on the date the information was posted on the internet site/digital medium. Marketing authorisation holders may also consider utilising their websites to facilitate the collection of reports of suspected adverse reactions (see [VI.C.2.2.1.](#)).

If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in any non-company sponsored digital medium, the report should be assessed to determine whether it qualifies for reporting.

Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied (see [VI.B.7.](#)).

In relation to cases from the internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., an email address under a valid format has been provided). If the country of the primary source is missing, the country where the information was received, or where the review took place, should be used as the primary source country.

VI.B.1.2. Solicited reports

As defined in ICH-E2D (see [GVP Annex IV](#)), solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or named patient use, or information gathering on efficacy or patient compliance. Reports of suspected adverse reactions obtained from any of these data collection systems should not be considered spontaneous. This is with the exception of:

- suspected adverse reactions in relation to those adverse events for which the protocol of non-interventional post-authorisation studies provides differently and does not require their systematic collection (see [VI.C.1.2.1.](#)),
- suspected adverse reactions originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is not required (see [VI.C.1.2.2.](#)).

For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they refer to suspected adverse reactions and therefore meet the criteria for reporting.

⁶ Although not exhaustive, the following list should be considered as digital media: web site, web page, blog, vlog, social network, internet forum, chat room, health portal.

⁷ A donation (financial or otherwise) to an organisation/site by a marketing authorisation holder does not constitute ownership, provided that the marketing authorisation holder does not control the final content of the site.

General reporting rules for suspected adverse reactions occurring in organised data collection systems conducted in the EU under the scope of Directive 2001/83/EC, Regulation (EC) No 726/2004 or Directive 2001/20/EC, are presented in [VI.C.1.](#)

VI.B.2. Validation of reports

Only valid ICSRs qualify for reporting. All reports of suspected adverse reactions should therefore be validated before reporting them to the competent authorities to make sure that the minimum criteria for reporting are included in the reports (see ICH-E2D (see [GVP Annex IV](#))). These are:

- one or more identifiable reporter (primary source), characterised by qualification (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional) name, initials or address⁸. Whenever possible, contact details for the reporter should be recorded so that follow-up activities can be performed. However, if the reporter does not wish to provide contact details, the ICSR should still be considered as valid providing the organisation who was informed of the case was able to confirm it directly with the reporter. All parties providing case information or approached for case information should be identifiable, not only the initial reporter.
- one single identifiable patient characterised by initials, patient identification number, date of birth, age, age group or gender. The information should be as complete as possible⁹.
- one or more suspected substance/medicinal product (see [VI.A.2.2.](#)).
- one or more suspected adverse reaction (see [VI.A.2.1.](#)). If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the receiver (competent authority or marketing authorisation holder) agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete¹⁰. The report does not also qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information provided on the type of adverse reaction experienced. Similarly, the report is not valid if only an outcome (or consequence) is notified and (i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or (ii) the primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance a marketing authorisation holder is made aware that a patient was hospitalised or died, without any further information. In this particular situation, medical judgement should always be applied in deciding whether the notified information is an adverse reaction or an event. For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and reported.

The lack of any of these four elements means that the case is considered incomplete and does not qualify for reporting. Competent authorities and marketing authorisation holders are expected to exercise due diligence in following up the case to collect the missing data elements. Reports, for which the minimum information is incomplete, should nevertheless be recorded within the pharmacovigilance system for use in on-going safety evaluation activities. Recommendations on the electronic reporting of valid ICSRs, when missing information has been obtained, are provided in [VI.C.6.2.3.8.](#)

When collecting reports of suspected adverse reactions via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a reporter and a patient (see [VI.B.1.1.4.](#)).

⁸ Local data privacy laws regarding patient’s and reporter’s identifiability might apply.

⁹ See Footnote 9.

¹⁰ There is no suspected adverse reaction.

When one party (competent authority or a marketing authorisation holder) is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR¹¹.

A valid case of suspected adverse reaction initially submitted by a consumer cannot be downgraded to a report of non-related adverse event if the contacted healthcare professional (nominated by the consumer for follow-up information) disagrees with the consumer's suspicion (see [VI.A.2.1.1.](#)). In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR. Guidance on the reporting of the medical confirmation of a case, provided in ICH-E2B(R2) Section A.1.14 ("Was the case medically confirmed, if not initially from a healthcare professional?") (see [GVP Annex IV](#)), should be followed.

For solicited reports of suspected adverse reactions (see [VI.B.1.2.](#)), where the receiver disagrees with the reasonable possibility of causal relationship between the suspected medicinal product and the adverse reaction expressed by the primary source, the case should not be downgraded to a report of non-related adverse event. The opinions of both, the primary source and the receiver, should be recorded in the ICSR.

The same principle applies to the ICSR seriousness criterion, which should not be downgraded from serious to non-serious if the receiver disagrees with the seriousness reported by the primary source.

VI.B.3. Follow-up of reports

When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum information (see [VI.B.2.](#)). Any attempt to obtain follow-up information should be documented.

Follow-up methods should be tailored towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern. The use of targeted specific forms in the local language should avoid requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting. Therefore, consideration should be given to pre-populating some data fields in those follow-up report forms to make their completion by the primary source easy.

When information is received directly from a consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information. When such a case, initially reported by a consumer, has been confirmed (totally or partially) by a healthcare professional, this information should be clearly highlighted in the ICSR¹².

For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch

¹¹ For further guidance on reporting of other duplicate ICSRs, refer to section A.1.11 "Other case identifiers in previous transmission" of ICH-E2B(R2) (see [GVP Annex IV](#)).

¹² For further guidance on reporting this information, refer to ICH-E2B(R2), section A.1.14 ("Was the case medically confirmed, if not initially from a healthcare professional?") (see [GVP Annex IV](#)).

number. A business process map in relation to the mandatory follow-up of information for the identification of suspected biological medicinal products is presented in [VI.Appendix 1](#).

For cases related to vaccines, [GVP P.1](#), should also be followed as appropriate.

VI.B.4. Data management

Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability and in accordance with local data privacy laws. Confidentiality of patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting healthcare professionals should be kept in confidence. With regards to patient's and reporter's identifiability, case report information should be transmitted between stakeholders (marketing authorisation holders or competent authorities) in accordance with local data privacy laws (see [VI.C.6.2.2.8](#) for the processing of personal data in ICSRs in the EU).

In order to ensure pharmacovigilance data security and confidentiality, strict access controls should be applied to documents and to databases to authorised personnel only. This security extends to the complete data path. In this aspect, procedures should be implemented to ensure security and non-corruption of data during data transfer.

When transfer of pharmacovigilance data occurs within an organisation or between organisations having concluded contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.

Correct data entry, including the appropriate use of terminologies, should be verified by quality assurance auditing, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency confirmed.

Data received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as imputations should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source or an accurate translation of it. The original verbatim text should be coded using the appropriate terminology as described in [VI.B.8](#). In order to ensure consistency in the coding practices, it is recommended to use, where applicable, the translation of the terminology in the local language to code the verbatim text.

Electronic data storage should allow traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

A procedure should be in place to account for identification and management of duplicate cases at data entry and during the generation of aggregated reports (see [VI.C.6.2.4](#)).

VI.B.5. Quality management

Competent authorities and marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR reporting and case archiving (see [VI.C.6.2.4](#) and [Module I](#)). Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. In this aspect, the source data (e.g., letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible.

Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

Staff directly performing pharmacovigilance activities, should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures.

VI.B.6. Special situations

VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding

a. Pregnancy

Reports, where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. The recommendations provided in the [Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data](#) (see [GVP Annex III](#)) should be considered as regard the monitoring, collection and reporting of information in these specific situations in order to facilitate the scientific evaluation. When an active substance (or one of its metabolites) has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the medicinal product was taken before conception.

Not infrequently, pregnant women or healthcare professionals will contact either competent authorities or marketing authorisation holders to request information on the teratogenicity of a medicinal product and/or experience of use during pregnancy. Reasonable attempts should be made to obtain information on any possible medicinal product exposure to an embryo or foetus and to follow-up on the outcome of the pregnancy.

Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product. In this context the use of standard structured questionnaires is recommended.

Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported, in accordance with the requirements outlined in [VI.B.7](#).¹³

This especially refers to:

- reports of congenital anomalies or developmental delay, in the foetus or the child;
- reports of foetal death and spontaneous abortion; and
- reports of suspected adverse reactions in the neonate that are classified as serious.

¹³ See [VI.C.6.2.3.1](#) for electronic reporting recommendations in the EU.

Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome, should not be reported since there is no suspected adverse reaction. These reports should however be collected and discussed in the periodic safety update reports (see [Module VII](#)).

However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate to be reported. This may be a condition of the marketing authorisation or stipulated in the risk management plan; for example pregnancy exposure to medicinal products contraindicated in pregnancy or medicinal products with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin).

A signal of a possible teratogen effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the competent authorities in accordance with the recommendations presented in [VI.C.2.2.6](#).

b. Breastfeeding

Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported in accordance with the criteria outlined in [VI.B.7](#).¹⁴

VI.B.6.2. Use of a medicinal product in a paediatric or elderly population

The collection of safety information in the paediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population.

As regards the paediatric population, the guidance published by the Agency¹⁵ on the conduct of pharmacovigilance in this population should be followed.

VI.B.6.3. Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure

For the purpose of this Module, medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or consumer.

Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported as ICSRs. They should be considered in periodic safety update reports as applicable. When those reports constitute safety issues impacting on the risk-benefit balance of the medicinal product, they should be notified to the competent authorities in accordance with the recommendations provided in [VI.C.2.2.6](#).

Reports associated with suspected adverse reactions should be subject to reporting in accordance with the criteria outlined in [VI.B.7](#) and with the electronic reporting requirements described in [VI.C.6.2.3.3](#). They should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, context of occurrence (e.g., error in prescription, administration, dispensing, dosage, unauthorised indication or population, etc.).

¹⁴ See Footnote 16.

¹⁵ [Guideline on conduct of pharmacovigilance for medicines used by the paediatric population](#).

VI.B.6.4. Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy should be recorded and followed-up if incomplete. They should not normally be reported, but should be discussed in periodic safety update reports as applicable. However, in certain circumstances, reports of lack of therapeutic efficacy may require to be reported within a 15-day time frame (see [VI.C.6.2.3.4](#) as regards electronic reporting in the EU). Medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases. This applies unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the medicinal product.

Clinical judgement should be used when considering if other cases of lack of therapeutic efficacy qualify for reporting. For example, an antibiotic used in a life-threatening situation where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, a life-threatening infection, where the lack of therapeutic efficacy appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be reported within 15 days.

For vaccines, cases of lack of therapeutic efficacy should be reported, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of therapeutic efficacy by a healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorisation safety studies as appropriate. General guidance regarding the monitoring of vaccines failure, provided in the [Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance](#)¹⁶, may be followed.

VI.B.7. Reporting of Individual case safety reports (ICSRs)

Only valid ICSRs (see [VI.B.2.](#)) should be reported. The clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the national or regional pharmacovigilance centre of a competent authority or of any personnel of the marketing authorisation holder, including medical representatives and contractors. This date should be considered as day zero. It is the first day when a receiver gains knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. Reporting timelines are based on calendar days.

Where the marketing authorisation holder has set up contractual arrangements with a person or an organisation, explicit procedures and detailed agreements should exist between the marketing authorisation holder and the person/organisation to ensure that the marketing authorisation holder can comply with the reporting obligations. These procedures should in particular specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the competent authorities.

For ICSRs described in the scientific and medical literature (see [VI.B.1.1.2.](#)), the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where contractual arrangements are made with a person/organisation to perform literature searches and/or report valid ICSRs, detailed agreements should exist to ensure that the marketing authorisation holder can comply with the reporting obligations.

¹⁶ Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012. <http://www.cioms.ch/>

When additional significant information is received for a previously reported case, the reporting time clock starts again for the submission of a follow-up report from the date of receipt of the relevant follow-up information. For the purpose of reporting, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case or could change its seriousness criteria; non-significant information includes updated comments on the case assessment or corrections of typographical errors in the previous case version. See also [VI.C.6.2.2.7](#) as regards the distinction between significant and non-significant follow-up information.

VI.B.7.1. Reporting time frames

In general, the reporting of serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information by the national or regional pharmacovigilance centre of a competent authority or by any personnel of the marketing authorisation holder, including medical representatives and contractors. This applies to initial and follow-up information. Where a case initially reported as serious becomes non-serious, based on new follow-up information, this information should still be reported within 15 days; the reporting time frame for non-serious reports should then be applied for the subsequent follow-up reports.

Information as regards the reporting time frame of non-serious valid ICSRs in the EU is provided in [VI.C.3](#).

VI.B.8. Reporting modalities

Taking into account the international dimension of adverse reactions reporting and the need to achieve harmonisation and high quality between all involved parties, ICSRs should be submitted electronically as structured data with the use of controlled vocabularies for the relevant data elements where applicable. In this aspect, with regard to the content and format of electronic ICSRs, competent authorities and marketing authorisation holders should adhere to the following internationally agreed ICH¹⁷ guidelines and standards:

- ICH M1 terminology - Medical Dictionary for Regulatory Activities (MedDRA) (see [GVP Annex IV](#));
- MedDRA Term Selection: Points to Consider Document - The latest version of the ICH-endorsed Guide for MedDRA Users (see [GVP Annex IV](#));
- ICH M2 EWG - Electronic Transmission of Individual Case Safety Reports Message Specification (see [GVP Annex IV](#));
- ICH E2B(R2) - Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (see [GVP Annex IV](#));
- ICH E2B Implementation Working Group - Questions & Answers (R5) (March 3, 2005) (see [GVP Annex IV](#)).

As technical standards evolve over time, the above referred documents may require revision and maintenance. In this context, the latest version of these documents should always be taken into account.

Information regarding EU specific reporting modalities is provided in [VI.C.4](#).

¹⁷ <http://www.ich.org/>

VI.C. Operation of the EU network

Section C of this Module highlights the EU specific requirements, as defined in Directive 2001/83/EC and Regulation (EC) No 726/2004, in relation to the collection, management and reporting of reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the EU, independently of their condition of use. They are applicable to competent authorities in Member States and/or to marketing authorisation holders. Section C should be read in conjunction with the definitions and general principles detailed in [VI.A](#) and [VI.B](#) of this Module and with the requirements provided in chapters IV, V and IX of the Commission Implementing Regulation (EU) No 520/2012 [IR].

VI.C.1. Reporting rules for clinical trials and post-authorisation studies in the EU

The pharmacovigilance rules laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004 do not apply to investigational medicinal products and non-investigational medicinal products¹⁸ used in clinical trials conducted in accordance with Directive 2001/20/EC¹⁹.

Post-authorisation safety or efficacy studies requested by competent authorities in Member States or the Agency in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, or conducted voluntarily by marketing authorisation holders, can either be clinical trials or non-interventional post-authorisation studies as shown in Figure VI.1. The safety reporting falls therefore either under the scope of Directive 2001/20/EC for any clinical trials or under the provisions set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 for any non-interventional post-authorisation studies. Suspected adverse reactions should not be reported under both regimes, that is Directive 2001/20/EC as well as Regulation (EC) No 726/2004 and Directive 2001/83/EC as this creates duplicate reports.

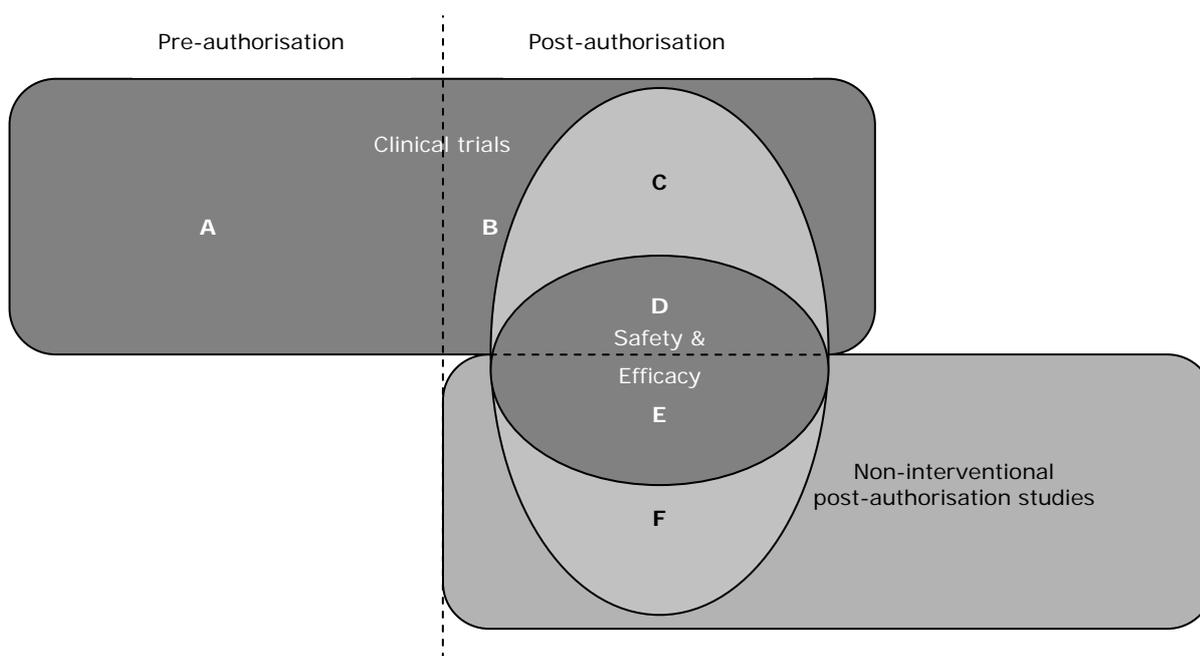
Further guidance on post-authorisation safety studies is provided in [Module VIII](#).

The different types of studies and clinical trials which can be conducted in the EU are illustrated in Figure VI.1. The safety reporting for clinical trials corresponding to sections A, B, C and D of Figure VI.1. follows the requirements of Directive 2001/20/EC. The safety reporting for non-interventional post-authorisation studies corresponding to section E and F follows the requirements of Directive 2001/83/EC and Regulation (EC) No 726/2004. The reporting rules of reports of suspected adverse reactions to the EudraVigilance database modules are dependent on the types of organised collection systems where they occurred; recommendations provided in [VI.C.6.2.1](#) should be followed.

¹⁸ For guidance on these terms, see [The Rules Governing Medicinal Products in the European Union, Volume 10, Guidance Applying to Clinical Trials, Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products \(NIMPs\) \(Ares\(2011\)300458 - 18/03/2011\)](#).

¹⁹ See DIR Art 3(3), Art 107(1) third subparagraph.

Figure VI.1. Diagram illustrating different types of clinical trials and studies in the EU



- Section A: Clinical trials, which fall under the scope of Directive 2001/20/EC and which are conducted when no marketing authorisation exists in the EU.
- Section B: Clinical trials, which fall under the scope of Directive 2001/20/EC and which are conducted in the post-authorisation period, e.g. for new indication.
- Section C: Post-authorisation clinical trials conducted in accordance with the summary of product characteristics (SmPC) indication and condition of use, but which fall under the scope of Directive 2001/20/EC due to the nature of the intervention.
- Section D: Post-authorisation safety or efficacy clinical trials requested in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 or conducted voluntarily by marketing authorisation holders, but which fall under the scope of Directive 2001/20/EC due to the nature of the intervention.
- Section E: Non-interventional post-authorisation safety or efficacy studies requested in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 or conducted voluntarily by the marketing authorisation holders and which follow the same legal requirements.
- Section F: Non-interventional post-authorisation studies conducted in accordance with SmPC indication and condition of use and which fall under the scope of Directive 2001/83/EC or Regulation (EC) No 726/2004.

VI.C.1.1. Reporting rules for clinical trials

A suspected adverse reaction to an investigational medicinal product occurring in a clinical trial which falls under the scope of Directive 2001/20/EC is only to be addressed by the sponsor based on the requirements detailed in that Directive. It is therefore excluded from the scope of this Module even if the clinical trial where the suspected adverse reaction occurred is a post-authorisation safety or efficacy study, requested in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, or conducted voluntarily.

If a clinical trial, conducted under the scope of Directive 2001/20/EC, yields safety concerns which impact on the risk-benefit balance of an authorised medicinal product, the competent authorities in the Member States where the medicinal product is authorised and the Agency should be notified immediately in accordance with the modalities detailed in [VI.C.2.2.6](#). This applies as well if a safety concern arises from a clinical trial conducted exclusively outside the EU.

The safety data from clinical trials to be presented in the relevant sections of the periodic safety update report of the authorised medicinal product are detailed in [Module VII](#).

Where an untoward and unintended response originating from a clinical trial conducted in accordance with Directive 2001/20/EC, is suspected to be related only to a non-investigational medicinal product (or another medicinal product, which is not part of the clinical trial protocol) and does not result from a possible interaction with the investigational medicinal product, it does not follow the expedited reporting requirements of Directive 2001/20/EC, which apply only to the investigational medicinal product. The investigator or the sponsor is encouraged to report the case to the competent authority in the Member State where the reaction occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both to avoid duplicate reporting²⁰. Where made aware of such case, the competent authority or the marketing authorisation holder should apply the reporting requirements described in [VI.C.3](#), [VI.C.4](#) and [VI.C.6](#). As regards electronic reporting, the recommendations detailed in [VI.C.6.2.3.7](#) should be followed.

VI.C.1.2. Reporting rules for non-interventional post-authorisation studies, compassionate use and named patient use

This Section applies to non-interventional post-authorisation studies, compassionate use and named patient use. For these organised data collection schemes, a system should be put in place to record and document complete and comprehensive case information on solicited adverse events²¹ which need to be collected as specified in [VI.C.1.2.1](#), and in [VI.C.1.2.2](#). These adverse events should be systematically assessed to determine whether they are possibly related to the studied (or supplied) medicinal products (see ICH-E2D (see [GVP Annex IV](#))). A method of causality assessment should be applied for assessing the causal role of the studied (or supplied) medicinal products in the solicited adverse events (for example, the [WHO-UMC system for standardised case causality assessment](#)). An adverse event should be classified as an adverse reaction, if there is at least a reasonable possibility of causal relationship. Only valid ICSRs (see [VI.B.2](#)) of adverse reactions, which are suspected to be related to the studied (or supplied) medicinal product by the primary source or the receiver of the case, should be reported in accordance with the requirements provided in [VI.C.3](#), [VI.C.4](#) and [VI.C.6.2.3.7](#). Other reports of adverse events should be summarised as part of any interim safety analysis and in the final study report, where applicable. In situations where adverse reactions are suspected to be related to medicinal products other than the studied (or supplied) medicine, these reports should be managed, classified and reported as spontaneous ICSRs. They should be notified by the primary source to the competent authority in the Member State where the reactions occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

Where made aware, in the frame of these organised data collection schemes, of events which affect the known risk-benefit balance of the studied (or supplied) medicinal product and/or impact on public health, the marketing authorisation holder should notify the concerned competent authorities and the Agency in accordance with the modalities detailed in [VI.C.2.2.6](#).

Further guidance on post-authorisation studies conducted by marketing authorisation holders is provided in [VI.C.2.2.2](#).

The requirements provided in this Module do not apply to non-interventional post-authorisation studies conducted by organisations such as academia, medical research charities or research organisations in the public sector. These organisations should follow local requirements as regards the reporting of cases of suspected adverse reactions to the competent authority in the Member State where the

²⁰ See [The Rules Governing Medicinal Products in the European Union, Volume 10, Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use \('CT-3'\), \(2011/C 172/01\)](#).

²¹ See [GVP Annex I](#) for definition of adverse event.

reaction occurred. However, where a study conducted by one of these organisations is directly initiated, managed, financed, or where its design is controlled by a marketing authorisation holder (voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a of Directive 2001/83/EC and Articles 10 or 10(a) of Regulation 726/2004), the requirements provided in this Module are applicable²². In this context, contractual agreements should be in place to clearly define the role and responsibilities for implementing these requirements (see [Module I](#)).

VI.C.1.2.1. Non-interventional post-authorisation studies

Non-interventional post-authorisation studies²³ should be distinguished between those with primary data collection directly from healthcare professionals or consumers and study designs which are based on the secondary use of data. Depending on the study design, the requirements provided hereafter apply²⁴. In case of doubt, the reporting requirements should be clarified with the concerned competent authorities in Member States. National legislation should be followed as applicable regarding the obligations towards local ethics committees.

a. Non-interventional post-authorisation studies with primary data collection

Information on all adverse events should be collected from healthcare professionals or consumers in the course of the study unless the protocol provides differently with a due justification for not collecting certain adverse events. For all collected adverse events, comprehensive and high quality information should be sought in a manner which allow for valid ICSRs to be reported within the appropriate timeframes (see [VI.C.3.](#)).

For all collected adverse events, cases of adverse reactions, which are suspected to be related to the studied medicinal product by the primary source or the receiver of the case, should be reported in accordance with the requirements provided in [VI.C.3.](#) and [VI.C.4.](#). Valid ICSRs should be classified as solicited reports (see [VI.C.2.2.2.](#) and [VI.C.6.2.3.7.](#)). See summary in [Table VI.1.](#)

All fatal outcomes should be considered as adverse events which should be collected. In certain circumstances, suspected adverse reactions with fatal outcome may not be subject to expedited reporting as ICSRs, for example because they refer to study outcomes (efficacy end points), because the patients included in the study have a disease with high mortality, or because the fatal outcomes have no relation to the objective of the study. For these particular situations, the rationale for not reporting certain adverse reactions with fatal outcomes should be clearly described in the protocol.

All collected adverse events should be summarised as part of any interim safety analysis and in the final study report.

²² This does not concern donation of a medicinal product for research purpose if the marketing authorisation holder has no control on the study.

²³ See [GVP Annex I](#) for definition of non-interventional study.

²⁴ For combined study designs with primary and secondary data collection, the same requirements as for studies with primary data collection should be followed.

Table VI.1. Non-interventional post-authorisation studies with primary data collection: Requirements concerning adverse events collection and suspected adverse reactions reporting.

	Adverse events for which the protocol does not provide differently and those with fatal outcomes
Collection requirements	<ul style="list-style-type: none"> • Collect comprehensive and high quality information. • Perform causality assessment.
Reporting requirements for suspected adverse reactions	<ul style="list-style-type: none"> • Cases of adverse reactions, which are suspected to be related to the studied medicinal product by the primary source or the receiver of the case, should be reported in the form of valid ICSRs in line with the appropriate timeframes (See VI.C.3) • In certain circumstances, fatal outcome may not be subject to expedited reporting as ICSRs. A justification should always be provided in the protocol.
Reporting requirements for adverse events	<ul style="list-style-type: none"> • Summarise all collected adverse events as part of any interim safety analysis and in the final study report.

For adverse events for which the protocol provides differently and does not require their systematic collection, healthcare professionals and consumers should be informed in the protocol (or other study documents) of the possibility to report adverse reactions (for which they suspect a causal role of a medicine) to the marketing authorisation holder of the suspected medicinal product (studied or not) or to the concerned competent authorities via the national spontaneous reporting system. Valid ICSRs should be managed, classified and reported as spontaneous by the receiver of the reports. When made aware of them, these reports should also be summarised in the relevant study reports.

b. Non-interventional post-authorisation studies based on secondary use of data

The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses.

For these studies, the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting.

VI.C.1.2.2. Compassionate use and named patient use

The guidance provided in this Module applies, subject to amendments where appropriate, to medicinal products supplied in the context of compassionate use as defined in Article 83(2) of Regulation (EC) No 726/2004. As the case may be, this guidance may also apply to named patient use as defined under Article 5(1) of Directive 2001/83/EC. Local requirements should be followed as applicable.

Where an organisation²⁵ or a healthcare professional, supplying a medicinal product under compassionate use or named patient use, is notified or becomes aware of an adverse event, it should be managed as follows depending on the requirements in the concerned Member State:

- For compassionate use and named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is required, reports of adverse

²⁵ E.g. sponsor, applicant, marketing authorisation holder, hospital or wholesaler.

reactions, which are suspected to be related to the supplied medicinal product by the primary source or the receiver of the case, should be reported. They should be considered as solicited reports (see [VI.C.2.2.2.](#) and [VI.C.6.2.3.7.](#)).

- For compassionate use and named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is not required, any notified noxious or unintended response to the supplied medicinal product should be reported. It should be considered as a spontaneous report of suspected adverse reaction.

VI.C.2. Collection of reports

VI.C.2.1. Responsibilities of Member States

Each Member State shall have in place a system for the collection and recording of unsolicited and solicited reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, consumers, or marketing authorisation holders²⁶ [DIR Art 101(1) and 107a(1)]. In this context, competent authorities in Member States shall establish procedures for collecting and recording all reports of suspected adverse reactions that occur in their territory [IR Art 15 (2)]. The general principles detailed in [VI.B](#), together with the reporting modalities presented in [VI.C.3](#), [VI.C.4](#) and [VI.C.6](#) should be applied to those reports. Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has expired. However, the documents shall be retained for a longer period where Union law or national law so requires [IR Art 16(2)].

Each Member State shall take all appropriate measures to encourage healthcare professionals and consumers in their territory to report suspected adverse reactions to their competent authority. In addition, the competent authority in a Member State may impose specific obligations on healthcare professionals. To this end, competent authorities in Member States shall facilitate in their territory the reporting of suspected adverse reactions by means of alternative straightforward reporting systems, accessible to healthcare professionals and consumers, in addition to web-based formats [DIR Art 102]. Information on the different ways of reporting suspected adverse reactions related to medicinal products, shall be made publicly available including by means of national medicines web-based portals [DIR 106(e)]. To increase awareness of the reporting systems, organisations representing consumers and healthcare professionals may be involved as appropriate [DIR Art 102].

Standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and consumers shall be developed by the Agency in collaboration with Member States in order to collect across the EU harmonised information relevant for the evaluation of suspected adverse reactions, including errors associated with the use of medicinal products [REG Art 25]. In this context, core data fields for reporting will be made available by the Agency to the competent authorities in Member States for use in their national reporting systems as applicable.

The reports of suspected adverse reactions received from healthcare professionals and consumers should be acknowledged where appropriate and further information should be provided to the reporters as requested and when available.

For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports [DIR Art 107a(2)].

²⁶ Marketing authorisation holders shall report ICSRs to the competent authorities in Member States in accordance with the transitional provisions set out in Article 2(4) and Article 2(5) of Directive 2010/84/EU and further detailed in [VI.C.4.1](#).

Each Member State shall ensure that the competent authority responsible for medicinal products within that Member State is informed of any suspected adverse reaction, brought to the attention of any other authority, body, institution or organisation responsible for patient safety within that Member State, and that valid ICSRs are made available to the EudraVigilance database. Therefore, where reports of suspected adverse reactions are sent directly to other authorities, bodies, organisations and/or institutions within a Member State, the competent authority in that Member State shall have data exchange agreements in place so that these reports are brought to its attention and are made available to EudraVigilance in a timely manner [DIR Art 107a(5)]. This applies as well to reports of suspected adverse reactions arising from an error associated with the use of a medicinal product. Those error reports of suspected adverse reactions for which a competent authority in a Member State is made aware of, including those received from the EudraVigilance database in accordance with Article 24(4) of Regulation (EC) No 726/2004, shall also be brought to the attention of other authorities, bodies, organisations and/or institutions responsible for patient safety within that Member State [DIR Art 107a(5)].

Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions [DIR Art 107a(6)].

VI.C.2.2. Responsibilities of the marketing authorisation holder in the EU

Each marketing authorisation holder shall have in place a system for the collection and recording of all reports of suspected adverse reactions which are brought to its attention, whether reported spontaneously by healthcare professionals or consumers or occurring in the context of a post-authorisation study [DIR Art 104(1), Art 107(1)]. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals [Art 107(2)]. All those reports shall be accessible at a single point within the Union [Dir Art 107(1)].

Marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with the data protection legislation [IR Art 12 (1)]. Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires [IR Art 12 (2)].

With regard to the collection and recording of reports of suspected adverse reactions, marketing authorisation holders responsibilities apply to reports related to medicinal products (see [VI.A.2.2.](#)) for which ownership cannot be excluded on the basis of one the following criteria: medicinal product name, active substance name, pharmaceutical form, batch number or route of administration. Exclusion based on the primary source country or country of origin of the adverse reaction is possible if the marketing authorisation holder can demonstrate that the suspected medicinal product has never been supplied or placed on the market in that territory or that the product is not a travel medicine (e.g., anti-malarial medicinal product).

The marketing authorisation holder shall ensure that any information on adverse reactions, suspected to be related to at least one of the active substances of its medicinal products authorised in the EU, is brought to its attention by any company outside the EU belonging to the same mother company (or group of companies)²⁷. The same applies to the marketing authorisation holder when having

²⁷ As outlined in the Commission Communication on the Community Marketing Authorization Procedures for Medicinal Products ([98/C 229/03](#)).

concluded a commercial agreement with a company outside the EU for one of its medicinal product authorised in the EU. The clock for reporting (see [VI.B.7.](#)) starts when a valid ICSR is first received by one of these companies outside the EU.

In addition to the requirements presented in this Section, the general principles detailed in Section [VI.B.](#), together with the reporting modalities presented in [VI.C.3.](#), [VI.C.4.](#) and [VI.C.6.](#) should be applied by marketing authorisation holders to all reports of suspected adverse reactions.

VI.C.2.2.1. Spontaneous reports

Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which are brought to their attention spontaneously by healthcare professionals, or consumers. This includes reports of suspected adverse reactions received electronically or by any other appropriate means [DIR Art 107(1), Art 107(2)]. In this context, marketing authorisation holders may consider utilising their websites to facilitate the collection of reports of suspected adverse reactions by providing adverse reactions forms for reporting, or appropriate contact details for direct communication (see [VI.B.1.1.4.](#)).

VI.C.2.2.2. Solicited reports

In accordance with Art 107(1) of Directive 2001/83/EC, marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which occur in post-authorisation studies, initiated, managed, or financed by them²⁸. For non-interventional post-authorisation studies, this requirement applies to study designs based on primary data collection and the guidance provided in [VI.C.1.2.1.](#) should be followed. For all solicited reports (see [VI.B.1.2.](#)), marketing authorisation holders should have mechanisms in place to record and document complete and comprehensive case information and to evaluate that information, in order to allow meaningful assessment of individual cases and reporting of valid ICSRs (see [VI.B.2.](#)) related to the studied (or supplied) medicinal product. Marketing authorisation holders should therefore exercise due diligence in establishing such system, in following-up those reports (see [VI.B.3.](#)) and in seeking the view of the primary source as regard the causal role of the studied (or supplied) medicinal product on the notified adverse event. Where this opinion is missing, the marketing authorisation holder should exercise its own judgement based on the information available in order to decide whether the report is a valid ICSR, which should be reported to the competent authorities. This requirement does not apply to study designs based on secondary use of data since reporting of ICSRs is not required (see [VI.C.1.2.1.](#)). Safety data from solicited reports to be presented in the relevant sections of the periodic safety update report of the authorised medicinal product are detailed in [Module VII](#).

VI.C.2.2.3. Case reports published in the scientific literature

General principles in relation to the monitoring for individual cases of suspected adverse reactions described in the scientific and medical literature are provided in [VI.B.1.1.2.](#). As regards the screening of the scientific and medical literature, the requirements provided in this Module are part of the wider literature searches which need to be conducted for periodic safety update reports (see [Module VII](#)).

In accordance with Article 107(3) of Directive 2001/83/EC, in order to avoid the reporting of duplicate ICSRs, marketing authorisation holders shall only report those ICSRs described in the scientific and medical literature which is not reviewed by the Agency, for all medicinal products containing active substances which are not included in the list monitored by the Agency pursuant to Article 27 of

²⁸ This does not concern donation of a medicinal product for research purpose if the marketing authorisation holder has no control on the study.

Regulation (EC) No 726/2004. Until such lists of scientific and medical literature and active substance names are published by the Agency, marketing authorisation holders should monitor all the active substances for which they hold a marketing authorisation in the EU by accessing a widely used systematic literature review and reference database, in line with the principles detailed in [VI.B.1.1.2.](#) and in [VI. Appendix 2.](#)

Articles can be excluded from the reporting of ICSRs by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance, unless alternative reasons for exclusion detailed hereafter apply:

- where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the criteria detailed in [VI.C.2.2.](#);
- for individual case safety reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product;
- for literature ICSRs which are based on an analysis from a competent authority database within the EU. The reporting requirements remain for those ICSRs which are based on the analysis from a competent authority database outside the EU;
- for literature articles, which present data analyses from publicly available databases or, which summarise results from post-authorisation studies (see [VI.C.1.2.](#)). This type of literature article describes adverse reactions, which occur in a group of patients with a designated medicinal product with the aim of identifying or quantifying a safety hazard related to a medicinal product, and aggregated data on patients are often presented in tables or line listings. The main objective of those studies is to detect/evaluate specific risks that could affect the overall risk-benefit balance of a medicinal product.

New and significant safety findings presented in these articles, for which reporting is not required, should however be discussed in the relevant sections of the concerned periodic safety update report (see [Module VII](#)) and analysed as regards their overall impact on the medicinal product risk-benefit profile. In addition, any new safety information, which may impact on the risk-benefit profile of a medicinal product, should be notified immediately to the competent authorities in Member States where the medicinal product is authorised and to the Agency in accordance with the recommendations provided in [VI.C.2.2.6.](#)

A detailed guidance on the monitoring of the scientific and medical literature has been developed in accordance with Article 27(3) of Regulation (EC) No 726/2004; it is included in [VI. Appendix 2.](#)

The electronic reporting recommendations regarding suspected adverse reactions reports published in the scientific and medical literature are provided in [VI.C.6.2.3.2.](#)

VI.C.2.2.4. Suspected adverse reactions related to quality defect or falsified medicinal products

When a report of suspected adverse reactions is associated with a suspected or confirmed falsified medicinal product or quality defect of a medicinal product, a valid ICSR should be reported. The seriousness of the ICSR is linked to the seriousness of the reported suspected adverse reactions in accordance with the definitions provided in [VI.A.2.4.](#) Electronic reporting recommendations provided in [VI.C.6.2.3.5.](#) should be followed.

In addition in order to protect public health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product from the market. Therefore, marketing authorisation holders should have a system in place to ensure that reports of suspected adverse reactions related to falsified medicinal products or to quality defects of a medicinal products are investigated in a timely fashion and that confirmed quality defects are notified separately to the manufacturer and to competent authorities in accordance with the provisions described in Article 13 of [Directive 2003/94/EC](#).

VI.C.2.2.5. Suspected transmission via a medicinal product of an infectious agent

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction and such cases should be reported within 15 days in accordance with the requirements outlined in [VI.C.4.](#)²⁹. If no other criterion is applicable, the seriousness of this ICSR should be considered as important medical event (see [VI.A.2.4.](#)). This also applies to vaccines. Electronic reporting recommendations provided in [VI.C.6.2.3.6.](#) should be followed.

In the case of medicinal products derived from human blood or human plasma, haemovigilance procedures may also apply in accordance with [Directive 2002/98/EC](#). Therefore the marketing authorisation holder should have a system in place to communicate suspected transmission via a medicinal product of an infectious agent to the manufacturer, the relevant blood establishment(s) and national competent authorities in Member States.

Any organism, virus or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

A transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product.

Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a medicinal product, but the occurrence of unknown agents should also always be considered.

In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g. injection/ administration) and the source (e.g. contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno-suppressed /vaccinee).

Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect for which the procedures detailed in [VI.C.2.2.4.](#) should be applied.

Medicinal products should comply with the recommendations provided in the [Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Products](#)³⁰. For advanced therapy medicinal products, Article 14(5) of [Regulation \(EC\) No 1394/2007](#) and the [Guideline on Safety and Efficacy Follow-up - Risk Management of Advanced Therapy Medicinal Products](#)³¹, should also be followed as appropriate.

²⁹ See [VI.C.6.2.3.6.](#) for electronic reporting recommendations.

³⁰ Latest revision. (Ref.: [EMA/410/01](#)).

³¹ Ref.: [EMA/149995/2008](#)

VI.C.2.2.6. Emerging safety issues

Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements, even though they may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health. Examples include:

- major safety findings from a newly completed non-clinical study;
- major safety concerns identified in the course of a non-interventional post-authorisation study or of a clinical trial;
- signal of a possible teratogen effect or of significant hazard to public health;
- safety issues published in the scientific and medical literature;
- safety issues arising from the signal detection activity (see [Module IX](#)) or emerging from a new ICSR and which impact on the risk-benefit balance of the medicinal product and/or have implications for public health;
- safety issues related to the use outside the terms of the marketing authorisation;
- safety issues due to misinformation in the product information;
- marketing authorisation withdrawal, non-renewal, revocation or suspension outside the EU for safety-related reasons;
- urgent safety restrictions outside the EU;
- safety issues in relation to the supply of raw material;
- lack of supply of medicines.

These events/observations, which may affect the risk-benefit balance of a medicinal product, are not to be submitted as ICSRs. They should be notified as emerging safety issues in writing to the competent authorities in Member States where the medicinal product is authorised and to the Agency via email (P-PV-emerging-safety-issue@ema.europa.eu); this should be done immediately when becoming aware of them. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorisation for the concerned medicinal product. Those safety issues should also be analysed in the relevant sections of the periodic safety update report of the authorised medicinal product.

VI.C.2.2.7. Period between the submission of the marketing authorisation application and the granting of the marketing authorisation

In the period between the submission of the marketing authorisation application and the granting of the marketing authorisation, information (quality, non-clinical, clinical) that could impact on the risk-benefit balance of the medicinal product under evaluation may become available to the applicant³². It is the responsibility of the applicant to ensure that this information is immediately submitted in accordance with the modalities described in [VI.C.2.2.6.](#) to the competent authorities in the Member States where the application is under assessment (including Reference Member State and all concerned Member States for products assessed under the mutual recognition or decentralised procedures) and to the Agency. For applications under the centralised procedure, the information should also be provided to the (Co-) Rapporteur.

³² See also chapter 1, section 5.1.1 of Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the European Union. http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm.

In the situation where a medicinal product application is under evaluation in the EU while it has already been authorised in a third country, valid ICSRs from outside the EU, originating from unsolicited reports (see [VI.B.1.1.](#)) or solicited reports (see [VI.B.1.2.](#)), should be reported in accordance with the requirements provided in [VI.C.3.](#), [VI.C.4.](#) and [VI.C.6.](#)

VI.C.2.2.8. Period after suspension, revocation or withdrawal of marketing authorisation

The marketing authorisation holder shall continue to collect any reports of suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorisation. The reporting requirements outlined in [VI.C.4.](#) remain.

Where a marketing authorisation is withdrawn or revoked, the former marketing authorisation holder is encouraged to continue to collect spontaneous reports of suspected adverse reactions originating within the EU to for example facilitate the review of delayed onset adverse reactions or of retrospectively notified cases.

VI.C.2.2.9. Period during a public health emergency

A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Community in the framework of [Decision No. 2119/98/EC](#) as amended of the European Parliament and of the Council. In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified on the Agency website.

VI.C.2.2.10. Reports from class action lawsuits

Stimulated reports arising from class action lawsuits should be managed as spontaneous reports. Valid ICSRs should describe adverse reactions related to the concerned medicinal product. They should be reported in accordance with the time frames and modalities described in [VI.C.3.](#), [VI.C.4.](#) and [VI.C.6.](#)

Where large batches of potential ICSRs are received, marketing authorisation holders may request, in exceptional circumstances, for an exemption in order to submit serious cases of suspected adverse reactions within 30 days from their date of receipt instead of 15 days. The 90 days reporting time frame for non-serious ICSRs remains unchanged. It will be possible to apply for this exemption only once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established. The request should be made to the Agency's pharmacovigilance department.

VI.C.2.2.11. Reports from patient support programmes and market research programmes

A patient support programme is an organised system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products. Examples are post-authorisation patient support and disease management programmes, surveys of patients and healthcare providers, information gathering on patient compliance, or compensation/re-imburement schemes.

A market research programme refers to the systematic collection, recording and analysis by a marketing authorisation holder of data and findings about its medicinal products, relevant for marketing and business development.

Safety reports originating from those programmes should be considered as solicited reports. Marketing authorisation holders should have the same mechanisms in place as for all other solicited reports (see [VI.C.2.2.2.](#)) to manage that information and report valid cases of adverse reactions, which are suspected to be related to the concerned medicinal product.

Valid ICSRs should be reported as solicited in accordance with the electronic reporting requirements provided in [VI.C.6.2.3.7.](#)

VI.C.3. Reporting time frames

The general rules in relation to the reporting of initial and follow-up reports, including those for defining the clock start are detailed in [VI.B.7.](#)

According to Articles 107(3) and 107a(4) of Directive 2001/83/EC,

- serious valid ICSRs shall be reported by competent authorities in Member States or by marketing authorisation holders within 15 days from the date of receipt of the reports;
- non-serious valid ICSRs shall be reported by competent authorities in Member States or by marketing authorisation holders within 90 days from the date of receipt of the reports.

This should be done in accordance with the reporting modalities detailed in [VI.C.4.](#)

VI.C.4. Reporting modalities

In addition to the recommendations provided in [VI.B.8.](#), competent authorities in Member States and marketing authorisation holders shall use the formats, standards and terminologies for the electronic transmission of suspected adverse reactions as referred to in chapter IV of the Commission Implementing Regulation (EU) No 520/2012. ICSRs shall be used for reporting to the Eudravigilance database suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time [IR Art 27]. Competent authorities in Member States and marketing authorisation holders shall also ensure that all reported electronic ICSRs are well documented and as complete as possible in accordance with the requirements provided in [IR Art 28].

The time frames for reporting serious and non-serious valid ICSRs are provided in [VI.C.3.](#) The recommendations provided in [VI.C.6.](#) should be adhered to as regards the electronic exchange of pharmacovigilance information between competent authorities in Member States, marketing authorisation holders and the Agency.

ICSRs reported electronically to the EudraVigilance database will be made accessible to stakeholders such as competent authorities, healthcare professionals, consumers, as well as marketing authorisation holders and research organisations in accordance with Article 24(2) of Regulation (EC) No 726/2004 and the [EudraVigilance Access Policy for Medicines for Human Use](#)³³. This policy defines the overall principles of the provision of access to EudraVigilance data in line with the current legal framework, while guaranteeing personal data protection. As detailed in the EudraVigilance access policy, a selection of ICSRs could be downloaded by marketing authorisation holders in ICH E2B format and in accordance with the ICH M2 message specifications, to facilitate their pharmacovigilance activities.

VI.C.4.1. Interim arrangements

In accordance with the provisions set out in Article 2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EU, until the Agency can ensure the functionalities of the EudraVigilance database as specified in Article 24(2) of Regulation (EC) No 726/2004, the following reporting requirements shall apply to valid unsolicited and solicited ICSRs reported by healthcare professionals and non-healthcare professionals. This is independently of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction.

³³ <http://www.ema.europa.eu>

a. Serious ICSRs

- Marketing authorisation holders shall report all serious ICSRs that occur in the EU to the competent authority of the Member State on whose territory the suspected adverse reactions occurred.
- Marketing authorisation holders shall report to the EudraVigilance database all serious ICSRs that occur outside the EU, including those received from competent authorities. If required by Member States, those reports shall also be submitted to the competent authorities in the Member States in which the medicinal product is authorised.
- Competent authorities in Member States shall ensure that all serious ICSRs that occur in their territory and that are reported to them, including those received from marketing authorisation holders, are made available to the EudraVigilance database. Competent authorities in Member States should also make available, to the marketing authorisation holders of the suspected medicinal products, all serious ICSRs reported directly to them.

b. Non-Serious ICSRs

- If required by Member States, marketing authorisation holders shall report all non-serious ICSRs that occur in the EU to the competent authority of the Member State on whose territory the suspected adverse reactions occurred.

Overviews of the reporting requirements of serious and non-serious reports during the interim period, applicable to marketing authorisation holders or competent authorities in Member States, are presented in [VI.App3.1](#), together with a detailed business process map.

Member States reporting requirements for serious non-EU ICSRs and for non-serious EU ICSRs are also included in this Appendix.

VI.C.4.2. Final arrangements

Once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established, the following requirements, detailed in Articles 107(3) and 107a(4) of Directive 2001/83/EC, shall apply within 6 months of the announcement by the Agency to valid unsolicited and solicited ICSRs reported by healthcare professionals and non-healthcare professionals. This is independently of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction.

a. Serious ICSRs

- Marketing authorisation holders shall submit all serious ICSRs that occur within or outside the EU, including those received from competent authorities outside the EU, to the EudraVigilance database only.
- Competent authorities in Member States shall submit to the EudraVigilance database all serious ICSRs that occur in their territory and that are directly reported to them.

b. Non-Serious ICSRs

- Marketing authorisation holders shall submit all non-serious ICSRs that occur in the EU to the EudraVigilance database only.
- Competent authorities in Member States shall submit all non-serious ICSRs that occur in their territory to the EudraVigilance database.

Overviews of the reporting requirements of serious and non-serious reports, applicable to marketing authorisation holders or competent authorities in Member States once the final arrangements are implemented, are presented in [VI.App3.2](#), together with a detailed business process map.

In accordance with the requirement detailed in Article 24(4) of Regulation (EC) No 726/2004 for the final arrangements, the ICSRs submitted to the EudraVigilance database by marketing authorisation holders shall be automatically transmitted upon receipt, to the competent authority of the Member State where the reaction occurred. A detailed business process map is included in [VI.App3.3](#).

VI.C.5. Collaboration with the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction

The Agency shall make available to the WHO (in practice the WHO Collaborating Centre for International Drug Monitoring) all suspected adverse reaction reports occurring in the EU [REG Art 28c(1)]. This will take place on a weekly basis after their transmission to the EudraVigilance database by competent authorities in Member States or marketing authorisation holders. It will replace the requirements of Member States participating in the WHO Programme for International Drug Monitoring to directly report to WHO suspected adverse reactions reports occurring in their territory. This will be implemented once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established.

A detailed business process map for the reporting of ICSRs, from the EudraVigilance database to the WHO Collaborating Centre for International Drug Monitoring, is presented in [VI. Appendix 4](#).

The Agency and the European Monitoring Centre for Drugs and Drug Addiction shall also exchange information that they receive on the abuse of medicinal products including information related to illicit drugs [REG Art 28c(2)].

VI.C.6. Electronic exchange of safety information in the EU

[VI.C.6](#) highlights the requirements, as defined in Articles 24(1) and 24(3) of Regulation (EC) No 726/2004, for the establishment and maintenance of the European database and data processing network (the EudraVigilance database) in order to collate and share pharmacovigilance information electronically between competent authorities in Member States, marketing authorisation holders and the Agency, in ways which ensure the quality and integrity of the data collected.

The information provided here is relevant for the electronic exchange of ICSRs in the EU between all stakeholders and for the electronic submission of information on medicinal products to the Agency.

VI.C.6.1. Applicable guidelines, definitions, international formats, standards and terminologies

For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, Member States, marketing authorisation holders and the Agency shall adhere to the legal requirements provided in chapter IV of the Commission Implementing Regulation (EU) No 520/2012.

In addition the following guidelines should be applied:

- Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) ([EMA/H/20665/04/Final Rev. 2](#)) (EudraVigilance Business Rules);

- Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Products (MPRS) in Pharmacovigilance during the pre- and post-authorisation phase in the European economic area (EEA) ([EMEA/115735/2004](#));
- The ICH guidelines detailed in [VI.B.8](#);
- The ICH-M5 guideline 'Routes of Administration Controlled Vocabulary' ([CHMP/ICH/175860/2005](#)), which provides standard terms for routes of administration;

The latest version of these documents should always be considered.

VI.C.6.2. Electronic reporting of individual case safety reports

The reporting of valid ICSRs electronically, by competent authorities in Member States and marketing authorisation holders, is mandatory for all medicinal products authorised in the EU [DIR Art 107(3), Art 107a(4)]. Non-adherence to this requirement constitutes a non-compliance with EU legislation. Responsibilities in case of communication failure (including adherence to compliance for reporting) are detailed in chapter IV of the Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA) ([EMEA/115735/2004](#)).

Technical tools (EVWEB) have been made available by the Agency to interested electronic data interchange partners, including small and medium-sized enterprises, to facilitate compliance with the electronic reporting requirements as defined in EU legislation. Information is available on EudraVigilance website³⁴.

VI.C.6.2.1. EudraVigilance Database Modules

Two modules are available in the EudraVigilance database to address the collection of reports of suspected adverse reactions related to medicinal products for human use, in accordance with EU legislation:

- EudraVigilance Post-Authorisation Module (EVPM), implemented based on the requirements defined in Regulation (EC) No 726/2004 and Directive 2001/83/EC; and
- EudraVigilance Clinical Trial Module (EVCTM), implemented based on the requirements defined in Directive 2001/20/EC.

VI.C.6.2.1.1. Adverse reaction data collected in the EudraVigilance Post-Authorisation Module

The adverse reaction reports collected in the EudraVigilance Post-Authorisation Module (EVPM) refer to unsolicited reports and solicited reports which do not fall under the scope of the Clinical Trials Directive 2001/20/EC (see [VI.C.1](#)). The ICSRs should be submitted with the value 'EVHUMAN' in the data element 'Message receiver identifier' (ICH M2 M.1.6).

Depending on their type, these ICSRs should be classified with one of the following options, in accordance with the EudraVigilance Business Rules³⁵:

- Data element 'Type of report' (ICH-E2B(R2) A.1.4):
 - spontaneous report;

³⁴ <http://eudravigilance.ema.europa.eu>

³⁵ Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) ([EMA/H/20665/04/Final Rev. 2](#)).

- other;
 - not available to sender (unknown); or
 - report from study.
- In addition, when the value in the data element ICH-E2B(R2) A.1.4 is 'Report from study', the data element 'Study type in which the reaction(s)/event(s) were observed' (ICH-E2B(R2) A.2.3.3) should be populated with:
 - individual patient use, e.g. compassionate use or named-patient basis; or
 - other studies, e.g. pharmacoepidemiology, pharmacoconomics, intensive monitoring, PMS.

VI.C.6.2.1.2. Adverse reaction data collected in the EudraVigilance Clinical Trial Module

Only cases of suspected unexpected serious adverse reactions (SUSARs), related to investigational medicinal products studied in clinical trials which fall under the scope of Directive 2001/20/EC (see [VI.C.1.](#)), should be reported by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM). The requirements provided in chapter II of [EudraLex Volume 10 of The Rules Governing Medicinal Products in the European Union](#) should be applied. The ICSRs should be submitted with the value 'EVCTMPROD' in the data element 'Message receiver identifier' (ICH M2 M.1.6) and should be classified as followed, in accordance with the [EudraVigilance Business Rules](#)³⁶:

- data element 'Type of report' (ICH-E2B(R2) A.1.4):
 - report from study; and
- data element 'Study type in which the reaction(s)/event(s) were observed' (ICH-E2B(R2) A.2.3.3):
 - clinical trials.

VI.C.6.2.2. Preparation of individual case safety reports

VI.C.6.2.2.1. General principles

The content of each valid ICSR transmitted electronically between all stakeholders should comply with the legal requirements and guidelines detailed in the Commission Implementing Regulation (EU) No 520/2012 and in [VI.C.6.1.](#), particularly:

- the requirements provided in chapters IV and V of the Commission Implementing Regulation (EU) No 520/2012;
- the latest version of the [ICH-Endorsed Guide for MedDRA Users - MedDRA Term Selection: Points to Consider Document](#) (see [GVP Annex IV](#));
- the EudraVigilance business rules for the electronic transmission of ICSRs detailed in the [Note for Guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports \(ICSRs\)](#) ([EMA/H/20665/04/Final Rev. 2](#)).

It is recognised that it is often difficult to obtain all the details on a specific case. However, the complete information (medical and administrative data) for a valid ICSR that is available to the sender should be reported in a structured manner in the relevant ICH-E2B(R2) data elements (see [GVP Annex IV](#)) (which should be repeated as necessary when multiple information is available) and in the

³⁶ See Footnote 38.

narrative section (see [VI.C.6.2.2.4](#)). This applies to all types of ICSRs, such as reports with initial information on the case, follow-up information and cases highlighted for nullification³⁷.

In the situation where it is evident that the sender has not transmitted the complete information available on the case, the receiver may request the sender to re-transmit the ICSR within 24 hours with the complete case information in electronic format in accordance with the requirements applicable for the electronic reporting of ICSRs. This should be seen in the light of the qualitative signal detection and evaluation activity, where it is important for the receiver to have all the available information on a case to perform the medical assessment (see [VI.C.6.2.4](#)).

Where the suspected adverse reactions reported in a single ICSR impact on the known risk-benefit balance of a medicinal product, this should be considered as an emerging safety issue (see [VI.C.2.2.6](#)), which should be immediately notified in writing to the competent authorities of the Member States where the medicinal product is authorised and to the Agency. This is in addition to the reporting requirements detailed in [VI.C.4](#). A summary of the points of concerns and the action proposed should be recorded in the ICSR in data element 'Sender's comments' (ICH-E2B(R2) B.5.4).

VI.C.6.2.2.2. Information on suspect, interacting and concomitant medicinal products

The suspect, interacting and/or concomitant active substances/invented names of the reported medicinal products should be provided in accordance with IR Art 28 (3) (g) to (i), ICH-E2B(R2) (see [GVP Annex IV](#)) and the [EudraVigilance Business Rules](#).

The characterisation of medicinal products as suspect, interacting or concomitant is based on the information provided by primary source.

For combination medicinal products, which contain more than one active substance, each active substance needs to be reflected individually in the data element 'Active substance name(s)' (ICH E2B(R2) B.4.k.2.2), which needs to be repeated for each active substance contained in the combination medicinal product.

When the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the active substance(s) of the medicinal product and where the proprietary medicinal product can be one of two or more possible generics, which have a different composition depending on the country where the medicinal product is marketed, the ICSR should be populated as follows:

- data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the proprietary/branded medicinal product name as reported by the primary source;
- data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with the active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred.

However if the information is available on:

- the 'Identification of the country where the drug was obtained' (data element ICH E2B(R2) B.4.k.2.3),
- the 'Authorization/application number' (data element ICH-E2B(R2) B.4.k.4.1),
- the 'Country of authorization/application' (data element ICH-E2B(R2) B.4.k.4.2), and/or
- the 'Batch/lot number' (data element ICH-E2B(R2) B.4.k.3),

³⁷ See also [VI.C.6.2.2.10](#) on nullification of individual cases.

the composition with regard the active substance(s) of the proprietary medicinal product should be provided accordingly.

Where the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the pharmaceutical form/presentation of the product and where the proprietary/branded medicinal product can be one of two or more possible pharmaceutical forms/presentations, which have different compositions in a country, the ICSR should be populated as follows:

- data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the medicinal product name as reported by the primary source;
- data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with those active substances which are in common to all pharmaceutical forms/presentations in the country of authorisation.

Where medicinal products cannot be described on the basis of the active substances or the invented names, for example when only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should only be reflected in the case narrative (data element ICH-E2B(R2) B.5.1). The data elements 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) and 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should not be populated. The same applies if a suspected food interaction is reported (e.g. to grapefruit juice).

Where a case of adverse reactions is reported to be related only to a therapeutic class, it is considered incomplete and does not qualify for reporting (see [VI.B.2.](#)). Efforts should be made to follow-up the case in order to collect the missing information regarding the suspected medicinal product (see [VI.B.3.](#)).

As regards the reporting of drug interactions, which concerns drug/drug (including biological products), drug/food, drug/device, and drug/alcohol interactions, the coding of the interaction should be performed in section 'Reactions/Events' (ICH-E2B(R2) B.2) in line with the latest version of the [ICH-Endorsed Guide for MedDRA Users - MedDRA Term Selection: Points to Consider Document](#) (see [GVP Annex IV](#)). In addition, for drug/drug interactions, information on the active substances/proprietary medicinal product names should be provided in the section 'Drug information' (ICH-E2B(R2) B.4), which should be characterised as interacting in the data element 'Characterisation of drug role' (ICH-E2B(R2) B.4.k.1).

If the primary source suspects a possible causal role of one of the ingredients (e.g., excipient or adjuvant) of the suspected medicinal product, this information should be provided in the section 'Drug information' (ICH-E2B(R2) B.4) as a separate entry in addition to the information given regarding the suspected medicinal product. This should also be specified in the case narrative (data element ICH-E2B(R2) B.5.1). If available, tests results (positive or negative) in relation to the causal role of the suspected ingredient should be included in the section 'Results of tests and procedures relevant to the investigation of the patient' (ICH E2B(R2) B.3).

VI.C.6.2.2.3. Suspected adverse reactions

All available information as described in [IR Art 28 (3) (j)] shall be provided for each individual case. The coding of diagnoses and provisional diagnoses with signs and symptoms in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1) should be performed in line with the latest version of the [ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider](#) (see [GVP Annex IV](#)).

In practice, if a diagnosis is reported with characteristic signs and symptoms, the preferred option is to select a term for the diagnosis only and to MedDRA code it in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'. If no diagnosis is provided, all reported signs and symptoms should be listed and MedDRA coded in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'. If these signs and symptoms are typically part of a diagnosis, the diagnosis can be MedDRA coded in addition by competent authorities in Member States or marketing authorisation holders in the ICH-E2B(R2) data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event'.

If in the narrative other events have been reported, which are not typically signs or symptoms of the primary source's diagnosis or provisional diagnosis, and those events are suspected to be adverse reactions, they should also be listed and MedDRA coded in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'.

In case a competent authority in a Member State or a marketing authorisation holder disagrees with the diagnosis reported by the primary source, an alternative diagnosis can be provided in the ICH-E2B(R2) data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' in addition to the reported diagnosis provided in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'. In this situation, a reasoning should be included in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4) (see [VI.C.6.2.2.4](#)).

In the event of death of the patient, the date, cause of death including autopsy-determined causes shall be provided as available [IR 28 (3) (I)]. If the death is unrelated to the reported suspected adverse reaction(s) and is linked for example to disease progression, the seriousness criterion of the ICSR should not be considered as fatal; the recommendation provided in the [EudraVigilance Business Rules](#) should be followed.

VI.C.6.2.2.4. Case narrative, causality assessment and comments

In accordance with [IR Art 28 (3) (m)], a case narrative (data element ICH-E2B(R2) B.5.1) shall be provided, where possible³⁸, for all cases with the exception of non-serious cases. The information shall be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained. Any relevant autopsy or post-mortem findings shall also be summarised.

The narrative should be presented in line with the recommendations described in chapter 5.2 of ICH-E2D (see [GVP Annex IV](#)). In this aspect, it should serve as a comprehensive, stand-alone "medical report" containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse reactions. An example of a standard narrative template is available in the [Report of the CIOMS Working Group V](#)³⁹.

The information provided in the narrative should be consistent with the data appropriately reflected in all the other relevant ICH-E2B(R2) data elements of the ICSR (see [GVP Annex IV](#)).

During the interim arrangements (see [VI.C.4.1](#)), the case narratives included in the ICSRs submitted to the competent authorities in Member States by marketing authorisation holders, should not be modified or deleted when the ICSRs are forwarded to the EudraVigilance database by the competent authorities.

³⁸ 'Where possible' should be interpreted as having received sufficient information from the primary source to prepare a concise clinical summary of the individual case.

³⁹ Council for International Organizations of Medical Sciences (CIOMS). Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V). Geneva: CIOMS; 2001. <http://www.cioms.ch/>.

Where available, comments from the primary source on the diagnosis, causality assessment or other relevant issue, should be provided in the data element 'Reporter's comments' (ICH-E2B(R2) B.5.2). Competent authorities in Member States and marketing authorisation holders may provide an assessment of the case and describe a disagreement with, and/or alternatives to the diagnoses given by the primary source (see [VI.C.6.2.2.3](#)). This should be done in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4), where discrepancies or confusions in the information notified by the primary source may also be highlighted. Where applicable, a summary of the points of concerns and actions proposed should also be included in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4), if the ICSR leads to notification of an emerging safety issue (see [VI.C.2.2.6](#)). The degree of suspected relatedness of each medicinal product to the adverse reaction(s) may be indicated in the data element 'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18), which should be repeated as necessary. This also allows presenting the degree of relatedness from different sources or with different methods of assessment.

VI.C.6.2.2.5. Test results

Results of tests and procedures relevant to the investigation of the patient shall be provided [IR Art 28 (3) (k)].

As described in ICH-E2B(R2) (see [GVP Annex IV](#)), the section B.3 'Results of tests and procedures relevant to the investigation of the patient' should capture the tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate (exclude) a non-drug cause, (e.g., serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative results should be reported.

The coding of investigations should be performed in line with the latest version of the [ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider](#) (see [GVP Annex IV](#)). If it is not possible to provide information on tests and test results in a structured manner, provisions have been made to allow for the transmission of the information as free text in the data element ICH-E2B(R2) B.3.2. 'Results of tests and procedures relevant to the investigation'.

VI.C.6.2.2.6. Supplementary information

Key information from supplementary records should be provided in the relevant section of the ICSR, and their availability should be mentioned in the data element 'List of documents held by sender' (ICH-E2B(R2) A.1.8.2).

Other known case identifiers relevant for the detection of duplicates should be presented systematically in the data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11).

VI.C.6.2.2.7. Follow-up information

ICSRs are sent at different times to multiple receivers. Therefore the initial/follow-up status is dependent upon the receiver. For this reason an item to capture follow-up status is not included in the ICH-E2B(R2) data elements. However, the data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) taken together with the data element 'Sender identifier' (ICH-E2B(R2) A.3.1.2) and the data element 'Sender's (case) report unique identifier' (ICH-E2B(R2) A.1.0.1) provide a mechanism for each receiver to identify whether the report being transmitted is an initial or a follow-up report. For this reason these items are considered critical for each transmission and a precise date should always be used (i.e. day, month, year). The data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) should therefore always be updated

each time a follow-up information is received by a competent authority or a marketing authorisation holder, independently whether the follow-up information received is significant enough to be reported. The data element 'Date report was first received from the source' (ICH-E2B(R2) A.1.6) should remain unchanged to the date the competent authority or the marketing authorisation holder became aware of the initial report.

New information should be clearly identifiable in the case narrative (data element ICH-E2B(R2) B.5.1) and provided in a structured format in the applicable ICH-E2B(R2) data elements.

Competent authorities in Member States or marketing authorisation holders should report follow-up information if significant new medical information has been received. Significant new information relates to for example new suspected adverse reaction(s), a change in the causality assessment and any new or updated information on the case that impacts on its medical interpretation. Therefore, the identification of significant new information requiring to be reported always necessitates medical judgement.

Situations where the seriousness criteria and/or the causality assessment are downgraded (e.g. follow-up information leads to a change of the seriousness criteria from serious to non-serious; causality assessment is changed from related to non-related) should also be considered as significant changes and thus reported (see [VI.B.7.1](#) for reporting time frames).

In addition, competent authorities in Member States or marketing authorisation holders should also report follow-up information, where new administrative information is available, that could impact on the case management; for example, if new case identifiers have become known to the sender, which may have been used in previous transmissions (data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11)). This information may be specifically relevant to manage potential duplicates. Another example refers to data element 'Additional available documents held by sender' (ICH-E2B(R2) A.1.8), whereby new documents that have become available to the sender may be relevant for the medical assessment of the case.

In contrast, a follow-up report which contains non-significant information does not require to be reported. This may refer, for example, to minor changes to some dates in the case with no implication for the evaluation or transmission of the case, or corrections of typographical errors in the previous case version. Medical judgement should be applied since a change to the birth date may constitute a significant modification (e.g. with implications on the age information of the patient). Similarly, a change of the status of a MedDRA code/term from current to non-current, due to a version change of MedDRA, can be considered as a non-significant change as long as this change has no impact on the medical content of a case. However, an amendment of the MedDRA coding due to a change in the interpretation of a previously reported suspected adverse reaction may constitute a significant change and therefore should be reported.

In situations where the case is modified without impacting on its medical evaluation, while no new follow-up is received (e.g., for correcting a mistake or typographical error), the date of receipt of the most recent information reported in the data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) should not be changed. This data element should however be updated in any other situations, to the date when new follow-up information is received (independently whether it is significant or not) or to the date when changes are made which impact on the interpretation of the case.

Where follow-up information of a case initially reported by a marketing authorisation holder is received directly by a competent authority, the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) of the initial report should be maintained, in adherence with ICH-E2B(R2) (see [GVP Annex IV](#)).

The same principle should be applied if a follow-up is received by a marketing authorisation holder of a case initially reported by a competent authority.

VI.C.6.2.2.8. What to take into account for data privacy laws

To detect, assess, understand and prevent adverse reactions and to identify, and take actions to reduce the risks of, and increase the benefits from medicinal products for the purpose of safeguarding public health, the processing of personal data within the EudraVigilance database is possible while respecting EU legislation in relation to data protection (Directive 95/46/EC, Regulation (EC) No 45/2001).

Where in accordance with applicable national legislation, information related to personal data cannot be transferred to the EudraVigilance database, pseudonymisation may be applied by competent authorities in Member States and by marketing authorisation holders, thereby replacing identifiable personal data such as name and address with pseudonyms or key codes, for example in accordance with the ISO Technical Specification DD ISO/TS 25237:2008, Health informatics – Pseudonymization [IR Recital 17]. The application of pseudonymisation will facilitate the ability of the EudraVigilance system to adequately support case processing and detect duplicates. This should however be done without impairing the information flow in the EudraVigilance database and the interpretation and evaluation of safety data relevant for the protection of public health; given the high-level nature of the information, data elements such as patient's age, age group and gender should in principle be kept un-redacted/visible.

VI.C.6.2.2.9. Handling of languages

The ICH-E2B(R2) (see [GVP Annex IV](#)) concept for the electronic reporting of ICSRs is based on the fact that structured and coded information is used for data outputs of pharmacovigilance systems (e.g. listings) and for signal detection. However, for scientific case assessment and signal evaluation, the medical summary provided in the data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1) is normally required (see [VI.6.2.2.4](#)).

Where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and the summary thereof in English shall be provided by the marketing authorisation holder⁴⁰. Member States may report case narratives in their official language(s). For those reports, case translations shall be provided when requested by the Agency or other Member States for the evaluation of potential signals. For suspected adverse reactions originating outside the EU, English shall be used in the ICSR [IR 28 (4)].

Additional documents held by the sender, which may be only available in a local language, should only be translated if requested by the receiver.

VI.C.6.2.2.10. Nullification of cases

In line with ICH-E2B(R2) (see [GVP Annex IV](#)), the nullification of individual cases should be used to indicate that a previously transmitted report should be considered completely void (nullified), for example when the whole case was found to be erroneous or in case of duplicate reports. It is essential to use the same case report numbers previously submitted in the data element 'Sender's (case) safety

⁴⁰ In practice, the original verbatim text reported by the primary source in an official language of the Union other than English should be included in the ICSR, if it is requested by the Member State where the reaction occurred or by the Agency.

report unique identifier' (ICH-E2B(R2) A.1.0.1) and in the data element 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10).

A nullified case is one that should no longer be considered for scientific evaluation. The process of the nullification of a case is by means of a notification by the sender to the receiver that this is no longer a valid case. However, the case should be retained in the sender's pharmacovigilance database for auditing purposes.

The principles to be considered when nullifying a case are detailed in [VI. Appendix 5](#).

VI.C.6.2.3. Special situations

VI.C.6.2.3.1. Use of a medicinal product during pregnancy or breastfeeding

General recommendations are provided in [VI.B.6.1.](#)

With regard to the electronic reporting of parent-child/foetus cases, the following should be adhered to:

- In the situation where a foetus or nursing infant is exposed to one or several medicinal products through the parent and experiences one or more suspected adverse reactions (other than early spontaneous abortion/foetal demise), information on both the parent and the child/foetus should be provided in the same report. These cases are referred to as parent-child/foetus reports. The information provided in the section 'Patients characteristics' (ICH-E2B(R2) B.1) applies only to the child/foetus. The characteristics concerning the parent (mother or father), who was the source of exposure to the suspect medicinal product should be provided in the data element 'For a parent-child/fetus report, information concerning the parent' (ICH-E2B(R2) B.1.10). If both parents are the source of the suspect drug(s) then the case should reflect the mother's information in the data element 'For a parent-child/fetus report, information concerning the parent' (ICH E2B(R2) B.1.10). The data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1) should describe the entire case, including the father's information.
- If both the parent and the child/foetus experience suspected adverse reactions, two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be created but they should be linked by using the data element 'Identification number of the report which is linked to this report' (ICH-E2B(R2) A.1.12) in each report.
- If there has been no reaction affecting the child, the parent-child/foetus report does not apply; i.e. the section 'Patients characteristics' (ICH-E2B(R2) B.1) applies only to the parent (mother or father) who experienced the suspected adverse reaction.
- For those cases describing miscarriage or early spontaneous abortion, only a parent report is applicable, i.e. the section 'Patients characteristics' (ICH-E2B(R2) B.1) apply to the mother. However, if the suspect medicinal product was taken by the father, the data element 'Additional information on drug' (ICH-E2B(R2) B.4.k.19) should specify that the medication was taken by the father.

VI.C.6.2.3.2. Suspected adverse reaction reports published in the scientific literature

EU requirements in relation to the monitoring of suspected drug reactions reported in the scientific and medical literature are provided in [VI.C.2.2.3.](#) With regard to the electronic reporting of ICSRs published in the scientific and medical literature, the following applies:

- The literature references shall be included in the data element 'Literature reference(s)' (ICH-E2B(R2) A.2.2) in the Vancouver Convention (known as "Vancouver style"), developed by the International Committee of Medical Journal Editors [IR Art 28 (3) (b)]. The standard format as well as those for special situations can be found in the following reference: [International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997; 336: 309-16](#), which is in the Vancouver style⁴¹.
- A comprehensive English summary of the article shall be provided in the data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1) [IR Art 28 (3) (b)].
- Upon request of the Agency, for specific safety review, a full translation in English and a copy of the relevant literature article shall be provided by the marketing authorisation holder that transmitted the initial report, taking into account copyright restrictions [IR 28 (3)]. The recommendations detailed in [VI.App2.10](#), regarding the mailing of the literature article, should be adhered to.
- Recommendations presented in [VI.App2.10](#), for the reporting of several cases when they are published in the same literature article, should be followed.

VI.C.6.2.3.3. Suspected adverse reactions related to overdose, abuse, off-label use, misuse, medication error or occupational exposure

General principles are provided in [VI.B.6.3](#).

If a case of overdose, abuse, off-label use, misuse, medication error or occupational exposure is reported with clinical consequences, the MedDRA Lowest Level Term code, corresponding to the term closest to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1), in line with recommendations included in the latest version of the [ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'](#) (see GVP Annex IV).

VI.C.6.2.3.4. Lack of therapeutic efficacy

General principles are provided in [VI.B.6.4](#).

If the primary source suspects a lack of therapeutic efficacy, the MedDRA Lowest Level Term code, corresponding to the term closest to the description of the reported lack of therapeutic efficacy, should be provided in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1), in line with recommendations included in the latest version of the [ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'](#) (see GVP Annex IV).

Unless aggravation of the medical condition occurs, the indication for which the suspected medicinal product was administered should not be included in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)'.

The same reporting modalities as for serious ICSRs (see [VI.C.4](#)) should be applied for those cases related to classes of medicinal products where, as described in [VI.B.6.4](#), reports of lack of therapeutic efficacy should be reported within a 15-day time frame. If no seriousness criterion is available, it is acceptable to submit the ICSR within 15 days as non-serious.

⁴¹ The Vancouver recommendations are also available on the International Committee of Medical Journal Editors website <http://www.icmje.org>.

VI.C.6.2.3.5. Suspected adverse reactions related to quality defect or falsified medicinal products

EU requirements are provided in [VI.C.2.2.4.](#) In order to be able to clearly identify cases related to quality defect or falsified medicinal products when they are exchanged between stakeholders, the following recommendations should be applied:

a. Quality defect

Where a report of suspected adverse reactions is associated with a suspected or confirmed quality defect of a medicinal product, the MedDRA Lowest Level Term code of the term corresponding most closely to the product quality issue, should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).

b. Falsified medicinal products

Where a report of suspected adverse reactions is associated with a suspected or confirmed falsified⁴² ingredient, active substance or medicinal product, the MedDRA Lowest Level Term code of the term corresponding most closely to the reported information should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1). Information on the suspected medicinal product, active substance(s) or excipient(s) should be provided in the data elements 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) and/or 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) as reported by the primary source.

VI.C.6.2.3.6. Suspected transmission via a medicinal product of an infectious agent

EU requirements are provided in [VI.C.2.2.5.](#)

The coding of a suspected transmission of an infectious agent via a medicinal product in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1) should be performed in line with the latest version of the [ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'](#) (see [GVP Annex IV](#)).

In addition, if the infectious agent is specified, the MedDRA Lowest Level Term code corresponding to the infectious agent should also be included in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).

VI.C.6.2.3.7. Reports of suspected adverse reactions originating from organised data collection systems and other systems

General safety reporting requirements in the EU for post-authorisation studies are provided in [VI.C.1.](#) and [VI.C.2.2.2.](#) Individual case safety reports originating from those studies shall contain information on study type, study name and the sponsor's study number or study registration number [IR Art 28 (3)(c)]. This should be provided in ICH E2B(R2) section A.2.3 'Study identification'.

Safety reporting requirements regarding patient support programmes or market research programmes are provided in [VI.C.2.2.11.](#)

The following reporting rules should be applied based on (i) the type of data collection system and (ii) whether the suspected medicinal product is part of the scope of the data collection system.

1. For cases of suspected adverse reactions (i) in relation to those adverse events for which the protocol of non-interventional post-authorisation studies does not provide differently and requires

⁴² As presented in EU legislation ([Directive 2011/62/EU](#)).

their systematic collection (see [VI.C.1.2.1.](#)), (ii) originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is required (see [VI.C.1.2.2.](#)), or (iii) originating from patient support programmes, or market research programmes (see [VI.C.2.2.11.](#)):

a) Where the adverse reaction is suspected to be related at least to the studied (or supplied) medicinal product:

- the report should be considered as solicited;
- the ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Report from study';
- the ICH E2B(R2) data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with the value 'Other studies' or 'Individual patient use'.

b) Where the adverse reaction is only suspected to be related to a medicinal product which is not subject to the scope of the organised data collection system and there is no interaction with the studied (or supplied) medicinal product:

- the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;
- The ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.

2. For suspected adverse reactions (i) in relation to those adverse events for which the protocol of non-interventional post-authorisation studies provides differently and does not require their systematic collection (see [VI.C.1.2.1.](#)) or (ii) originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is not required (see [VI.C.1.2.2.](#)):

- the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;
- the ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.

3. For clinical trial conducted in accordance with Directive 2001/20/EC and where the adverse reaction is only suspected to be related to a non-investigational medicinal product (or another medicinal product which is not subject to the scope of the clinical trial) and there is no interaction with the investigational medicinal product:

- the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;
- the ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.

All ICSRs which are reportable to the EudraVigilance database and which originate from post-authorisation studies which do not fall under the scope of the clinical trials Directive 2001/20/EC, should be submitted to EVPM (see [VI.C.6.2.1.](#)). The same applies to cases of adverse reactions originating in clinical trials if they are not suspected to be related to the investigational medicinal product.

VI.C.6.2.3.8. Receipt of missing minimum information

When missing minimum information (see [VI.B.2.](#)) has been obtained about a non-valid ICSR, the following rules should be applied:

- the data element 'Date report was first received from source' (ICH-E2B(R2) A.1.6) should contain the date of receipt of the initial non-valid ICSR;
- the data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) should contain the date when all the four elements of the minimum information required for reporting have become available;
- clarification should be provided in the case narrative (data element ICH-E2B(R2) B.5.1) that some of the four elements were missing in the initial report.;
- as for any reported cases, compliance monitoring is performed against the data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7).

VI.C.6.2.4. Data quality of individual case safety reports transmitted electronically and duplicate management

The EudraVigilance database should contain all cases of suspected adverse reactions that are reportable according to Directive 2001/83/EC and Regulation (EC) No 726/2004 to support pharmacovigilance activities. This applies to all medicinal products authorised in the EU independent of their authorisation procedure.

The EudraVigilance database should also be based on the highest internationally recognised data quality standards.

To achieve these objectives, all competent authorities in Member States and marketing authorisation holders should adhere to:

- the electronic reporting requirements as defined in EU legislation;
- the concepts of data structuring, coding and reporting in line with the EU legislation, guidelines, standards and principles referred to in [VI.C.6.2.2.1.](#)

This is a pre-requisite to maintain a properly functioning EudraVigilance database intended to fully support the protection of public health.

The Agency shall, in collaboration with the stakeholder that submitted an ICSR to the EudraVigilance database, be responsible for operating procedures that ensure the highest quality and full integrity of the information collected in the EudraVigilance database [REG Art 24(3)]. This includes as well the monitoring of use of the terminologies referred to in chapter IV of the Commission Implementing Regulation (EU) No 520/2012 [IR Art 25(3)].

Specific quality system procedures and processes shall be in place in order to ensure:

- the submission of accurate and verifiable data on serious and non-serious suspected adverse reactions to the Eudravigilance database within the 15 or 90-day time frame [IR Art 11 (1) (c)];
- the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions [IR Art 11 (1) (d)].

In this regard, marketing authorisation holders and competent authorities in Member States should have in place an audit system, which ensures the highest quality of the ICSRs transmitted electronically to the EudraVigilance database within the correct time frames, and which enables the

detection and management of duplicate ICSRs in their system. Those transmitted ICSRs should be complete, entire and undiminished in their structure, format and content.

High level business process maps and process descriptions in relation to the quality review of ICSRs and the detection and management of duplicate ICSRs are provided in [VI. Appendix 6](#) and [VI. Appendix 7](#). Further guidance on the detection of duplicate ICSRs is available in the [Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports \(ICSRs\) \(EMA/13432/2009\)](#).

A review of the ICSRs quality, integrity and compliance with the reporting time frames will be performed by the Agency at regular intervals for all organisations reporting to the EudraVigilance database. Feedback from these reviews will be provided to those organisations.

VI.C.6.2.5. Electronic re-transmission of ICSRs between multiple senders and receivers

The electronic re-transmission of cases refers to the electronic exchange of ICSRs between multiple senders and receivers, for example where in case of contractual agreement, a third country ICSR is first reported by a marketing authorisation holder outside the EU to another marketing authorisation holder in the EU and from there to the Agency. This applies as well for the interim arrangements period, where based on the reporting requirements detailed in [VI.C.4.1](#), ICSRs originating in the EU are submitted by marketing authorisation holders to the competent authorities in the Member State where the reaction occurred and then re-transmitted to the EudraVigilance database.

During this re-transmission process, information on the case should not in principle be omitted or changed if no new information on the case is available to the re-transmitting sender.

Exceptions apply to the following data elements or sections:

- 'Sender's (case) safety report unique identifier' (ICH-E2B(R2) A.1.0.1);
- 'Date of this transmission' (ICH-E2B(R2) A.1.3);
- 'Date report was first received from source' (ICH-E2B(R2) A.1.6), for initial reports;
- 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7);
- 'Information on sender and receiver of case safety report' (ICH-E2B(R2) A.3);
- 'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18);
- 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' (ICH-E2B(R2) B.5.3);
- 'Sender's comments' (ICH-E2B(R2) B.5.4).

In the interest of improving data quality, in case of errors or inconsistencies in the report, the re-transmitters should go back to the originator of the report to correct the case accordingly. However, if this cannot be done within normal reporting time frame, the re-transmitter can correct information that has been incorrectly structured.

In addition, any electronic data interchange partner should adhere to the ICH-E2B(R2) rules regarding the provision of follow-up information, whereby the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should be maintained in accordance with the [ICH-E2B\(R2\) guideline](#) (see [GVP Annex IV](#)). Non-adherence to these administrative requirements endangers the electronic case management and leads to the potential for unnecessary duplication of reports in the receiver's database.

VI.C.6.2.6. Electronic reporting through company's headquarters

If a pharmaceutical company decides to centralise the electronic reporting of ICSRs (e.g. by reporting through the company's global or EU headquarter), the following should be taken into account:

- the central reporting arrangement should be clearly specified in the marketing authorisation holder's pharmacovigilance system master file and in the internal standard operating procedures;
- the company's headquarter designated for reporting the ICSRs should be registered with EudraVigilance;
- the same principles may be applied for reporting ICSRs from the competent authorities in Member States to the marketing authorisation holders during the interim arrangements period, that is the competent authorities in Member States report electronically to the company's headquarter instead of to the local affiliates.

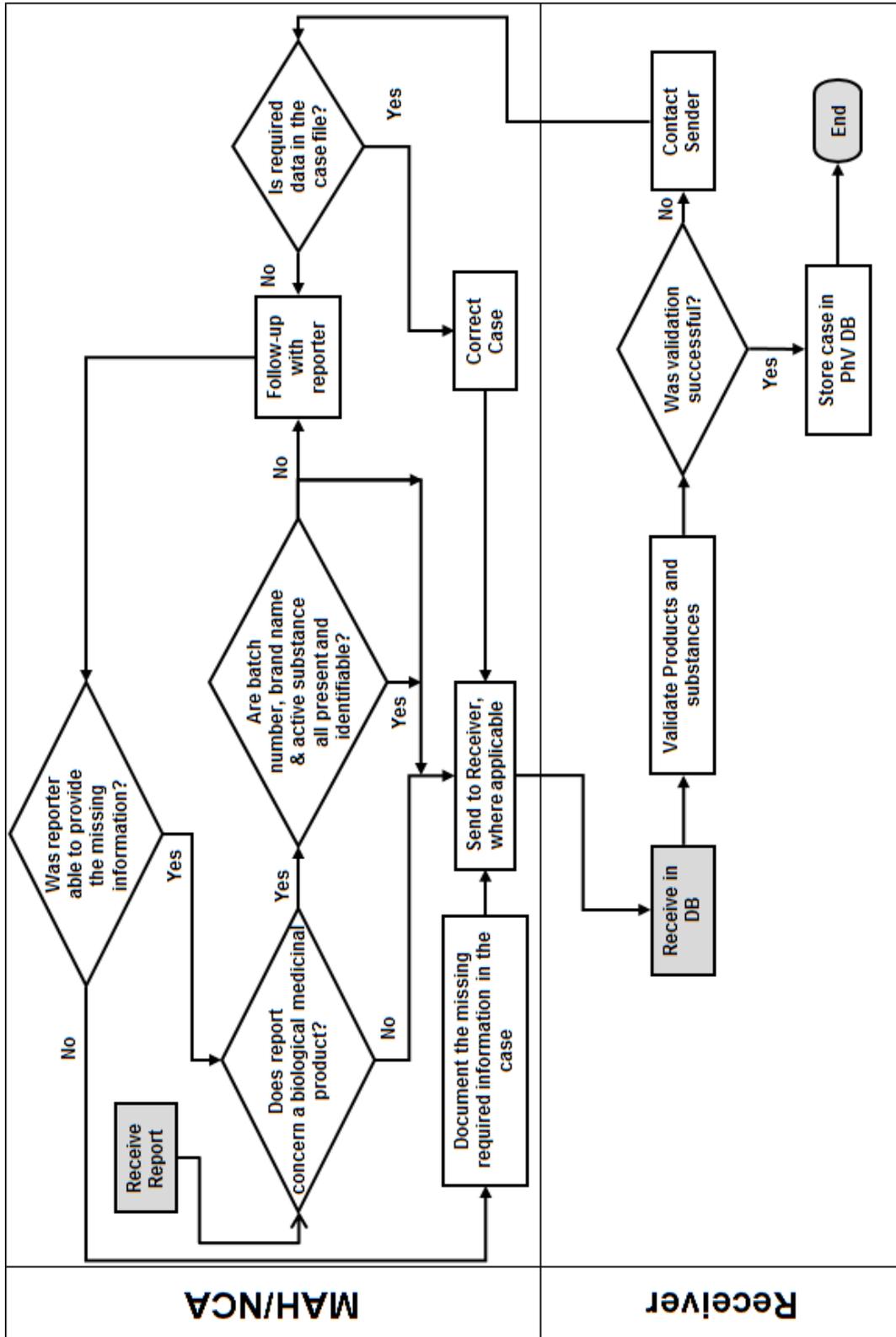
VI.C.6.3. Electronic submission of information on medicinal products

To support the objectives of Directive 2001/83/EC and Regulation (EC) No 726/2004, the provisions provided in second sub-paragraph of Article 57(2) of Regulation (EC) No 726/2004, regarding the electronic submission and update of information on medicinal products for human use authorised or registered in the EU, shall be followed by marketing authorisation holders. In this aspect marketing authorisation holders shall apply the internationally agreed formats and terminologies described in chapter IV of the Commission Implementing Regulation (EU) No 520/2012. Recommendations related to the electronic submission of information on medicines are provided on the Agency's website⁴³.

⁴³ See EMA documents for electronic submission of information on medicines:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000336.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580410138&jsenabled=true

VI. Appendix 1 Identification of biological medicinal products⁴⁴

Figure VI.2. Business process map - Identification of biological medicinal products



⁴⁴ Mandatory when they are the subject of reports of suspected adverse reactions [DIR Art 102(e) and IR Art 28 (3)].

Table VI.2. Process description - Identification of biological medicinal products

No.	Step	Description	Responsible Organisation
1	Start. Receive report.	Day 0. Receipt of the information for the case that indicates that one of the suspect drugs is of biological origin.	MAH/NCA
2	Does report concern a biological medicinal product?	If Yes, go to step 3 If No, go to step 4	
3	Are batch number, brand name & active substance all present and identifiable?	If Yes, create the case and send it to the correct receiver (step 3). If there is more than one batch number, structure the batch number that coincided with the adverse reaction in the Drug section (ICH-E2B(R2) B.4) and enter the other batch numbers in the case narrative. If No, create the case and send it to the correct receiver (step 3) and follow-up with the reporter (step 3.1).	MAH/NCA
3.1	Follow-up with reporter.	Follow-up with the reporter to attempt to identify the missing information.	MAH/NCA
3.2	Was reporter able to provide the missing information?	If Yes, return to step 1 – the information should be treated as follow-up and a new version created & transmitted. If No, document this (step 3.3).	MAH/NCA
3.3	Document the required missing information in the case.	Document in the case that the missing required information has been sought but the reporter was not able or willing to provide it.	MAH/NCA
4	Send to receiver, where applicable.	If the case requires transmission to a receiver, transmit the case electronically, in E2B(R2) format within the relevant timelines (15 or 90 days), to the relevant receiver.	MAH/NCA
5	Receive in PharmacoVigilance DataBase (PhV DB).	Receive the case electronically and load it into the PharmacoVigilance DataBase.	Receiver
6	Validate products and substances	Validate the products and substances to ensure that the brand name, active substance & batch number are all present and identifiable. This validation should be complementary to the usual business rules validations.	Receiver
7	Was validation successful?	If Yes, store the case in the PharmacoVigilance DataBase (step 8). If No, contact the sender (Step 7.1).	Receiver
7.1	Contact sender.	Contact the sender regarding the missing or not identifiable information.	Receiver

No.	Step	Description	Responsible Organisation
7.2	Is required data in the case file?	Upon receipt of communication from the receiver, check in the case file to see if the missing or unidentifiable information is already on file. If it is on file, correct the case (step 7.3). If the information is not on file, contact the reporter to request the missing information (step 3.1).	MAH/NCA
7.3	Correct case.	Correct the case to include the missing information & send updated version to receiver (step 4).	MAH/NCA
8	Store case in Pharmacovigilance DataBase (PhV DB).	The case should now be stored in the pharmacovigilance database.	Receiver
9	End.	The case is now available for signal detection and data quality analyses.	

VI. Appendix 2 Detailed guidance on the monitoring of scientific literature

VI.App2.1. When to start and stop searching in the scientific literature

EU specific requirements, as regards the monitoring of scientific and medical literature are provided in [VI.C.2.2.3.](#)

In addition to the reporting of serious and non-serious ICSRs or their presentation in periodic safety update reports, the marketing authorisation holder has an obligation to review the worldwide experience with medicinal product in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation. The worldwide experience includes published scientific and medical literature. For the period between submission and granting of a marketing authorisation, literature searching should be conducted to identify published articles that provide information that could impact on the risk-benefit assessment of the product under evaluation. For the purpose of the preparation of periodic safety update reports (see [Module VII](#)) and the notification of emerging safety issues (see [VI.C.2.2.6.](#)), the requirement for literature searching is not dependent on a product being marketed. Literature searches should be conducted for all products with a marketing authorisation, irrespective of commercial status. It would therefore be expected that literature searching would start on submission of a marketing authorisation application and continue while the authorisation is active.

VI.App2.2. Where to look

Articles relevant to the safety of medicinal products are usually published in well-recognised scientific and medical journals, however, new and important information may be first presented at international symposia or in local journals. Although the most well-known databases (e.g. Medline) cover the majority of scientific and medical journals, the most relevant publications may be collated elsewhere in very specialised medical fields, for certain types of product (e.g. herbal medicinal products) or where safety concerns are subject to non-clinical research. A marketing authorisation holder should establish the most relevant source of published literature for each product.

Medline, Embase and Excerpta Medica are often used for the purpose of identifying ICSRs. These databases have broad medical subject coverage. Other recognised appropriate systems may be used. The database providers can advise on the sources of records, the currency of the data, and the nature of database inclusions. It is best practice to have selected one or more databases appropriate to a specific product. For example, in risk-benefit assessment, safety issues arising during non-clinical safety studies may necessitate regular review of a database that has a less clinical focus and includes more laboratory-based publications.

Relevant published abstracts from meetings and draft manuscripts should be reviewed for reportable ICSRs and for inclusion in periodic safety update reports. Although it is not a requirement for marketing authorisation holders to attend all such meetings, if there are company personnel at such a meeting, or it is sponsored by a marketing authorisation holder, it is expected that articles of relevance would be available to the marketing authorisation holder's pharmacovigilance system. In addition, literature that is produced or sponsored by a marketing authorisation holder should be reviewed, so that any reportable ICSRs can be reported as required in advance of publication.

If ICSRs are brought to the attention of a marketing authorisation holder from this source, they should be processed in the same way as ICSRs found on searching a database or reviewing a journal.

Abstracts from major scientific meetings are indexed and available in some databases, but posters and communications are rarely available from this source.

VI.App2.3. Database Searches

A search is more than a collection of terms used to interrogate a database. Decisions about the database selection, approach to records retrieval, term or text selection and the application of limits need to be relevant to the purpose of the search. For searches in pharmacovigilance, some of the considerations for database searching are described below.

VI.App2.3.1. Precision and recall

Medical and scientific databases are a collection of records relating to a set of publications. For any given record, each database has a structure that facilitates the organisation of records and searching by various means, from simple text to complex indexing terms with associated subheadings. Search terms (text or indexed) can be linked using Boolean operators and proximity codes to combine concepts, increasing or decreasing the specificity of a search. In addition, limits to the output can be set. When searching, the application of search terms means that the output is less than the entire database of the records held. The success of a search can be measured according to precision and recall (also called sensitivity). Recall is the proportion of records retrieved ("hits") when considering the total number of relevant records that are present in the database. Precision is the proportion of "hits" that are relevant when considering the number of records that were retrieved. In general, the higher recall searches would result in low precision.

VI.App2.3.2. Search construction

Databases vary in structure, lag time in indexing and indexing policy for new terms. While some database providers give information about the history of a particular indexing term or the application of synonyms, other databases are less sophisticated. In addition, author abstracts are not always consistent in the choice of words relating to pharmacovigilance concepts or medicinal products/active substances names.

When constructing a search for pharmacovigilance, the highest recall for a search would be to enter the medicinal product name and active substance name (in all their variants) only. In practice, additional indexing terms and text are added to increase precision and to reduce the search result to return records that are of relevance to pharmacovigilance. There is a balance to be achieved. It is, therefore, expected that complicated searches are accompanied by initial testing to check that relevant records are not omitted, however, there is no defined acceptable loss of recall when searching for pharmacovigilance purposes. Term selection should be relevant to the database used and the subject of the search.

VI.App2.3.3. Selection of product terms

Searches should be performed to find records for active substances and not for brand names only. This can also include excipients or adjuvants that may have a pharmacological effect. When choosing search terms for medicinal products, there are a number of considerations.

- Is the active substance an indexed term?
- What spellings might be used by authors (particularly if the active substance is not indexed)?

- What alternative names might apply (numbers or codes used for products newly developed, chemical names, brand names, active metabolites)?
- Is it medically relevant to search only for a particular salt or specific compound for an active substance?

During searches for ICSRs, it may be possible to construct a search that excludes records for pharmaceutical forms or routes of administration different to that of the subject product, however, restrictions should allow for the inclusion of articles where this is not specified. Search construction should also allow for the retrieval of overdose, medication error, abuse, misuse, off-label use or occupational exposure information, which could be poorly indexed. Searches should also not routinely exclude records of unbranded products or records for other company brands.

VI.App2.3.4. Selection of search terms

As described previously, there is no acceptable loss of recall when searching published literature for pharmacovigilance. The use of search terms (free text or use of indexing) to construct more precise searches may assist in managing the output. Deficiencies that have been found frequently during Competent Authority inspections include:

- the omission of outcome terms, for example "death" as an outcome may be the only indexed term in a case of sudden death;
- the omission of pregnancy terms to find adverse outcomes in pregnancy for ICSR reporting;
- the omission of terms to include special types of reports which needs to be addressed as well in periodic safety update reports, for example,
 - Reports of asymptomatic overdose, medication error, off-label use, misuse, abuse, occupational exposure;
 - Reports of uneventful pregnancy.

VI.App2.3.5. Limits to a search

Some databases apply indexing that allows the application of limits to a search, for example by subject age, sex, publication type. The limits applied to a search are not always shown in the "search strategy" or search string.

If limits are applied, they should be relevant to the purpose of the search. When searching a worldwide scientific and medical literature database, titles and abstracts are usually in English language. The use of limits that reduce the search result to only those published in the English language is generally not acceptable. Limits applied to patient types, or other aspects of an article, for example human, would need to be justified in the context of the purpose of a search.

Limits can be applied to produce results for date ranges, for example, weekly searches can be obtained by specifying the start and end date for the records to be retrieved. Care should be taken to ensure that the search is inclusive for an entire time period, for example, records that may have been added later in the day for the day of the search should be covered in the next search period. The search should also retrieve all records added in that period, and not just those initially entered or published during the specified period (so that records that have been updated or retrospectively added are retrieved). This should be checked with the database provider if it is not clear.

Although one of the purposes of searching is to identify ICSRs for reporting, the use of publication type limits is not robust. ICSRs may be presented within review or study publications, and such records may

not be indexed as "case-reports", resulting in their omission for preparation of periodic safety update reports from search results limited by publication type.

VI.App2.4. Record keeping

Records of literature searches should be maintained in accordance with the requirements described in [IR Art 12]. Marketing authorisation holders should demonstrate due diligence in searching published scientific and medical literature. It is always good practice to retain a record of the search construction, the database used and the date the search was run. In addition, it may be useful to retain results of the search for an appropriate period of time, particularly in the event of zero results. If decision making is documented on the results, it is particularly important to retain this information.

VI.App2.5. Outputs

Databases can show search results in different ways, for example, titles only or title and abstract with or without indexing terms. Some publications are of obvious relevance at first glance, whereas others may be more difficult to identify. Consistent with the requirement to provide the full citation for an article and to identify relevant publications, the title, citation and abstract (if available) should always be retrieved and reviewed.

VI.App2.6. Review and selection of articles

It is recognised that literature search results are a surrogate for the actual article. Therefore, it is expected that the person reviewing the results of a search is trained to identify the articles of relevance. This may be an information professional trained in pharmacovigilance or a pharmacovigilance professional with knowledge of the database used. Recorded confirmation that the search results have been reviewed will assist in demonstrating that there is a systematic approach to collecting information about suspected adverse reactions from literature sources. It is recommended that quality control checks are performed on a sample of literature reviews / selection of articles to check the primary reviewer is identifying the relevant articles.

A common issue in selecting relevant articles from the results of a search is that often this process is conducted for the purposes of identification of ICSRs only. Whereas the review should also be used as the basis for collating articles for the periodic safety update report production, therefore relevant studies with no ICSRs should also be identified, as well as those reports of events that do not qualify for reporting.

Outputs from searches may contain enough information to be a valid ICSR, in which case the article should be ordered. All articles for search results that are likely to be relevant to pharmacovigilance requirements should be obtained, as they may contain valid ICSRs or relevant safety information. The urgency with which this occurs should be proportionate to the content of the material reviewed and the resulting requirement for action as applicable for the marketing authorisation holder.

Articles can be excluded from reporting by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance. Alternative reasons for the exclusion of a published article for the reporting of ICSRs are detailed in [VI.C.2.2.3.](#)

VI.App2.7. Day zero

As described in [VI.B.7.](#), day zero is the date on which an organisation becomes aware of a publication containing the minimum information for an ICSR to be reportable. Awareness of a publication includes any personnel of that organisation, or third parties with contractual arrangements with the organisation. It is sometimes possible to identify the date on which a record was available on a database, although with weekly literature searching, day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available. Organisations should take appropriate measures to obtain articles promptly in order to confirm the validity of a case.

VI.App2.8. Duplicates

Consistent with the requirements for reporting ICSRs, literature cases should be checked to prevent reporting of duplicates, and previously reported cases should be identified as such when reported. It is, therefore, expected that ICSRs are checked in the organisation database to identify literature articles that have already been reported.

VI.App2.9. Contracting out literature search services

It is possible to use the services of another party to conduct searches of the published scientific and medical literature. In this event, the responsibility for the performance of the search and subsequent reporting still remains. The transfer of a pharmacovigilance task or function should be detailed in a contract between the organisation and the service provider. The nature of third party arrangements for literature searching can range from access to a particular database interface only (access to a technology) to full literature searching, review and reporting (using the professional pharmacovigilance services of another organisation). It is recognised that more than one organisation may share services of a third party to conduct searches for generic active substances. In this instance, each organisation should satisfy itself that the search and service is appropriate to their needs and obligations.

Where an organisation is dependent on a particular service provider for literature searching, it is expected that an assessment of the service(s) is undertaken to determine whether it meets the needs and obligations of the organisation. In any case, the arrangement should be clearly documented.

The clock start for the reporting of ICSRs begins with awareness of the minimum information by either the organisation or the contractual partner (whichever is the earliest). This also applies where a third party provides a review or a collated report from the published scientific and medical literature, in order to ensure that published literature cases are reported as required within the correct time frames. That is, day zero is the date the search was run if the minimum criteria are available in the abstract and not the date the information was supplied to the organisation.

VI.App2.10. Electronic submission of copies of articles published in the scientific literature

Until standards for the electronic transmission of attachments (e.g. copies of literature articles) are developed in the framework of ICH, the sender should follow the rules outlined below for the submission of a copy of the literature article as detailed in [VI.C.6.2.3.2.](#):

1. Mailing address and format of literature articles:

Literature articles reportable to the Agency should be provided in PDF format and sent via e-mail to the following e-mail address: EVLIT@ema.europa.eu.

In relation to copies of articles from the published scientific and medical literature, marketing authorisation holders are recommended to consider potential copyright issues specifically as regards the electronic transmission and handling of electronic copies in the frame of regulatory activities.

2. File name of literature articles sent in electronic format to the Agency:

The file name of a literature article sent in PDF format should match exactly the 'World-Wide Unique Case Identification Number' (ICH-E2B(R2) A.1.10.1 or A.1.10.2 as applicable) assigned to the individual case, which is described in the article and which is reported in the E2B(R2) ICSR format.

If there is a follow-up article to the individual case published in the literature, the file name with the World-Wide Unique Case Identification Number must be maintained but should include a sequence number separated with a dash.

Examples:

- Initial ICSR published in the literature: FR-ORGABC-23232321 (data element 'World-Wide Unique Case Identification Number' (ICH-E2B(R2) A.1.10.1));
 - File name of the literature article: FR-ORGABC-23232321.pdf.
- Follow-up information published in the literature in a separate article:
 - ICSR: FR-ORGABC-23232321 (data element World-Wide Unique Case Identification Number remains unchanged (ICH-E2B(R2) A.1.10.1));
 - File name: FR-ORGABC-23232321-1.pdf.

3. Reporting of cases reported in the scientific and medical literature referring to more than one patient:

When the literature article refers to the description of more than one patient, the copy of the literature article should be sent only once.

The file name of a literature article sent in PDF format should match exactly the 'World-Wide Unique Case Identification Number' (data element ICH-E2B(R2) A.1.10.1 or A.1.10.2 as applicable) assigned to the first reportable individual case described in the article.

In addition, all ICSRs which relate to the same literature article should be cross referenced in the data element 'Identification number of the report which is linked to this report' (ICH-E2B(R2) A.1.12). The data element should be repeated as necessary to cross refer all related cases (see [Table VI.2.](#)).

Table VI.3. Examples for the reporting of ICSRs described in the scientific and medical literature and referring to more than one patient

Ex.	Scenario	Action
1	<p>A literature article describes suspected adverse reactions that have been experienced by up to 3 single patients.</p> <p>3 ICSRs should be created and reported for each individual identifiable patient described in the literature article.</p> <p>Each ICSR should contain all the available information on the case.</p>	<p>For Case 1 described in the literature article:</p> <ul style="list-style-type: none"> • ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003 • ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • File name for the copy of literature article to be sent via e-mail to EVLIT@ema.europa.eu: UK-ORGABC-0001.pdf <p>For Case 2 described in the literature article:</p> <ul style="list-style-type: none"> • ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003 • ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1. <p>For Case 3 described in the literature article:</p> <ul style="list-style-type: none"> • ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number': UK-ORGABC-0003 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002

Ex.	Scenario	Action
		<ul style="list-style-type: none"> • ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1.
2	<p>A literature article describes suspected adverse reactions that have been experienced by more than 3 single patients.</p> <p>ICSRs should be created and reported for each individual identifiable patient described in the literature article.</p> <p>Each ICSR should contain all the available information on the case.</p> <p>The cross reference with all the linked ICSRs from this literature article should only be provided in the first case, in the data element ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report'. There is no need to repeat all the cross references in the other ICSRs.</p>	<p>For the ICSRs which relate to the same literature article, the cross reference in the data element 'Identification number of the report which is linked to this report' ICH (E2B(R2) field A.1.12) should be conducted as follows:</p> <ul style="list-style-type: none"> • The first case should be linked to all other cases related to the same article; • All the other cases should be only linked to the first one, as in the example below. <p><i>Example for the reporting of cases originally reported in the scientific and medical literature referring to a large number of patients:</i></p> <p>For Case 1 described in the literature article:</p> <ul style="list-style-type: none"> • ICH E2B(R2) A.1.10.1 'Worldwide Unique Case Identification Number': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0004 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-000N • ICH-E2B(R2) A.2.2 'Literature reference(s)': N Engl J Med. 1997;336:309-15. • File name for the copy of literature article to be sent via e-mail to EVLIT@ema.europa.eu: UK-ORGABC-0001.pdf. <p>For Case 2 described in the literature article:</p> <ul style="list-style-type: none"> • ICH E2B(R2) A.1.10.1 'Worldwide Unique Case Identification Number': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • ICH-E2B(R2) A.2.2 'Literature reference(s)':

Ex.	Scenario	Action
		<p>N Engl J Med. 1997;336:309-15.</p> <ul style="list-style-type: none"> No copy of the literature article required since the copy was already submitted for case 1. <p>For Case N described in the literature article:</p> <ul style="list-style-type: none"> ICH-E2B(R2) A.1.10.1 'Worldwide Unique Case Identification Number': UK-ORGABC-000N ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 ICH-E2B(R2) A.2.2 'Literature reference(s)': N Engl J Med. 1997;336:309-15. No copy of the literature article required since the copy was already submitted for case 1.

VI. Appendix 3 Modalities for reporting

VI.App3.1. Interim arrangements

Figure VI.3. Business process map - Suspected adverse reaction reporting in EU – Interim arrangements

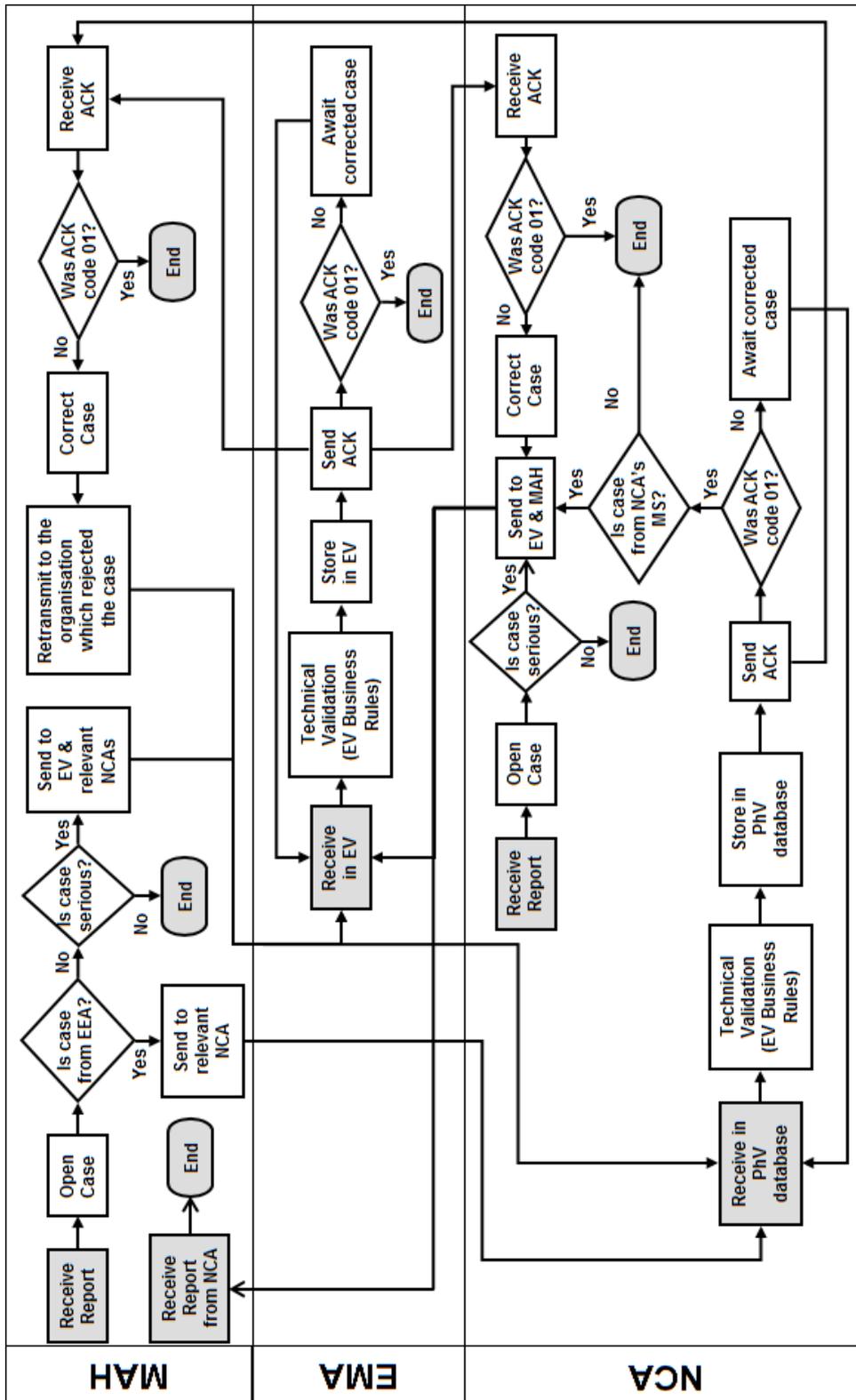


Table VI.4. Process description - Suspected adverse reaction reporting in EU - Interim arrangements

No.	Step	Description	Responsible Organisation
1	Start. Receive report.	Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter. If the case has been received from an EU NCA, <u>do not retransmit it to EudraVigilance (EV).</u>	MAH
2	Open case.	Open and create an individual case safety report.	MAH
3	Is case from EEA?	Did the adverse reactions occur in the EU? If No, go to step 3.1. If Yes, got so step 5.	MAH
3.1	Is case serious?	If No, go to step 3.2. If Yes, got to step 4.	MAH
3.2	End.	The case is now stored in the MAHs pharmacovigilance database. Normal follow-up activities should continue and if any follow-up is received, return to step 1.	MAH
4	Send to EV & relevant NCAs.	Transmit the serious case electronically, in ICH E2B(R2) format as an xml message within the 15-day time frame to EV and to the relevant NCAs, where required. The case goes to step 4.1 & step 6.	MAH
4.1	Receive in EV.	Receive the message in EV database from MAH or NCA.	EMA
4.2	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
4.3	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
4.4	Send ACK.	The acknowledgement message created in step 4.2 is transmitted to the case sender, no later than 2 business days following receipt of the case. Go to step 16 for MAHs receiving the ACK. Go to step 20 for NCAs receiving the ACK.	EMA

No.	Step	Description	Responsible Organisation
		Go to step 4.5 for the EMA's next step.	
4.5	Was ACK code 01?	If No, go to step 4.6. If Yes, go to step 4.7.	EMA
4.6	Await corrected case.	The sender should correct every case with an error ACK and retransmit within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for Pharmacovigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, then this information should be incorporated into data quality assessments and the appropriate committees should be informed. Go back to step 4.1 upon receipt of the corrected case.	EMA
4.7	End.	The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	EMA
5	Send to relevant NCA.	Transmit the case (serious, and if required non-serious) electronically, in ICH E2B(R2) format as an xml message within the relevant time frames (15 or 90 days, as applicable), to the relevant NCA for the Member State where the reaction occurred. If country of occurrence has not been specified, then country of primary source should normally be taken to be the occurrence country.	MAH
6	Receive in Pharmacovigilance DataBase (PhV DB).	Receive the message from MAH in the NCA's PhV DB.	NCA
7	Technical Validation (EV Business Rules).	Every message that is received in the NCA's PhV DB should be validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is	NCA

No.	Step	Description	Responsible Organisation
		not correctly formatted).	
8	Store in EV.	Once the case has been validated, it is stored in the NCA's PhV DB.	NCA
9	Send ACK.	The acknowledgement message created in step 7 is transmitted to the case sender no later than 2 business days following receipt of the case. Go to step 16 for MAHs receiving the ACK. Go to step 10 for the NCA's next step.	NCA
10	Was ACK code 01?	If No, go to step 10.1. If Yes, go to step 11.	NCA
10.1	Await corrected case.	The MAH should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically the NCA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the QPPV to inform them of these missing corrected cases. If a sender fails to correct cases, then this information should be incorporated into any data quality assessments performed and the appropriate action can be taken. Go back to step 6 upon receipt of the corrected case.	NCA
11	Was case from NCA's MS?	Did the case occur in the territory of the receiving NCA? If No, go to step 11.1. If Yes, go to step 12.	NCA
11.1	End.	The case is now stored in the NCA's Pharmacovigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	NCA
12	Send to EV & MAH.	Transmit the serious case electronically, in ICH E2B(R2) format as an xml message within the 15-day time frame to EV and to the relevant MAH(s). Go to step 4.1 for reception of the case in EV Go to step 24 for reception of the case by the relevant MAH(s)	NCA
13	Start. Receive report.	NCA receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter concerning a	NCA

No.	Step	Description	Responsible Organisation
		suspected adverse reaction occurring in the territory of the receiving competent authority.	
14	Open case.	Open and create an individual case safety report.	NCA
15	Is case serious?	If No, go to step 15.1 If Yes, go to step 12	NCA
15.1	End	The case is now stored in the NCA's Pharmacovigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	NCA
16	Receive ACK.	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	MAH
17	Was ACK code 01?	If yes, go to step 17.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 18 (Correct case).	MAH
17.1	End.	End the process of transmitting this version of the case to EV or NCA. Normal follow-up activities should continue and if any follow-up is received, return to step 1.	MAH
18	Correct case.	Correct the case to remove the errors identified in the ACK.	MAH
19	Retransmit to the organisation which rejected the case.	Retransmit the corrected case to the organisation which rejected the case with ACK code 02 or 03. Got to step 4.1 &/or step 6 as appropriate.	MAH
20	Receive ACK.	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	NCA
21	Was ACK code 01?	If yes, go to step 23. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting	NCA

No.	Step	Description	Responsible Organisation
		timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 22 (Correct case).	
22	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV and to the relevant MAH(s) (go back to step 12).	NCA
23	End.	End the process of transmitting this version of the case to EV and to the relevant MAH(s). Normal follow-up activities should continue and if any follow-up is received, return to step 6 or 13.	NCA
24	Receive report from NCA	MAH receives information on a suspected adverse reaction from an NCA. This case should not be retransmitted to EV and to the NCA which transmitted it to the MAH	MAH
25	End	The case is now stored in the MAH's Pharmacovigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	MAH

VI.App3.1.1. Interim arrangements applicable to marketing authorisation holders

Reporting requirements of individual case safety reports applicable to marketing authorisation holders during the interim period are detailed in the latest version of [Doc. EMA/321386/2012](#) available on EMA website.

VI.App3.1.2. Interim arrangements applicable to competent authorities in Member States

Table VI.5. Reporting requirements applicable to competent authorities in Member States - Interim arrangements

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
<ul style="list-style-type: none">• Centralised• Mutual recognition, decentralised or subject to referral• Purely national	EU	All serious	<ul style="list-style-type: none">• EudraVigilance database• Marketing authorisation holder of the suspected medicinal product	15 days

VI.App3.2. Final arrangements

Figure VI.4. Business process map - Suspected adverse reaction reporting in EU - Final arrangements

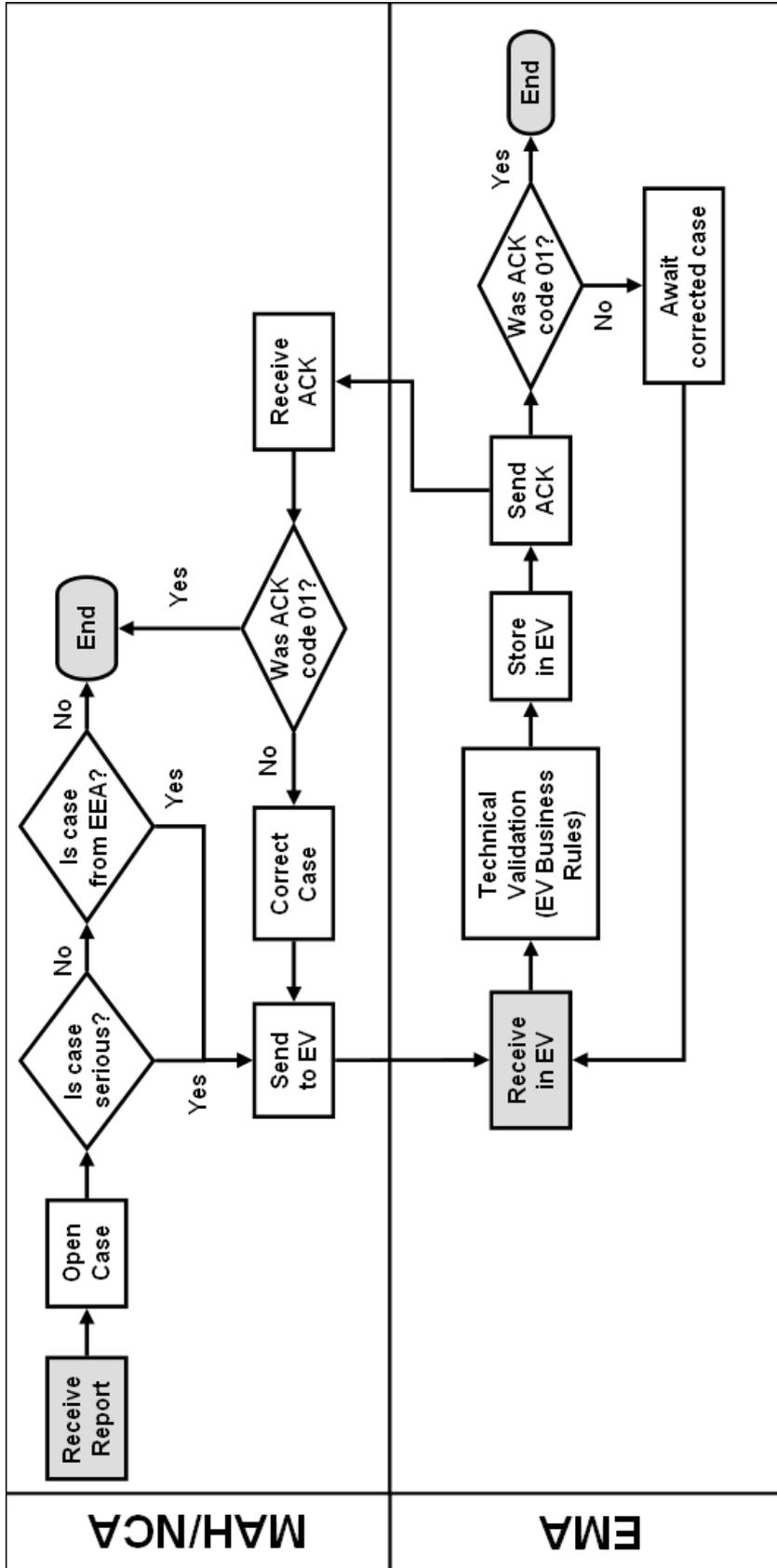


Table VI.6. Process description - Suspected adverse reaction reporting in EU - Final arrangements

No.	Step	Description	Responsible Organisation
1	Start. Receive report.	National Competent Authority (NCA) or Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter. If the case has been received from an EU NCA, <u>do not</u> retransmit it to EudraVigilance (EV).	MAH/NCA
2	Open case.	Open and create an individual case safety report.	MAH/NCA
3	Is case serious?	If No go to step 3.1. If Yes, go to step 4.	
3.1	Is case from EEA?	If No go to step 11.1. If Yes, go to step 4.	
4	Send to EV.	Transmit the case (all serious and EU non-serious) electronically, in ICH E2B(R2) format as an xml message within the relevant time frame (15 or 90 days, as applicable), to EV.	MAH/NCA
5	Receive in EV.	Receive the message in the EV.	EMA
6	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
7	Store in EV.	Once the case has been validated, it is stored in the EV.	EMA
8	Send ACK.	The acknowledgement message created in step 6 is transmitted to the case sender no later than 2 business days following receipt of the case. Go to step 9 for the EMA's next step. Go to step 10 for MAH/NCA's next step.	EMA
9	Was ACK code 01?	If No go to step 9.1. If Yes, go to step 9.2.	EMA
9.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit it within the	EMA

No.	Step	Description	Responsible Organisation
		regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for Pharmacovigilance (QPPV) to inform these missing corrected cases. If a sender fails to correct cases, this information should be incorporated into data quality assessments and the appropriate committees should be informed. Go back to step 5 upon receipt of the corrected case.	
9.2	End.	The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses. If the case occurred in the EU and was transmitted to EV by a MAH, it will be rerouted to the relevant NCA (see VI. Appendix 3.3)	EMA
10	Receive ACK.	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	MAH/NCA
11	Was ACK code 01?	If yes, go to step 11.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 12 (Correct case)	MAH/NCA
11.1	End.	End the process for this version of the case. Normal follow-up activities should continue and if any follow-up is received, return to step 1.	MAH/NCA
12	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 4).	MAH/NCA

VI.App3.2.1. Final arrangements applicable to marketing authorisation holders

Table VI.7. Reporting requirements applicable to marketing authorisation holders - Final arrangements

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
<ul style="list-style-type: none"> Centralised Mutual recognition, decentralised or subject to referral 	EU	All serious	<ul style="list-style-type: none"> EudraVigilance database 	15 days
		All non-serious	<ul style="list-style-type: none"> EudraVigilance database 	90 days
<ul style="list-style-type: none"> Purely national 	Non-EU	All serious	<ul style="list-style-type: none"> EudraVigilance database 	15 days

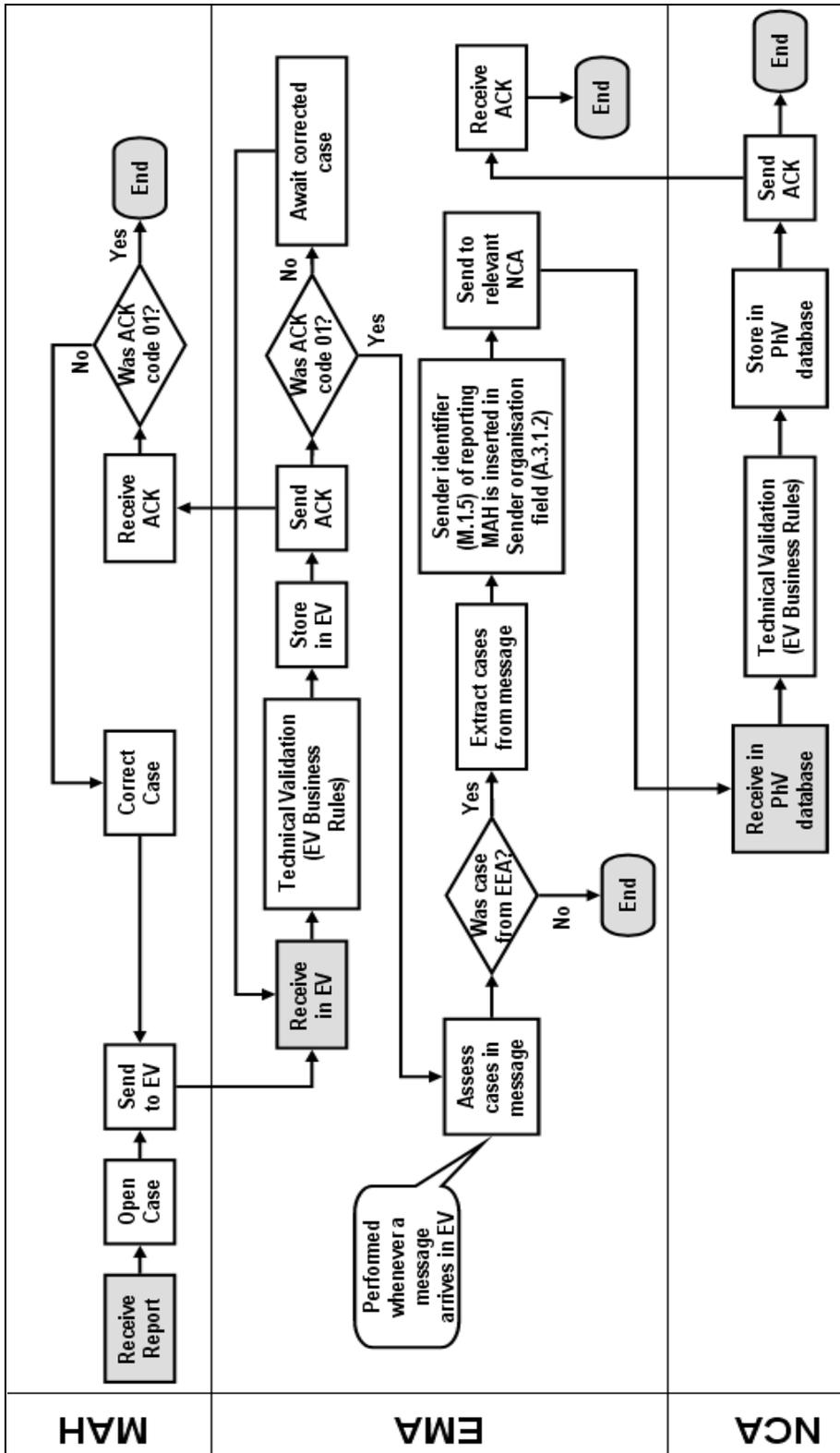
VI.App3.2.2. Final arrangements applicable to competent authorities in Member States

Table VI.8. Reporting requirements applicable to competent authorities in Member States - Final arrangements

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
<ul style="list-style-type: none"> Centralised Mutual recognition, decentralised or subject to referral 	EU	All serious	<ul style="list-style-type: none"> EudraVigilance database 	15 days
		All non-serious	<ul style="list-style-type: none"> EudraVigilance database 	90 days
<ul style="list-style-type: none"> Purely national 				

VI.App3.3. Transmission and rerouting of ICSRs to competent authorities in Member States ⁴⁵

Figure VI.5. Business process map - Transmission and rerouting of ICSRs to competent authorities in Member States



⁴⁵ Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

Table VI.9. Process description - Transmission and rerouting of ICSRs to competent authorities in Member States ⁴⁶

No.	Name	Description	Responsible Organisation
1	Start. Receive report.	Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.	MAH
2	Open case.	Open and create an individual case safety report.	MAH
3	Send to EudraVigilance (EV).	Transmit the case electronically, in ICH E2B(R2) format as an xml message within the relevant time frames (15 or 90 days, as applicable), to EV.	MAH
4	Receive in EV.	Receive the message in the EV.	EMA
5	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
6	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
7	Send ACK.	The acknowledgement message created in step 5 is transmitted to the case sender no later than 2 business days following receipt of the case.	EMA
7.1	Receive ACK.	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	MAH
7.2	Was ACK code 01?	If Yes, go to step 7.2.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 7.2.2 (Correct	MAH

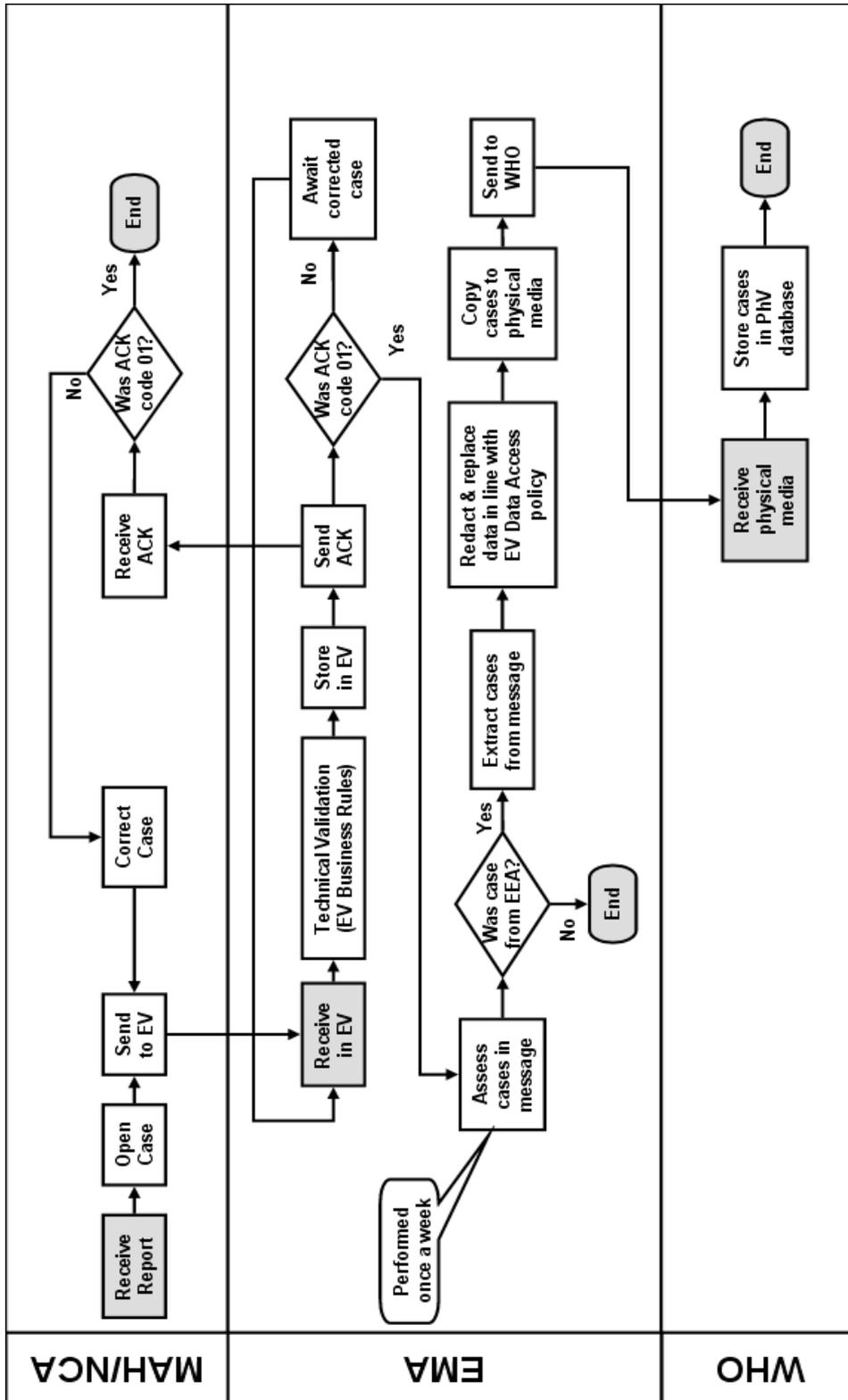
⁴⁶ Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

No.	Name	Description	Responsible Organisation
		case).	
7.2.1	End.	End the process of transmitting this version of the case to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.	MAH
7.2.2	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 3).	MAH
8	Was ACK code 01?	If yes, go to step 9. If no, perform no further processing on this version of the case and go to step 8.1	EMA
8.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for Pharmacovigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, his information should be incorporated into data quality assessments and the appropriate committees should be informed.	EMA
9	Assess cases in message.	Whenever a message has passed the technical validation, the cases therein should be immediately assessed to determine the country where the reaction occurred for regulatory reporting purposes.	EMA
10	Was case from EU?	For every case, assess whether the country of occurrence is in the EU. If Yes, go to step 11. If No, go to step 10.1	EMA
10.1	End.	The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	EMA
11	Extract cases from message.	The cases occurring in the EU will be extracted from the message for processing prior to retransmission.	EMA
12	Technical Validation.	Message sender identifier (ICH M2 M.1.5) of reporting MAH is inserted in Sender organisation field (ICH-E2B(R2) A.3.1.2) prior to retransmission. This is to permit	EMA

No.	Name	Description	Responsible Organisation
		the receiving National Competent Authority (NCA) to unambiguously identify the MAH responsible for transmitting the case to EV.	
13	Send to relevant NCA	The case is transmitted to the relevant NCA of the Member State where the reaction occurred with no other changes. Where a Member State has more than one NCA responsible for post-marketing reports, the cases occurring in that Member State are sent to all relevant NCAs.	EMA
14	Receive in Pharmacovigilance DataBase (PhV DB).	The relevant NCA receives the message in its PhV DB	NCA
15	Technical Validation (EV Business Rules).	Every message should be validated against the EudraVigilance Business Rules (the same business rules as in Step 5 and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	NCA
16	Store in Pharmacovigilance DataBase (PhV DB).	Once the case has been validated, it is stored in the PhV DB.	NCA
17	Send ACK.	The acknowledgement message created in step 15 is transmitted to EV no later than 2 business days following receipt of the case.	NCA
17.1	End	The case is now stored in the NCA's Pharmacovigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	NCA
18	Receive ACK	The acknowledgement message sent in step 17 is received & stored in EV.	EMA
19	End	The case has now been successfully retransmitted to the relevant NCA.	EMA

VI. Appendix 4 Transmission of ICSRs to World Health Organization (WHO)⁴⁷

Figure VI.6. Business process map - Transmission of ICSRs to World Health Organization (WHO) Collaborating Centre for International Drug Monitoring



⁴⁷ Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

Table VI.10. Process description - Transmission of ICSRs to World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring⁴⁸

No.	Step	Description	Responsible Organisation
1	Start. Receive report.	National Competent Authority (NCA) or Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.	MAH/NCA
2	Open case.	Open and create an individual case safety report.	MAH/NCA
3	Send to EV.	Transmit the case electronically, in ICH E2B(R2) format as an xml message within the relevant time frames (15 or 90 days, as applicable), to EudraVigilance (EV).	MAH/NCA
4	Receive in EV.	Receive the message in EV.	EMA
5	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
6	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
7	Send ACK.	The acknowledgement message created in step 5 is transmitted to the case sender no later than 2 business days following receipt of the case.	EMA
7.1	Receive ACK.	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	MAH/NCA
7.2	Was ACK code 01?	If Yes, go to step 7.2.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 7.2.2 (Correct	MAH/NCA

⁴⁸ Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

No.	Step	Description	Responsible Organisation
		case).	
7.2.1	End	End the process of transmitting this version of the case to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.	MAH/NCA
7.2.2	Correct case	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 3).	MAH/NCA
8	Was ACK code 01?	If yes, go to step 9 If no, perform no further processing on this version of the case and go to step 8.1	EMA
8.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for Pharmacovigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, this information should be incorporated into data quality assessments and the appropriate committees should be informed.	EMA
9	Assess cases in message.	Once a week, for every message that has passed the technical validation, the cases therein should be assessed to determine the country where the reaction occurred for regulatory reporting purposes.	EMA
10	Was case from EU?	For every case, assess whether the country of occurrence is in the EU. If Yes, go to step 11. If No, go to step 10.1.	EMA
10.1	End.	The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	EMA
11	Extract cases from message	The cases occurring in the EU is extracted from the message for processing prior to retransmission.	EMA
12	Redact & replace data in line with EV Data Access policy.	Prior to sending the cases to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, the extracted copies of the cases have some data elements redacted and	EMA

No.	Step	Description	Responsible Organisation
		replaced in line with the EV Data Access Policy in order to ensure personal data protection.	
13	Copy cases to physical media.	The cases are copied to physical media.	EMA
14	Send to WHO.	The physical media is sent to WHO Collaborating Centre.	EMA
15	Receive physical media	WHO Collaborating Centre receives the physical media.	WHO
16	Store cases in Pharmacovigilance DataBase (PhV DB).	Once the cases have been validated, they are stored in the PhV DB.	WHO
17	End.	Cases are stored in the WHO Collaborating Centre's Pharmacovigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	WHO

VI. Appendix 5 Nullification of cases

General principles regarding the nullification of cases are provided in [VI.C.6.2.2.10](#). The following recommendations should also be applied:

- The value in the data element 'Report nullification' (ICH-E2B(R2) A.1.13) should be set to 'Yes' and the nullification reason should be provided in the data element 'Reason for nullification' (ICH-EB(R2) A.1.13.1). The nullification reason should be clear and concise to explain why this case is no longer considered to be a valid report. For example a nullification reason stating, 'the report no longer meets the reporting criteria' or 'report sent previously in error' are not detailed enough explanations.
- An individual case can only be nullified by the sending organisation.
- Once an individual case has been nullified, the case cannot be reactivated.
- If it becomes necessary to resubmit the case that has been previously nullified, a new 'Sender's (case) safety report unique identifier' (ICH-E2B(R2) A.1.0.1) and 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should be assigned.
- Individual versions (i.e. follow-up reports) of a case cannot be nullified, only the entire individual case to which they refer.

Table VI.11. Examples of scenarios for which ICSRs should be nullified

Ex.	Scenario	Action
1	An individual case has been identified as a duplicate of another individual case previously submitted.	One of the individual cases should be nullified. The remaining valid case should be updated with any additional relevant information from the nullified case.
2	A wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) was accidentally used and does not refer to an existing case.	The case with the wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should be nullified. A new case should be created with a correct 'Worldwide unique case identification number'.
3	On receipt of further information it is confirmed that that the adverse reaction occurred before the suspect drug(s) was taken.	The case should be nullified.
4	On receipt of further information on an individual case, it is confirmed that the patient did not receive the suspect drug. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	The case should be nullified.
5	On receipt of further information it is confirmed by the same reporter that the reported adverse reaction(s) did not occur to the patient. Minimum reporting	The case should be nullified.

Ex.	Scenario	Action
	criteria for an ICSR as outlined in VI.B.2 are no longer met.	
6	On receipt of further information it is confirmed that there was no valid patient for the individual case. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	If it is not possible to obtain confirmation of the patient's existence, then the case should be nullified.

- Individual cases that have been nullified should not be used for scientific evaluation, however, they should remain in the database for auditing purposes.
- In addition, in case of duplicate reports where one report needs to be nullified, the update of the remaining case should be performed in the form of a follow-up report⁴⁹. Information on the identification of the nullified case(s) should be provided in the data element 'Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)' (ICH-E2B(R2) A.1.11.1) and in the data element 'Case identifier(s)' (ICH-E2B(R2) A.1.11.2).

Table VI.12. Examples of scenarios for which ICSRs should NOT be nullified

Ex.	Scenario	Action
7	A wrong 'Worldwide unique case identification number' (ICH E2B(R2) A.1.10) was accidentally used. This wrong ICH-E2B(R2) A.1.10 'Worldwide unique case identification number' referred to an existing case.	The report with the wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should not be nullified. A follow-up report should be submitted to correct the information previously submitted. A new ICSR should be created and submitted with the correct 'Worldwide unique case identification number'.
8	On receipt of further information on an individual case, it is confirmed that the patient did not receive the marketing authorisation holder's suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for an ICSR are still met.	The case should not be nullified.
9	On receipt of further information the reporter has confirmed that the reported adverse reaction is no longer considered to be related to the suspect medicinal product(s).	The case should not be nullified. A follow-up report should be submitted within the appropriate time frame with the updated information on the case.

⁴⁹ As presented in the [Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports \(ICSRs\)](#), [EMA/13432/2009](#).

Ex.	Scenario	Action
10	Change of the individual case from serious to non-serious (downgrading).	<p>The case should not be nullified.</p> <p>A follow-up report should be submitted with the data element 'Seriousness' (ICH-E2B(R2) A.1.5.1) populated with the value 'No' without selection of a value for the data element 'Seriousness criteria' (ICH-E2B(R2) A.1.5.2).</p> <p>The data element 'Does this case fulfil the local criteria for an expedited report?' (ICH-E2B(R2) field A.1.9) should remain populated with the value 'Yes'.</p>
11	The primary source country has changed, which has an impact on the ICH-E2B(R2) convention regarding the creation of the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10).	<p>The case should not be nullified.</p> <p>The 'Sender's (case) safety report unique identifier' (ICH-E2B(R2) A.1.0.1) can be updated on the basis of the new primary source country code. However, the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should remain unchanged.</p> <p>If, for some technical reason, the sender's local system is not fully ICH-E2B(R2) compliant and cannot follow this policy, then the sender should nullify the original case. A new case should be created with a new 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) reflecting the changed primary source country code. The 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) of the case that was nullified should be reflected in the data elements 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11).</p>
12	The suspected medicinal product belongs to another marketing authorisation holder (e.g. a product with the same active substance but marketed under a different invented name).	<p>The case should not be nullified.</p> <p>It is recommended that the initial sender informs the other marketing authorisation holder about this case (including the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) used). The original organisation should also submit a follow-up report to provide this new information.</p> <p>The other concerned marketing authorisation holder should create a new case and specify the reference case number and the name of the initial sending marketing authorisation holder in the data elements 'Source(s) of the case identifier (e.g. name of the company name of regulatory agency)' (ICH-E2B(R2) A.1.11.1) and 'Case identifier(s)' (ICH-E2B(R2) A.1.11.2). This will allow grouping the cases in the EudraVigilance database.</p>

Ex.	Scenario	Action
13	The suspected medicinal product taken does not belong to the marketing authorisation holder (same active substance, the invented name is unknown and the report originates from a country, where the marketing authorisation holder has no marketing authorisation for the medicinal product in question).	<p>The case should not be nullified.</p> <p>The marketing authorisation holder should submit a follow-up report with this information within the appropriate time frame.</p>
14	The case is mistakenly reported by the marketing authorisation holder A although the marketing authorisation holder B as co-marketer is responsible for reporting the case.	<p>The case should not be nullified.</p> <p>An explanation should be sent by the marketing authorisation holder A to the co-marketer marketing authorisation holder B that the case has already been reported. The marketing authorisation holder B should provide any additional information on the case as a follow-up report with the same 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10).</p>

VI. Appendix 6 Data quality monitoring of ICSRs transmitted electronically

Figure VI.7. Business process map - Data quality monitoring of ICSRs transmitted electronically

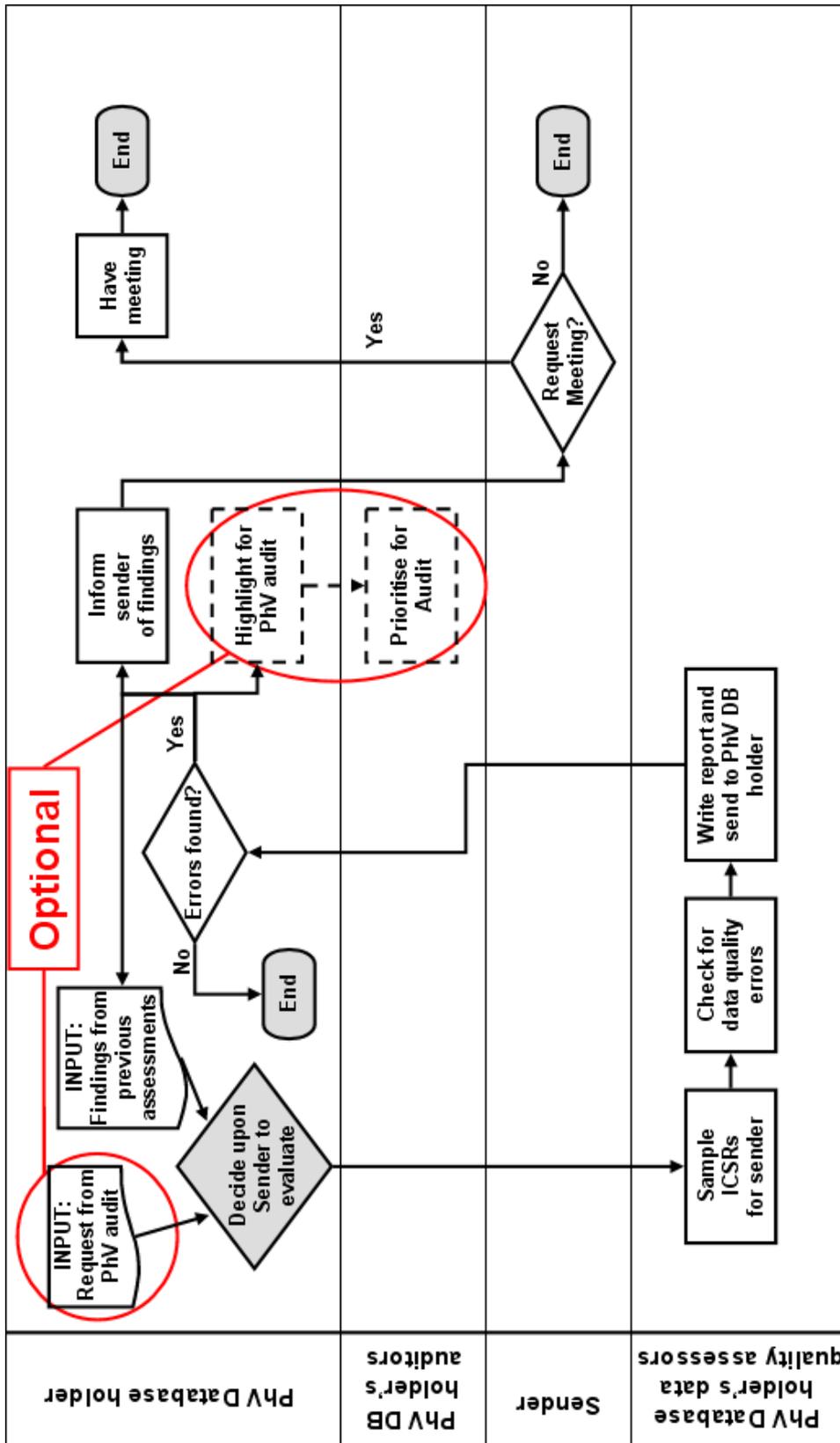


Table VI.13. Process description - Data quality monitoring of ICSRs transmitted electronically

The business map and process description describe a system where there is a separation between a Pharmacovigilance DataBase (PhV DB) holder, the PhV DB holder's data Quality Assessors (QA) and the PhV DB holder's auditors; however this is not mandatory and these functions may be performed by the same people or groups.

No.	Step	Description	Responsible Organisation
1	Start. Decide upon Sender to evaluate.	Select one of the organisations that has transmitted ICSRs to your database. Inputs into this decision can include, but need not be limited to findings from previous assessments and requests from pharmacovigilance audits.	PhV DB holder
2	Sample ICSRs from Sender.	Take a sample of ICSRs that were transmitted by the selected sender	QA
3	Check for data quality errors.	Check the cases for data quality errors. The cases should be assessed against appropriate published standards and similar documents, for example the MedDRA Term Selection Points to Consider document.	QA
4	Write report and send to PhV DB holder.	The findings from the data quality assessment should be collated into a single report. These can include related checks, such as 15-day reporting compliance, whether error reports are corrected and similar statistical information.	QA
5	Errors found?	Were any errors found during the analysis of the cases? If No, go to step 5.1. If Yes go to steps 5.2, 5.3 & 6.	PhV DB holder
5.1	End.	If there were no errors found, then no further action needs to be taken. The process can end until the next time the sender is assessed. The PhV DB holder may choose to share this information with the assessed sender and their auditors who may wish to factor this in to determinations of which sender to assess.	PhV DB holder
5.2	Highlight for PhV audit.	If the PhV DB holder's organisation has an audit department, any significant findings should always be shared with them.	PhV DB holder

No.	Step	Description	Responsible Organisation
5.2.1	Prioritise for Audit.	The audit or inspections department should use the information provided to them to feed into decisions about prioritising organisations for audit or inspection.	PhV DB holder's auditors
5.3	INPUT: Findings from previous assessments.	Any errors found (or even lack thereof) should be incorporated into decisions about which senders to evaluate & should also inform the performance of the assessments (e.g. targeting particular types of case) and the report (documenting whether previously identified issues have been addressed).	PhV DB holder
6	Inform sender of findings.	Inform the sender of the findings, including requested remedial actions (e.g. retransmitting certain cases) and time frames for those actions	PhV DB holder
7	Request meeting?	The sender should have the option to choose to request a meeting to discuss the findings and appropriate remedial action and time frames. If no meeting is requested, go to step 7.1. If a meeting is requested go to step 8.	Sender
7.1	Address the findings & retransmit any required cases.	Address all findings, take necessary steps to prevent recurrence of such findings & retransmit any required cases.	Sender
7.2	End.	Once all findings have been addressed, the necessary steps taken to prevent recurrence of such findings and any required cases have been retransmitted, the process can end until the next time the sender is assessed.	Sender
8	Have meeting.	Upon request from one party, a meeting should be held to discuss the findings of quality assessments and appropriate remedial and preventive actions to ensure that the cases in the database are correct and shall be so in the future.	PhV DB holder & Sender
9	End.	Unless further action has been specified (e.g. future meetings or assessments), the process can end until the next time the sender is assessed.	PhV DB holder

VI. Appendix 7 Duplicate detection and management of ICSRs

Figure VI.8. Business process map - Duplicate detection and management of ICSRs

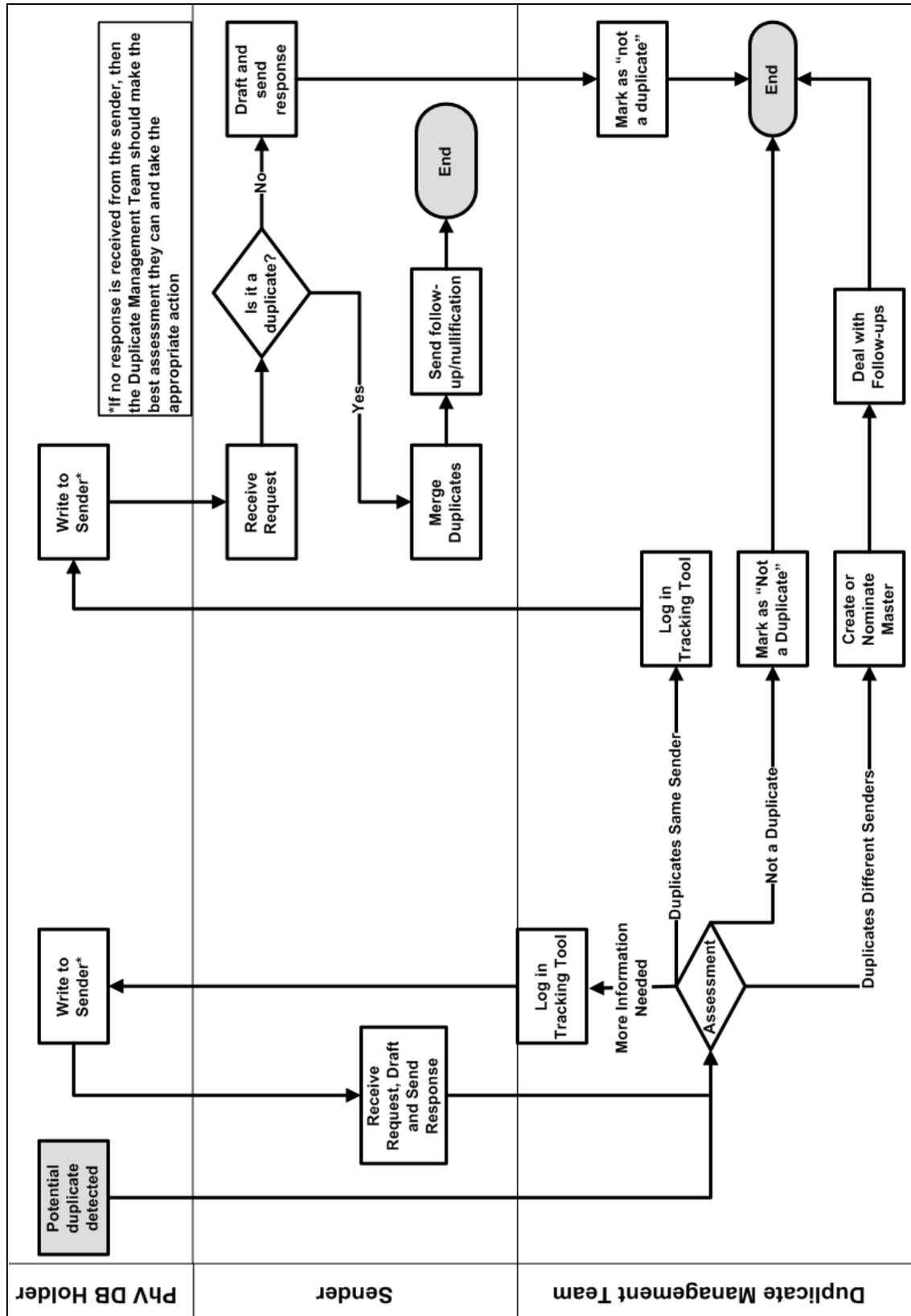


Table VI.14. Process description - Duplicate detection and management of ICSRs

No.	Step	Description	Responsible organisation
1	Start. Potential duplicate detected.	Potential duplicates have been detected by the Pharmacovigilance DataBase (PhV DB) holder organisation or the PhV DB holder organisation is notified of potential duplicates by a receiver of the cases.	PhV DB holder
2	Assessment.	<p>All potential duplicates need assessment by the organisation Duplicate Management Team (DMT) to confirm or deny their duplicate status.</p> <p>Following assessment there are 4 possible outcomes:</p> <ul style="list-style-type: none"> • Not a Duplicate (go to step 2.1), • More Information Needed (go to step 2.2), • Duplicates From Different Sender (go to step 2.3), • Duplicates From Same Sender (go to step 2.4). <p>The outcome of all assessments should be recorded to avoid continually reassessing the same cases when further versions arrive. These recorded outcomes can also be used to refine the duplicate detection methods during future development.</p>	DMT
2.1	Not a Duplicate: Mark as not a duplicate.	If the cases are assessed as not being duplicates of one another, then mark both cases as such. Go to step 3 (End).	DMT
2.2	More information needed: Log in tracking tool.	There should be some form of tool for tracking when more information is needed, when correspondence has been sent, whether an answer was received and, if so, when.	DMT
2.2.1	Write to Sender.	More information is required in order to be able to make a definite assessment. The sender (who transmitted the case(s) in question to the PhVDB holder's organisation) should be contacted to request specific information necessary to confirm or deny duplication. Personal data protection must remain paramount, so unsecured communications should not include sufficient data to	PhV DB holder

No.	Step	Description	Responsible organisation
		identify an individual.	
2.2.2	Receive request, draft and send response.	Once a request for more information has been received, the Sender of the case should respond promptly, either as a follow-up version of the case or by responding to the requester. The DMT should then reassess the case based on the new information (Go back to step 2).	Sender
2.3	Duplicates Different Senders: Create or nominate master.	Once cases have been determined to be duplicates of one another and have been transmitted to the PhV DB holder by different senders or reporters, then they should be merged under a master case, following the process described in chapter 2.3 "Management of duplicate cases" of the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009 .	DMT
2.3.1	Deal with follow-ups.	If any follow-ups arrive for any of the cases, this information may require a reassessment of the master case. Reassess and, if necessary, amend the master case as with any received follow-up information. Go to step 3 (End).	DMT
2.4	Duplicates Same Sender: Log in tracking tool.	Once cases have been determined to be duplicates of one another, and have been transmitted to the PhV DB holder by the same sender, then this decision and the correspondence referred to in step 2.4.1 should be logged in the tracking tool referred to in step 2.2.	DMT
2.4.1	Write to Sender.	The sender organisation, as the source of the duplicates, should be contacted in accordance with chapter 2.3.3 of the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009 . The sender should be asked to confirm or deny duplication and take appropriate steps in accordance with chapter 2.3.1 of the aforementioned Guideline.	PhV DB holder
2.4.2	Receive request.	Receive and log the communication	Sender

No.	Step	Description	Responsible organisation
		containing information on suspected duplicates in the Sender's PhV DB.	
2.4.3	Is it a duplicate?	Assess the potential duplicates. Are the cases duplicates of one another? If Yes, go to step 2.4.3.1. If No, go to step 2.4.3.2.	Sender
2.4.3.1	Merge duplicates.	Merge the duplicates, taking into account Flowchart 1 of chapter 2.3.1.3 of the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009 .	Sender
2.4.3.1.1	Send follow-up/nullification.	For the cases that are merged under the master, send a nullification message to the PhV DB holder. For the case that is master, send the updated case to the PhV DB holder as follow-up information. The merging & transmission should be completed promptly and in any case within 15 days of the date of receipt of the information from the PhV DB holder that the cases were considered to be possible duplicates. This date should be treated as the date of receipt of most recent information for regulatory reporting purposes.	Sender
2.4.3.1.2	End.	The duplicates have now been removed from both the Sender's system and that of the PhV DB holder and only the master should be available for signal detection and data quality analyses. Unless follow-up information is received, then no further steps need be taken.	Sender
2.4.3.2	Draft and send a response.	Reply to the PhV DB holder who sent the communication informing that the cases are not duplicates.	Sender
2.4.3.2.1	Mark as "Not a duplicate".	Upon receipt of confirmation from the Sender organisation that the cases are not duplicates, mark the cases as "Not a duplicate" & go to step 3 (End).	DMT
3	End.	No further action is required for this couple.	DMT

Appendix K: Periodic Safety Update Report

9 December 2013
EMA/816292/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1)

Date for coming into effect of first version	2 July 2012
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*Note: Revision 1 contains the following:

- updates in VII.B and VII.C.5. following finalisation of the ICH-E2C(R2) guideline on “Periodic Benefit-Risk Evaluation Report (PBRER)”, which reached Step 4 of the ICH process in November 2012, in order to harmonise the principles and agreements reached by the ICH Expert Working Group;
- further guidance regarding technical aspects on the implementation of Regulation (EU) No 1235/2010 and Directive 2010/84/EU based on the experience gained since July 2012;
- practical instructions for the application, description and maintenance of the EU reference date list in VII.C.3.2., VII.C.3.3. and VII.C.3.4. and amendments to the marketing authorisation in VII.C.3.7.;
- further instructions regarding the PSUR assessment process, product information and transitional arrangements within the EU regulatory network in VII.C..

See websites for contact details



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VII.A. Introduction

Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase.

The legal requirements for submission of PSURs are established in Regulation (EC) No 726/2004, Directive 2001/83/EC and in the Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (hereinafter referred to as IR). All applicable legal requirements in this Module are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

The format of PSURs shall follow the structure described in the IR Article 35. This Module provides guidance on the preparation, submission and assessment of PSURs.

The scope, objectives, format and content of the PSUR are described in VII.B.. The required format and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)). The PBRER format replaces the PSUR format previously described in the ICH-E2C(R1). In line with the EU legislation, the report is described as PSUR in the GVP Modules.

Further details and guidance for the submission of PSURs in the EU, including the list of Union references dates and frequency of submission are provided in VII.C., which also covers the single EU assessment of PSURs in VII.C.4.. Details related to the quality system are provided in VII.C.6. and the publication of PSUR-related documents in VII.C.7. as transparency provisions.

Each marketing authorisation holder shall be responsible for submitting PSURs for its own products [DIR Art 107b] [REG Art 28 (2)] and should submit PSURs to the Agency (see VII.C.9. for transitional arrangements) according to the following timelines:

- within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
- within 90 calendar days of the data lock point (day 0) for PSURs covering intervals in excess of 12 months;
- the timeline for the submission of ad hoc PSURs requested by competent authorities will normally be specified in the request, otherwise the ad hoc PSURs should be submitted within 90 calendar days of the data lock point.

It should be noted that detailed listings of individual cases shall not be included systematically [IR Art 34(4)]. The PSUR should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation.

Recital 23 of Directive 2010/84/EU states that the obligations imposed in respect of PSURs should be proportionate to the risks posed by medicinal products. PSUR reporting should therefore be linked to the risk management systems of a medicinal product (see Module V). The “modular approach” of the PSUR described in VII.B.5. aims to minimise duplication and improve efficiency during the preparation and review of PSURs along with other regulatory documents such as the development safety update report (DSUR)¹ or the safety specification in the Risk Management Plan (RMP), by enabling the

¹ See Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use; available on <http://ec.europa.eu/health/documents/eudralex/vol-10/>

common content of particular sections where appropriate to be utilised interchangeably across different PSURs, DSURs and RMPs.

The amended Directive 2001/83/EC also waives the obligation to submit PSURs routinely for generic medicinal products (authorised under DIR Art 10(1)), well-established use medicinal products (authorised under DIR Art 10a), homeopathic medicinal products (authorised under DIR Art 14) and traditional herbal medicinal products (authorised under DIR Art 16a), [DIR Art 107b(3)]. For such products, PSURs shall be submitted where there is a condition in the marketing authorisation or when requested by a competent authority in a Member State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs for an active substance after its authorisation [DIR Art 107b(3)(a) and (3)(b)].

Competent authorities in the Member States shall assess PSURs to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products [DIR Art 107d].

In order to increase the shared use of resources between competent authorities in Member States, a single assessment of PSURs should be performed in the EU for different medicinal products containing the same active substance or the same combination of active substances authorised in more than one Member State for which a Union reference date and frequency of submission of PSURs has been established. The EU single assessment can include joint assessment for medicinal products authorised through either national or centralised procedures for marketing authorisation. The Agency shall make available a list of Union reference dates and frequency of submission [REG Art 26(g)] which will be legally binding.

As part of the assessment, it should be considered whether further investigations need to be carried out and whether any action concerning the marketing authorisations of products containing the same active substance or the same combination of active substances, and their product information is necessary.

The Agency shall make the PSURs available to the competent authorities in Member States, members of the Pharmacovigilance Risk Assessment Committee (PRAC), of the Committee for Medicinal Products for Human use (CHMP) and of the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and the European Commission by means of a PSUR repository [DIR Art 107b(2)].

VII.B. Structures and processes

VII.B.1. Objectives of the periodic update safety report (PSUR)

The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the risk-benefit balance of the medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits. The PSUR is therefore a tool for post-authorisation evaluation at defined time points in the lifecycle of a product.

For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicine in everyday medical practice and long term use in the post-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trials. A different risk-benefit balance may emerge as pharmacovigilance reveals further information about safety. The marketing authorisation holder should therefore re-evaluate the risk-benefit balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance (see [Module XII](#)) and

risk management (see [Module V](#)) to facilitate optimisation of the risk-benefit balance through effective risk minimisation.

Urgent safety information should be reported through the appropriate mechanism. A PSUR is not intended, in the first instance, for notification of significant new safety or efficacy information or to provide the means by which new safety issues are detected, (see [Module IX](#) and [XII](#)). It is acknowledged that the review of the data in the PSUR may lead to new safety issues being identified.

VII.B.2. Principles for the evaluation of the risk-benefit balance within PSURs and scope of the information to be included

Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimisation.

After a marketing authorisation is granted, it is necessary to continue evaluating the benefits and risks of medicinal products in actual use and/or long term use, to confirm that the risk-benefit balance remains favourable.

The analysis of the risk-benefit balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available², with reasonable and appropriate effort, during the reporting interval for the medicinal product in the context of what was known previously.

The risk evaluation should be based on all uses of the medicinal product. The scope includes evaluation of safety in real medical practice including use in unauthorised indications and use which is not in line with the product information. If use of the medicinal product is identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PSUR (e.g. use in paediatric population or in pregnant women). Sources of information on use outside authorisation may include drug utilisation data, information from spontaneous reports and publications in the literature.

The scope of the benefit information should include both clinical trial and real world data in authorised indications.

The integrated benefit-risk evaluation should be performed for all authorised indications and should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorised indications).

The evaluation should involve:

1. Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.
2. Critically summarising relevant new safety, efficacy and effectiveness information that could have an impact on the risk-benefit balance of the medicinal product.
3. Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the marketing authorisation holder does not have access to data from the clinical development period, the earliest possible applicable date should be used as starting point for the inclusion and evaluation of the cumulative information.

² The ICH-E2C(R2) guideline should not serve to limit the scope of the information to be provided in the benefit-risk evaluation of a medicinal product. Please refer to the applicable laws and regulations in the countries and regions. For EU specific requirements, see [VII.C.5](#).

4. Summarising any risk minimisation actions that may have been taken or implemented during the reporting interval, as well as risk minimisation actions that are planned to be implemented.
5. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

VII.B.3. Principles for the preparation of PSURs

Unless otherwise specified by competent authorities, the marketing authorisation holder shall prepare a single PSUR for all its medicinal products containing the same active substance with information covering all the authorised indications, route of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, shall be presented in a separate section of the PSUR and any safety concerns shall be addressed accordingly [IR Art 34(6)]. There might be exceptional scenarios where the preparation of separate PSURs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement should be obtained from the relevant competent authorities preferably at the time of authorisation.

Case narratives shall be provided in the relevant risk evaluation section of the PSUR where integral to the scientific analysis of a signal or safety concern [IR Art 34(4)]. In this context, the term “case narratives” refers to clinical evaluations of individual cases rather than the CIOMS narratives. It should not be necessary to provide the actual CIOMS narrative text included in the individual case safety report (ICSR) but rather a clinical evaluation of important or illustrative cases in the context of the evaluation of the safety concern/signal.

When data received at the marketing authorisation holder from a partner might contribute meaningfully to the safety, benefit and/or benefit-risk analyses and influence the reporting marketing authorisation holder’s product information, these data should be included and discussed in the PSUR.

The format and table of contents of all PSURs shall be as described in the IR Art 35 and each report should include interval as well as cumulative data. As the PSUR should be a single stand-alone document for the reporting interval, based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C(R1) guideline, will not be accepted.

The GVP Modules on Product- or Population-Specific Considerations³ should be consulted as applicable when preparing a PSUR.

VII.B.4. Reference information

Risk minimisation activities evaluated in the PSUR include updates to the product information.

The reference product information for the PSUR should include “core safety” and “authorised indications” components. In order to facilitate the assessment of benefit and risk-benefit balance by indication in the evaluation sections of the PSUR, the reference product information document should list all authorised indications in ICH countries⁴ or regions. When the PSUR is also submitted to other countries in which there are additional locally authorised indications, these indications may be either added to the reference product information or handled as a regional appendix as considered most appropriate by the marketing authorization holder. The basis for the benefit evaluation should be the baseline important efficacy and effectiveness information summarised in the PSUR section 17.1 (“Important baseline efficacy and effectiveness information”).

³ <http://www.ema.europa.eu>

⁴ <http://www.ich.org/>

Information related to a specific indication, formulation or route of administration should be clearly identified in the reference product information.

The following possible options can be considered by the marketing authorisation holders when selecting the most appropriate reference product information for a PSUR:

- Company core data sheet (CCDS)
 - It is common practice for marketing authorisation holders to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PSUR is for each marketing authorisation holder to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR as well as the main authorised indications for which benefit is evaluated.
 - When the CCDS does not contain information on authorised indications, the marketing authorisation holder should clearly specify which document is used as reference information for the authorised indications in the PSUR.
- Other options for the reference product information
 - When no CCDS or CCSI exist for a product (e.g. where the product is authorised in only one country or region, or for established/generics products on the market for many years), the marketing authorisation holder should clearly specify the reference information being used. This may comprise national or regional product information such as the EU summary of product characteristics (SmPC).
 - Where the reference information for the authorised indications is a separate document to the reference safety information (the core safety information contained within the reference product information), the version in effect at the end of the reporting interval should be included as an appendix to the PSUR (see VII.B.5.20.).

The marketing authorisation holder should continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PSUR section 4 (“Changes to the reference safety information”) and where relevant, discussed in PSUR section 16 (“Signal and risk evaluation”). These changes may include:

- changes to contraindications, warnings/precautions sections;
- addition to adverse reactions and interactions;
- addition of important new information on use in overdose; and
- removal of an indication or other restrictions for safety or lack of efficacy reasons.

The marketing authorisation holder should provide a clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR) as an appendix to the PSUR (see VII.B.5.20.). The reference product information should be dated and version controlled.

Where new information on safety that could warrant changes to the authorised product information (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PSUR, this information should be included in the PSUR section 14 (“Late-breaking information”), if feasible.

If stipulated by applicable regional requirements, the marketing authorisation holder should provide, in the regional appendix, information on any final, ongoing and proposed changes to the national or local authorised product information (see VII.C.5.)

VII.B.5. Format and contents of the PSUR

The PSUR shall be based on all available data and shall focus on new information which has emerged since the data lock point of the last PSUR [IR Art 34(1)]. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment.

Because clinical development of a medicinal product frequently continues following marketing authorisation, relevant information from post-authorisation studies or clinical trials in unauthorised indications or populations should also be included in the PSUR. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk evaluation where relevant and appropriate.

The PSUR shall provide summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation [DIR Art 107b(1)(a)].

Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSURs include the following:

- non-clinical studies;
- spontaneous reports (e.g. on the marketing authorisation holder's safety database);
- active surveillance systems (e.g. sentinel sites);
- investigations of product quality;
- product usage data and drug utilisation information;
- clinical trials, including research in unauthorised indications or populations;
- observational studies, including registries;
- patient support programs;
- systematic reviews and meta-analysis;
- marketing authorisation holders sponsored websites⁵;
- published scientific literature or reports from abstracts, including information presented at scientific meetings;
- unpublished manuscripts;
- licensing partners, other sponsors or academic institutions and research networks;
- competent authorities (worldwide).

The above list is not intended to be all inclusive, and additional data sources may be used by the marketing authorisation holder to present safety, efficacy and effectiveness information in the PSUR and to evaluate the risk-benefit balance, as appropriate to the product and its known and emerging important benefits and risks. When desired by the marketing authorisation holder, a list of the sources of information used to prepare the PSUR can be provided as an appendix to the PSUR.

⁵ ICH-E2D [Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting](#).

A PSUR shall be prepared following the full modular structure set out in Annex II of the IR [IR Art 35].

For the purposes of this Module, sources of information include data regarding the active substance(s) included in the medicinal product, or the medicinal product that the marketing authorisation holder may reasonably be expected to have access to and that are relevant to the evaluation of the safety, and/or risk-benefit balance. It is therefore recognised that while the same format (as defined in the IR) shall be followed for all products, the extent of the information provided may vary where justified according to what is accessible to the marketing authorisation holder. For example, for a marketing authorisation holder sponsored clinical trial, there should be access to patient level data while for a clinical trial not sponsored by the marketing authorisation holder, only the published report may be accessible.

The level of detail provided in certain sections of the PSUR should depend on known or emerging important information on the medicinal product's benefits and risks. This approach is applicable to those sections of the PSUR in which there is evaluation of information about safety, efficacy, effectiveness, safety signals and risk-benefit balance.

When preparing the PSUR, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on PBRER should also be applied. Guidance on the titles, order and content of the PSUR sections is provided in VII.B.5.1. to VII.B.5.21. When no relevant information is available for any of the sections, this should be stated.

- Part I: Title page including signature⁶
- Part II: Executive Summary
- Part III: Table of Contents
 1. Introduction
 2. Worldwide marketing authorisation status
 3. Actions taken in the reporting interval for safety reasons
 4. Changes to reference safety information
 5. Estimated exposure and use patterns
 - 5.1. Cumulative subject exposure in clinical trials
 - 5.2. Cumulative and interval patient exposure from marketing experience
 6. Data in summary tabulations
 - 6.1. Reference information
 - 6.2. Cumulative summary tabulations of serious adverse events from clinical trials
 - 6.3. Cumulative and interval summary tabulations from post-marketing data sources
 7. Summaries of significant findings from clinical trials during the reporting interval
 - 7.1. Completed clinical trials
 - 7.2. Ongoing clinical trials
 - 7.3. Long-term follow-up
 - 7.4. Other therapeutic use of medicinal product

⁶ For PSURs submission in the EU, it is at the discretion of the QPPV to determine the most appropriate person to sign the document according to the marketing authorisation holder structure and responsibilities. A statement confirming the designation by the QPPV should be included. No delegation letters should be submitted.

- 7.5. New safety data related to fixed combination therapies
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
 - 9.1. Other clinical trials
 - 9.2. Medication errors
10. Non-clinical Data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview of signals: new, ongoing or closed
16. Signal and risk evaluation
 - 16.1. Summaries of safety concerns
 - 16.2. Signal evaluation
 - 16.3. Evaluation of risks and new information
 - 16.4. Characterisation of risks
 - 16.5. Effectiveness of risk minimisation (if applicable)
17. Benefit evaluation
 - 17.1. Important baseline efficacy and effectiveness information
 - 17.2. Newly identified information on efficacy and effectiveness
 - 17.3. Characterisation of benefits
18. Integrated benefit-risk analysis for authorised indications
 - 18.1. Benefit-risk context – Medical need and important alternatives
 - 18.2. Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices to the PSUR

PSUR title page

The title page should include the name of the medicinal product(s)⁷ and substance, international birth date (IBD) (the date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world), reporting interval, date of the report, marketing authorisation holder details and statement of confidentiality of the information included in the PSUR.

The title page shall also contain the signature.

⁷ For PSURs covering multiple products, for practical reasons, this information may be provided in the PSUR Cover Page (See [Annex II](#))

PSUR executive summary

An executive summary should be placed immediately after the title page and before the table of contents. The purpose of the executive summary is to provide a concise summary of the content and the most important information in the PSUR and should contain the following information:

- introduction and reporting interval;
- medicinal product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;
- estimated cumulative clinical trials exposure;
- estimated interval and cumulative exposure from marketing experience;
- number of countries in which the medicinal product is authorised;
- summary of the overall benefit-risk analysis evaluation (based on sub-section 18.2 “benefit-risk analysis evaluation” of the PSUR);
- actions taken and proposed for safety reasons, (e.g. significant changes to the reference product information, or other risk minimisation activities);
- conclusions.

PSUR table of contents

The executive summary should be followed by the table of contents.

VII.B.5.1. PSUR section “Introduction”

The marketing authorisation holder should briefly introduce the product(s) so that the PSUR “stands alone” but it is also placed in perspective relative to previous PSURs and circumstances. The introduction should contain the following information:

- IBD, and reporting interval;
- medicinal product(s), therapeutic class(es), mechanism(s) of action, authorised indication(s), pharmaceutical form(s), dose(s) and route(s) of administration;
- a brief description of the population(s) being treated and studied;

VII.B.5.2. PSUR section “Worldwide marketing authorisation status”

This section of the PSUR should contain a brief narrative overview including: date of the first authorisation worldwide, indications(s), authorised dose(s), and where authorised.

VII.B.5.3. PSUR section “Actions taken in the reporting interval for safety reasons”

This section of the PSUR should include a description of significant actions related to safety that have been taken worldwide during the reporting interval, related to either investigational uses or marketing experience by the marketing authorisation holder, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:

- a significant influence on the risk-benefit balance of the authorised medicinal product; and/or

- an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

If known, the reason for each action should be provided and any additional relevant information should be included as appropriate. Relevant updates to previous actions should also be summarised in this section.

Examples of significant actions taken for safety reasons include:

Actions related to investigational uses:

- refusal to authorise a clinical trial for ethical or safety reasons;
- partial⁸ or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
- recall of investigational drug or comparator;
- failure to obtain marketing authorisation for a tested indication including voluntary withdrawal of a marketing authorisation application;
- risk management activities, including:
 - protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
 - restrictions in study population or indications;
 - changes to the informed consent document relating to safety concerns;
 - formulation changes;
 - addition by regulators of a special safety-related reporting requirement;
 - issuance of a communication to investigators or healthcare professionals; and
 - plans for new studies to address safety concerns.

Actions related to marketing experience:

- failure to obtain or apply for a marketing authorisation renewal;
- withdrawal or suspension of a marketing authorisation;
- actions taken due to product defects and quality issues;
- suspension of supply by the marketing authorisation holder;
- risk management activities including:
 - significant restrictions on distribution or introduction of other risk minimisation measures;
 - significant safety-related changes in labelling documents including restrictions on use or population treated;
 - communications to health care professionals; and
 - new post-marketing study requirement(s) imposed by competent authorities.

⁸“Partial suspension” might include several actions (e.g. suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses). ICH-E2C(R2) guideline (see [Annex IV](#)).

VII.B.5.4. PSUR section “Changes to reference safety information”

This PSUR section should list any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR.

VII.B.5.5. PSUR section “Estimated exposure and use patterns”

PSURs shall provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the marketing authorisation holder, including the results of observational or drug utilisation studies [IR Art 34 (2)].

This PSUR section should provide estimates of the size and nature of the population exposed to the medicinal product including a brief description of the method(s) used to estimate the subject/patient exposure and the limitations of that method.

Consistent methods for calculating subject/patient exposure should be used across PSURs for the same medicinal product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR introducing the change and any important difference between the results using the two methods should be highlighted.

VII.B.5.5.1. PSUR sub-section “Cumulative subject exposure in clinical trials”

This section of the PSUR should contain the following information on the patients studied in clinical trials sponsored by the marketing authorisation holder, if applicable presented in tabular formats:

- cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD. It is recognised that for “old products”, detailed data might not be available;
- more detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex, and racial/ethnic group for the entire development programme);
- important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered;
- if clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate;
- when there are substantial differences in time of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years);
- investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;
- if the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available;

- for individual trials of particular importance, demographic characteristics should be provided separately.

Examples of tabular format for the estimated exposure in clinical trials are presented in VII. Appendix 1, Tables VII.2, VII.3 and VII.4.

VII.B.5.5.2. PSUR sub-section “Cumulative and interval patient exposure from marketing experience”

Separate estimates should be provided for cumulative exposure (since the IBD), when possible, and interval exposure (since the data lock point of the previous PSUR). Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should be provided whenever possible, along with the method(s) used to determine the estimate. Justification should be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, should be presented along with the method(s) used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

The data should be presented according to the following categories:

1. Post-authorisation (non-clinical trial) exposure:

An overall estimation of patient exposure should be provided. In addition, the data should be routinely presented by sex, age, indication, dose, formulation and region, where applicable. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment.

When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

2. Post-authorisation use in special populations:

Where post-authorisation use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data may include for instance non-interventional studies designed to obtain this information, including registries. Other sources of information may include data collection outside a study environment including information collected through spontaneous reporting systems (e.g. information on reports of pregnancy exposure without an associated adverse event may be summarised in this section). Populations to be considered for discussion include, but might not be limited to:

- paediatric population;
- elderly population;
- pregnant or lactating women;
- patients with hepatic and/or renal impairment;
- patients with other relevant co-morbidity;
- patients with disease severity different from that studied in clinical trials;
- sub-populations carrying relevant genetic polymorphism(s);
- populations with specific racial and/or ethnic origins.

3. Other post-authorisation use:

If the marketing authorisation holder becomes aware of a pattern of use of the medicinal product, which may be regional, considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include evidence of overdose, abuse, misuse and use beyond the recommendation(s) in the reference product information (e.g. an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Where relevant to the evaluation of safety and/or benefit-risk, information reported on patterns of use without reference to adverse reactions should be summarised in this section as applicable. Such information may be received via spontaneous reporting systems, medical information queries, customer's complaints, screening of digital media or via other information sources available to the marketing authorisation holder. If quantitative information on use is available, it should be provided.

If known, the marketing authorisation holder may briefly comment on whether other use beyond the recommendation(s) in the reference product information may be linked to clinical guidelines, clinical trial evidence, or an absence of authorised alternative treatments. For purposes of identifying patterns of use outside the terms of the reference product information, the marketing authorisation holder should use the appropriate sections of the reference product information that was in effect at the end of the reporting interval of the PSUR (e.g. authorised indication, route of administration, contraindications).

Signals or risks identified from any data or information source should be presented and evaluated in the relevant sections of the PSUR.

Examples of tabular format for the estimated exposure from marketing experience are presented in VII. Appendix 1, Tables VII.5 and VII.6.

VII.B.5.6. PSUR section "Data in summary tabulations"

The objective of this PSUR section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide)) and serious reactions from non-interventional studies and other non-interventional solicited source. At the discretion of the marketing authorisation holder graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) should be presented in the summary tabulations.

The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A⁹ (see Annex IV). When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSURs.

VII.B.5.6.1. PSUR sub-section "Reference information"

This sub-section of the PSUR should specify the version(s) of the coding dictionary used for presentation of adverse events/reactions.

⁹ ICH Topic E2A. Clinical safety data management: Definitions and standards for expedited reporting.

VII.B.5.6.2. PSUR sub-section “Cumulative summary tabulations of serious adverse events from clinical trials”

This PSUR sub-section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the marketing authorisation holder’s clinical trials, from the DIBD to the data lock point of the current PSUR. The marketing authorisation holder should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by MedDRA SOC (listed in the internationally agreed order), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, data can be presented by trial, indication, route of administration or other variables.

This sub-section should not serve to provide analyses or conclusions based on the serious adverse events.

The following points should be considered:

- Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.
- In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports.
- The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and marketing authorisation holders should not unblind data for the specific purpose of preparing the PSUR.
- Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

An example of summary tabulation of serious adverse events from clinical trials can be found in VII. Appendix 1 Table VII.7.

VII.B.5.6.3. PSUR sub-section “Cumulative and interval summary tabulations from post-marketing data sources”

This sub-section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies¹⁰. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional

¹⁰ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting.

studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The table should be organised by MedDRA SOC (listed in the internationally agreed order). For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables.

As described in ICH-E2D¹¹ (see Annex IV) guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter and should be considered to be suspected adverse reactions for regulatory reporting purposes.

Analysis or conclusions based on the summary tabulations should not be provided in this PSUR sub-section.

An example of summary tabulations of adverse drug reactions from post-marketing data sources can be found in VII. Appendix 1 Table VII.8.

VII.B.5.7. PSUR section “Summaries of significant findings from clinical trials during the reporting interval”

This PSUR section should provide a summary of the clinically important emerging efficacy and safety findings obtained from the marketing authorisation holder’s sponsored clinical trials during the reporting interval, from the sources specified in the sub-sections listed below. When possible and relevant, data categorised by sex and age (particularly paediatrics versus adults), indication, dose, and region should be presented.

Signals arising from clinical trial sources should be tabulated in PSUR section 15 (“Overview on signals: new, ongoing or closed”). Evaluation of the signals, whether or not categorised as refuted signals or either potential or identified risk, that were closed during the reporting interval should be presented in PSUR section 16.2 (“Signal evaluation”). New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in PSUR sections 16.3 (“Evaluation of risks and new information”) and 16.4 (“Characterisation of risks”) respectively.

Findings from clinical trials not sponsored by the marketing authorisation holder should be described in the relevant sections of the PSUR.

When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in authorised indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illness should be summarised in section 13 (“Lack of efficacy in controlled clinical trials”) (VII.B.5.13).

Information from other clinical trials/study sources should be included in the PSUR sub-section 9.1 (“other clinical trials”) (VII.B.5.9.1).

In addition, the marketing authorisation holder should include an appendix listing the sponsored post-authorisation interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval. The listing should include the following information for each trial:

- study ID (e.g. protocol number or other identifier);
- study title (abbreviated study title, if applicable);
- study type (e.g. randomised clinical trial, cohort study, case-control study);

¹¹ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting .

- population studied, including country and other relevant population descriptors (e.g. paediatric population or trial subjects with impaired renal function);
- study start (as defined by the marketing authorisation holder) and projected completion dates;
- status: ongoing (clinical trial has begun) or completed (clinical study report is finalised).

VII.B.5.7.1. PSUR sub-section “Completed clinical trials”

This sub-section of the PSUR should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis¹². It could include information that supports or refutes previously identified safety concerns as well as evidence of new safety signals.

VII.B.5.7.2. PSUR sub-section “Ongoing clinical trials”

If the marketing authorisation holder is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this sub-section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

VII.B.5.7.3. PSUR sub-section “Long term follow-up”

Where applicable, this sub-section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).

VII.B.5.7.4. PSUR sub-section “Other therapeutic use of medicinal product”

This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the marketing authorisation holder that follow a specific protocol, with solicited reporting as per ICH-E2D¹³ (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organised data collection).

VII.B.5.7.5. PSUR sub-section “New safety data related to fixed combination therapies”

Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:

- If the active substance that is the subject of the PSURs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarise important safety findings from use of the combination therapy.
- If the product itself is a fixed combination product, this PSUR sub-section should summarise important safety information arising from the individual components whether authorised or under development.

¹² Examples of synopses can be found in ICH-E3: Structure and Content of Clinical Study Reports and CIOMS VII (Council for International Organizations of Medical Sciences (CIOMS). Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials - Report of CIOMS Working Group VII). Geneva: CIOMS; 2006. <http://www.cioms.ch/>.

¹³ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting.

The information specific to the combination can be incorporated into a separate section(s) of the PSUR for one or all of the individual components of the combination.

VII.B.5.8. PSUR section “Findings from non-interventional studies”

This section should also summarise relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorisation holder-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when relevant to multiple regions

The marketing authorisation holder should include an appendix listing marketing authorisation holder-sponsored non-interventional studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed or ongoing during the reporting interval. (see VII.B.5.7. for the information that should be included in the listing).

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the PSUR (see VII.B.5.20. and VII.C.5.4.).

Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the PSUR. As for other information sources, the marketing authorisation holder should present signals or risks identified from such information in the relevant sections of the PSUR.

VII.B.5.9. PSUR section “Information from other clinical trials and sources”

VII.B.5.9 1. PSUR sub-section “Other clinical trials”

This PSUR sub-section should summarise information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources which are accessible by the marketing authorisation holder during the reporting interval (e.g. results from pool analysis or meta-analysis of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

VII.B.5.9 2. PSUR sub-section “Medication errors”

This sub-section should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process and may involve patients, consumers, or healthcare professionals.

VII.B.5.10. PSUR section “Non-clinical data”

This PSUR section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designated to address specific safety concerns should be included in the PSUR, regardless of the outcome. Implications of these findings should be discussed in the relevant evaluation sections of the PSUR.

VII.B.5.11. PSUR section “Literature”

This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the marketing authorisation holder became aware of during the reporting interval, when relevant to the medicinal product.

Literature searches for PSURs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.

The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:

- pregnancy outcomes (including termination) with no adverse outcomes;
- use in paediatric populations;
- compassionate supply, named patient use;
- lack of efficacy;
- asymptomatic overdose, abuse or misuse;
- medication error where no adverse events occurred;
- important non-clinical safety results.

If relevant and applicable, information on other active substances of the same class should be considered.

The publication reference should be provided in the style of the Vancouver Convention^{14,15}.

VII.B.5.12. PSUR section “Other periodic reports”

This PSUR section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSURs are prepared in agreement with the competent authority. In general, the marketing authorisation holder should prepare a single PSUR for a single active substance (unless otherwise specified by the competent authority); however if multiple PSURs are prepared for a single medicinal product, this section should also summarise significant findings from other PSURs if they are not presented elsewhere within the report.

When available, based on the contractual agreements, the marketing authorisation holder should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g. sponsors, other marketing authorisation holders or other contractual partners).

VII.B.5.13. PSUR section “Lack of efficacy in controlled clinical trials”

This section should summarise data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening

¹⁴ Uniform requirements for manuscripts submitted to biomedical journals. International Committee of Medical Journal Editors. N Engl J Med. 1997 Jan 23; 336(4):309-15. Available online: <http://www.nejm.org/doi/full/10.1056/NEJM199701233360422>

¹⁵ Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication [Updated April 2010] Publication Ethics: Sponsorship, Authorship, and Accountability, International Committee of Medical Journal Editors. http://www.icmje.org/urm_full.pdf

illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet medicine for acute coronary syndromes) that could reflect a significant risk to the treated population.

VII.B.5.14. PSUR section “Late-breaking information”

The marketing authorisation holder should summarise in this PSUR section the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the marketing authorisation holder, a data monitoring committee, or a competent authority (worldwide) has taken for safety reasons. New individual case reports should not be routinely included unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PSUR (e.g. a well documented case of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).

Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during this period, should also be included in this section of the PSUR (see VII.B.4.), where feasible.

The data presented in this section should also be taken into account in the evaluation of risks and new information (see VII.B.5.16.3.).

VII.B.5.15. PSUR section “Overview of signals: new, ongoing, or closed”

The general location for presentation of information on signals and risks within the PSUR is shown in figure VII.1 (see VII.B.5.21.). The purpose of this section is to provide a high level overview of signals¹⁶ that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. For the purposes of the PSUR, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the marketing authorisation holder¹⁷. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific medicine/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide) (see Module IX).

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation, involve medical judgement and scientific interpretation of available data, which is presented in section 16 (“Signal and risk evaluation”) of the PSUR.

A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PSUR, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognised risk warrants further action to verify. New signals may be

¹⁶ “Signal” means information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)].

¹⁷ In the EU-regulatory network and for the purpose of the PSUR, the term “signal” in this section corresponds with the term “validated signal” described in GVP Module IX.

classified as closed or ongoing, depending on the status of signal evaluation at the end of the reporting interval of the PSUR.

Examples of new signals would therefore include new information on a previously:

- Close and refuted signal, which would result in the signal being re-opened.
- Identified risk where the new information suggests a clinically significant difference in the severity or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new information indicative of a more severe outcome such as hepatic failure is received, or neutropenia is an identified risk and a well documented case report of agranulocytosis with no presence of possible alternative causes is received).
- Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an indicated subpopulation).
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.

Within this section, or as an appendix the marketing authorisation holder should provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation should include the following information:

- a brief description of the signal;
- date when the marketing authorisation holder became aware of the signal;
- status of the signal at the end of the reporting interval (close or ongoing);
- date when the signal was closed, if applicable;
- source of the signal;
- a brief summary of the key data;
- plans for further evaluation; and
- actions taken or planned.

An example of tabulation of signals can be found in VII. Appendix 2.

The detailed signal assessments for closed signals are not to be included in this section but instead should be presented in sub-section 16.2 ("Signal evaluation") of the PSUR.

Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a new signal should be provided in PSUR sub-section 16.3 ("Evaluation of risks and new information").

When a competent authority (worldwide) has requested that a specific topic (not considered a signal) be monitored and reported in a PSUR, the marketing authorisation holder should summarise the result of the analysis in this section if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed in sub-section 16.2 ("Signal evaluation").

VII.B.5.16. PSUR section "Signal and risk evaluation"

The purpose of this section of the PSUR is to provide:

- A succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the report (VII.B.5.16.1.).

- An evaluation of all signals closed during the reporting interval (VII.B.5.16.2).
- An evaluation of new information with respect to previously recognised identified and potential risks (VII.B.5.16.3).
- An updated characterisation of important potential and identified risks, where applicable (VII.B.5.16.4).
- A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (VII.B.5.16.5).

A flowchart illustrating the mapping of signals and risks to specific sections/sub-sections of the PSUR can be found in VII.B.5.21.

These evaluation sub-sections should not summarise or duplicate information presented in previous sections of the PSUR but should rather provide interpretation and critical appraisal of the information, with a view towards characterising the profile of those risks assessed as important. In addition, as a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PSUR but where integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g. the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided (see VII.B.3.).

VII.B.5.16.1. PSUR sub-section “Summary of safety concerns”

The purpose of this sub-section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section can be either the same as, or derived from the safety specification summary¹⁸ that is current at the start of the reporting interval of the PSUR. It should provide the following safety information:

- important identified risks;
- important potential risks; and
- missing information.

The following factors should be considered when determining the importance of each risk:

- medical seriousness of the risk, including the impact on individual patients;
- its frequency, predictability, preventability, and reversibility;
- potential impact on public health (frequency; size of treated population); and
- potential for avoidance of the use of a medicinal product with a preventive benefit due to a disproportionate public perception of risk (e.g. vaccines).

For products without an existing safety specification, this section should provide information on the important identified and potential risks and missing information associated with use of the product, based on pre- and post-authorisation experience. Important identified and potential risks may include, for example:

- important adverse reactions;
- interactions with other medicinal products;
- interactions with foods and other substances;

¹⁸ ICH-E2E – Pharmacovigilance planning (see Annex IV).

- medication errors;
- effects of occupational exposure; and
- pharmacological class effects.

The summary on missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

VII.B.5.16.2. PSUR sub-section “Signal evaluation”

This sub-section of the PSUR should summarise the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk, following evaluation. The two main categories to be included in this sub-section are:

1. Those signals that, following evaluation, have been refuted as “false” signals based on medical judgement and scientific evaluation of the currently available information.
2. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a concise description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was either refuted or considered to be a potential or identified risk by the marketing authorisation holder.

It is recommended that the level of detail provided in the description of the signal evaluation should reflect the medical significance of the signal (e.g. severe, irreversible, lead to increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:

- Closed and refuted signals.
- Closed signals that are categorised as important potential risks.
- Closed signals that are categorised as important identified risks.
- Closed signals that are potential risks not categorised as important.
- Closed signals that are identified risks not categorised as important.

Where applicable the evaluations of closed signals can be presented by indication or population.

The description(s) of the signal evaluations can be included in this sub-section of the PSUR or in an appendix. Each evaluation should include the following information as appropriate:

- source or trigger of the signal;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g. PTs, HLTs, SOCs, etc.) or Standardised MedDRA Queries (SMQs) that were reviewed), and analytical approaches;
- results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);

- discussion;
- conclusion.

Marketing authorisation holder's evaluations and conclusions for refuted signals should be supported by data and clearly presented.

VII.B.5.16.3. PSUR sub-section "Evaluation of risks and new information"

This sub-section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in sub-section 16.2 ("Signal evaluation").

New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the signals tabulation (see VII.B.5.15.) and evaluated in sub-section 16.2 ("Signal evaluation"), if the signal is also closed during the reporting interval of the PSUR.

Updated information on a previously recognised risk that does not constitute a signal should be included in this sub-section. Examples includes information that confirms a potential risk as an identified risk, or information which allows any other further characterisation of a previously recognised risk.

New information can be organised as follows:

1. New information on important potential risks.
2. New information on important identified risks.
3. New information on other potential risks not categorised as important.
4. New information on other identified risks not categorised as important.
5. Update on missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in sub-section 16.4 ("Characterisation of risks") of the report. It is recommended that the level of detail of the evaluation included in this sub-section should be proportional to the available evidence on the risk and its medical significance and public health relevance.

The evaluation(s) of the new information and missing information update(s) can be included in this sub-section of the PSUR, or in an appendix. Each evaluation should include the following information as appropriate:

- source of the new information;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- results – a summary and critical analysis of the data considered in the risk evaluation;
- discussion;
- conclusion, including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in sub-section 16.4 ("Characterisation of risks")

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this sub-section. Unresolved concerns and uncertainties should be acknowledged.

VII.B.5.16.4. PSUR sub-section “Characterisation of risks”

This sub-section should characterise important identified and potential risks based on cumulative data (i.e. not restricted to the reporting interval), and describe missing information.

Depending on the nature of the data source, the characterisation of risk may include, where applicable:

- frequency;
- numbers of cases (numerator) and precision of estimate, taking into account the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk and precision of estimate;
- estimate of absolute risk and precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- patient characteristics relevant to risk (e.g. patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);
- dose, route of administration;
- duration of treatment, risk period;
- preventability (i.e. predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker);
- reversibility;
- potential mechanism; and
- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed.

For PSURs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- risks relating to the active substance;
- risks related to a specific formulation or route of administration (including occupational exposure);
- risks relating to a specific population; and
- risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products).

VII.B.5.16.5. PSUR sub-section: “Effectiveness of risk minimisation (if applicable)”

Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse drug reaction. Risk minimisation activities may consist of routine risk minimisation (e.g. product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communication/educational materials).

The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment [IR Art 34(3)].

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this sub-section of the PSUR.

Insights into the effectiveness of risk minimisation activities in any country or region that may have utility in other countries or regions are of particular interest. Information may be summarised by region, if applicable and relevant.

When required for reporting in a PSUR, results of evaluations that became available during the reporting interval, which refer to an individual region should be provided in the PSUR regional appendix (see VII.B.5.20. and VII.C.5.5.).

VII.B.5.17. PSUR section “Benefit evaluation”

PSUR sub-sections 17.1 (“Important baseline efficacy and effectiveness information”) and 17.2 (“Newly identified information on efficacy and effectiveness”) provide the baseline and newly identified benefit information that support the characterisation of benefit described in sub-section 17.3 (“Characterisation of benefits”) that in turn supports the benefit-risk evaluation in section 18 (“Integrated benefit-risk analysis for authorised indications”).

VII.B.5.17.1. PSUR sub-section “Important baseline efficacy and effectiveness information”

This sub-section of the PSUR summarises information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval and provides the basis for the benefit evaluation. This information should relate to authorised indication(s) of the medicinal product listed in the reference product information (See VII.B.4.).

For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors when relevant.

The level of detail provided in this sub-section should be sufficient to support the characterisation of benefit in the PSUR sub-section 17.3 (“Characterisation of benefits”) and the benefit-risk assessment in section 18 (“Integrated benefit-risk analysis for authorised indications”).

VII.B.5.17.2. PSUR sub-section “Newly identified information on efficacy and effectiveness”

For some products, additional information on efficacy or effectiveness in authorised indications may have become available during the reporting interval. Such information should be presented in this sub-section of the PSUR. For authorised indications, new information on efficacy and effectiveness under conditions of actual use should also be described in this sub-section, if available. New information on efficacy and effectiveness in uses other than the authorised indications should not be included unless relevant for the benefit-risk evaluation in the authorised indications.

Information on indications newly authorised during the reporting interval should also be included in this sub-section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in sub-section 17.3 (“Characterisation of benefits”) and the benefit-risk assessment in section 18 (“Integrated benefit-risk analysis for authorised indications”).

In this sub-section, particular attention should be given to vaccines, anti-infective agents or other medicinal products where changes in the therapeutic environment may impact on efficacy/effectiveness over time.

VII.B.5.17.3. PSUR sub-section “Characterisation of benefits”

This sub-section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorised indications.

The level of detail provided in this sub-section should be sufficient to support the analysis of benefit-risk in section 18 (“Integrated benefit-risk analysis for authorised indications”).

When there are no new relevant benefit data, this sub-section should provide a characterisation of the information in sub-section 17.1 (“Important baseline efficacy and effectiveness information”).

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this sub-section should be succinct.

This sub-section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following when available:

- a brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
- new information that challenges the validity of a surrogate endpoint, if used;
- clinical relevance of the effect size;
- generalisability of treatment response across the indicated patient population (e.g. information that demonstrates lack of treatment effect in a sub-population);
- adequacy of characterization of dose-response;
- duration of effect;
- comparative efficacy; and
- a determination of the extent to which efficacy findings from clinical trials are generalisable to patient populations treated in medical practice.

VII.B.5.18. PSUR section “Integrated benefit-risk analysis for authorised indications”

The marketing authorisation holder should provide in this PSUR section an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. Whereas sub-sections 16.4 (“Characterisation of risks”) and 17.3 (“Characterisation of benefits”) present the risks and benefits, this section should provide a critical analysis and integration of the key information in the previous sections and should not simply duplicate the benefit and risk characterisation presented in the sub-sections mentioned above.

VII.B.5.18.1. PSUR sub-section “Benefit-risk context - medical need and important alternatives”

This sub-section of the PSUR should provide a brief description of the medical need for the medicinal product in the authorised indications and summarised alternatives (medical, surgical or other; including no treatment).

VII.B.5.18.2. PSUR sub-section “Benefit-risk analysis evaluation”

A risk-benefit balance is specific to an indication and population. Therefore, for products authorised for more than one indication, risk-benefit balances should be evaluated and presented by each indication individually. If there are important differences in the risk-benefit balance among populations within an indication, the benefit-risk evaluation should be presented by population, if possible.

The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks and should take into account the following points:

- Whereas previous sections/sub-sections should include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation, therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk section/sub-sections should be carried forward for integration in the benefit-risk evaluation.
- Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated (relatively healthy; chronic illness, rare conditions).
- With respect to the key benefit(s), consider its nature, clinical importance, duration, and generalisability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
- With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in unauthorised indications or populations, off-label use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:

- The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation should be clear.
- If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.
- Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk evaluation.

When there is important new information or an ad hoc PSUR has been requested, a detailed benefit-risk analysis should be presented based on cumulative data. Conversely, where little new information

has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

VII.B.5.19. PSUR section “Conclusions and actions”

A PSUR should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorised indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing authorisation holder should assess the need for changes to the reference product information and propose changes as appropriate.

In addition and as applicable, the conclusions should include preliminary proposal(s) to optimise or further evaluate the risk-benefit balance for further discussion with the relevant competent authority(ies). This may include proposals for additional risk minimisation activities.

For products with a pharmacovigilance or risk management plan, the proposals should also be considered for incorporation into the pharmacovigilance plan and/or risk minimisation plan, as appropriate (see [Module V](#)).

Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved summary of product characteristics (SmPC) for the product(s) for which the PSUR is submitted [IR Art 34(5)].

Proposed changes to the reference product information should be described in this section of the PSUR. The regional appendix should include proposals for product information (SmPC and package leaflet) together with information on ongoing changes when applicable.

VII.B.5.20. Appendices to the PSUR

A PSUR should contain the following appendices as appropriate, numbered as follows:

1. Reference information (see [VII.B.4.](#)).
2. Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
3. Tabular summary of safety signals (if not included in the body of the report)¹⁹.
4. Listing of all the marketing authorisation holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.
5. List of the sources of information used to prepare the PSUR (when desired by the marketing authorisation holder).
6. Regional appendix:

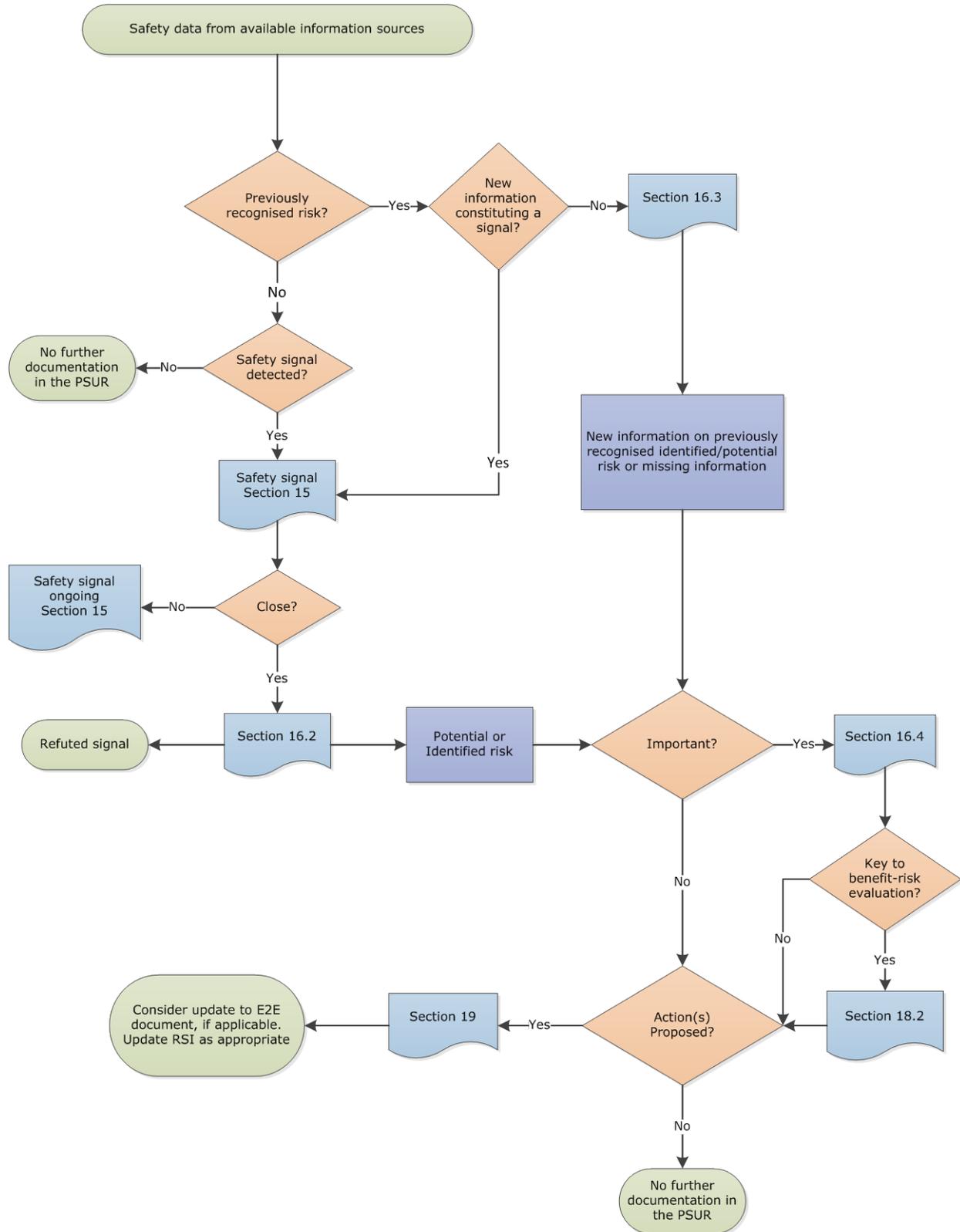
The requirements for the regional appendix in the EU are provided in section [VII.C.5.](#)

¹⁹ It is preferred to include the tabulation of signals in the body of the PSUR, if feasible.

VII.B.5.21. Mapping signals and risks to PSUR sections/sub-sections

The following flowchart (Figure VII.1) reflects the general location for the presentation of information on signals and risks within the PSUR.

Figure VII.1. PSUR Sections/subsections – signals and risks.



VII.B.6. Quality systems for PSURs at the level of marketing authorisation holders

Marketing authorisation holders should have in place structures and processes for the preparation, quality control, review and submission of PSURs including follow-up during and after their assessment. These structures and processes should be described by means of written policies and procedures in the marketing authorisation holder's quality system (see [Module I](#)).

There are a number of areas in the pharmacovigilance process that can directly impact the quality of PSURs, some examples are case management of spontaneous and study reports, literature screening, signal management, additional pharmacovigilance and post-marketing research activities, procedures for integration of information on benefits and risks from all available data sources and maintenance of product information. The quality system should describe the links between the processes, the communication channels and the responsibilities with the aim of gathering all the relevant information for the production of PSURs. There should be documented procedures including quality control checks in place to check the accuracy and completeness of the data presented in the PSURs. In ensuring completeness of data, a documented template or plan for drawing data from various data sources could be developed. The importance of an integrated approach to benefit-risk evaluation should underpin processes and cross departmental input to PSUR preparation.

The PSUR should also contain the assessment of specific safety issues requested by competent authorities in accordance with agreed timelines and procedures. The marketing authorisation holder should have mechanisms in place to ensure that the requests made by competent authorities during the time of their PSUR assessment are properly addressed.

The provision of the data included in the summary tabulations (see [VII.B.5.6.](#)) should undergo source data verification against the marketing authorisation holder's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.

An appropriate quality system should be in place in order to avoid failure to comply with PSUR requirements such as:

- non-submission: complete non-submission of PSURs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the competent authorities);
- unjustified omission of information required by [VII.B.5.](#);
- poor quality reports: poor documentation or insufficient information or evaluation provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted, absence of use of standardised medical terminology (e.g. MedDRA) and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;
- submission of a PSUR where previous requests from competent authorities have not been addressed;
- failure to provide an explicit evaluation of the risk-benefit balance of the medicinal product;
- failure to provide adequate proposals for the local authorised product information.

Any significant deviation from the procedures relating to the preparation or submission of PSURs should be documented and the appropriate corrective and preventive action should be taken. This documentation should be available at all times.

When marketing authorisation holders are involved in contractual arrangements (e.g. licensor-licensee), respective responsibilities for preparation and submission of the PSUR to the competent authorities should be clearly specified in the written agreement.

When the preparation of the PSUR is delegated to third parties, the marketing authorisation holder should ensure that they are subject to a quality system compliant with the current legislation. Explicit procedures and detailed agreements should exist between the marketing authorisation holder and third parties. The agreements may specifically detail the options to audit the PSUR preparation process.

VII.B.7. Training of staff members related to the PSUR process

For all organisations, it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in the preparation, review, quality control, submission and assessment of PSURs are adequately qualified, experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2) and this GVP Module VII). When appropriate, specific training for the different processes, tasks and responsibilities relating to the PSUR should be in place.

Training to update knowledge and skills should also take place as necessary.

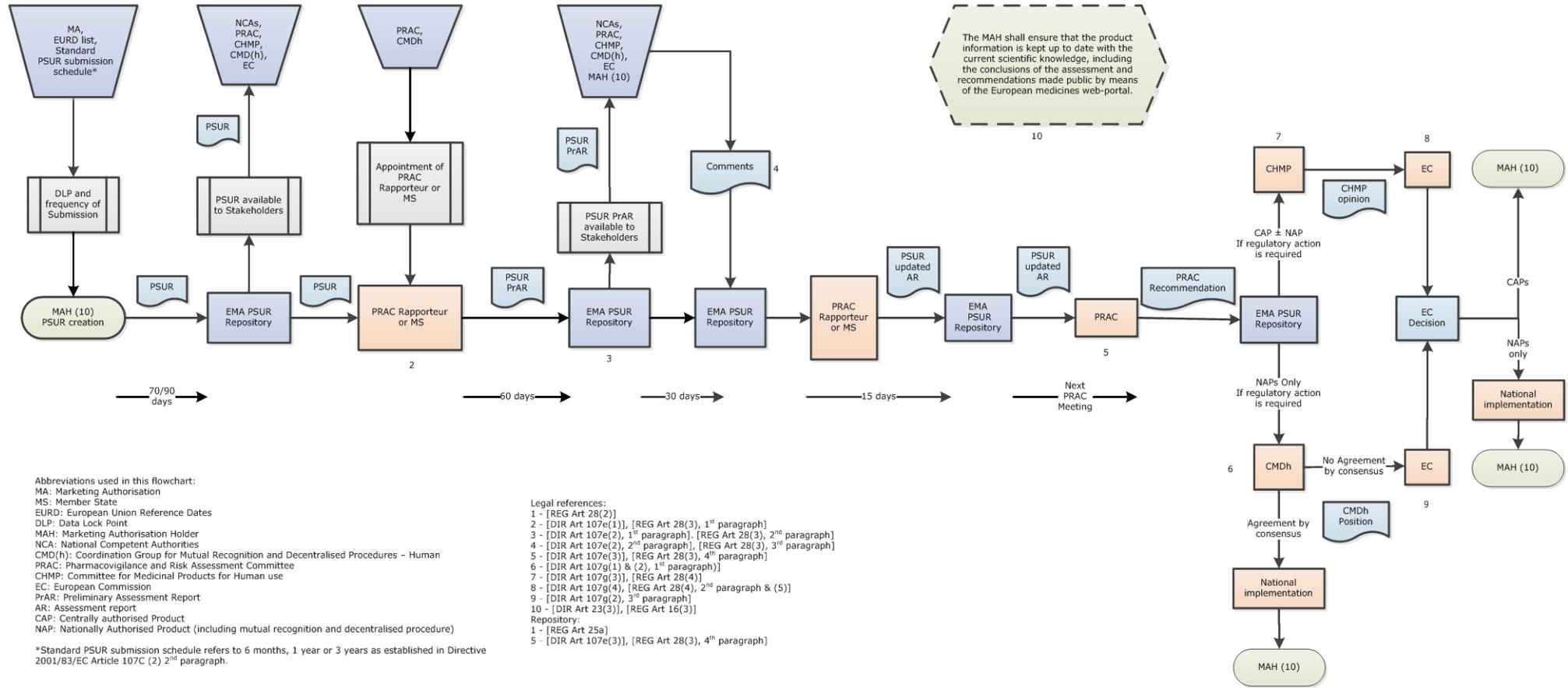
Training should cover legislation, guidelines, scientific evaluation and written procedures related to the PSUR process. Training records should demonstrate that the relevant training was delivered prior to performing PSUR-related activities.

VII.C. Operation of the EU network

VII.C.1. PSUR process in the EU - General process

The following flowchart (Figure VII.2.) reflects the general process cycle for the PSUR procedure at the EU level when recommendations by the PRAC are issued. This represents a high level cycle to outline the entire process, from the preparation of the report to the implementation of the European Commission decision/national actions when applicable. Different single steps in this flowchart are formed by intermediate steps further explained and developed in different sections in this Module.

Figure VII.2. PSUR procedure - general process



VII.C.2. Standard submission schedule of PSURs

Marketing authorisation holders for products authorised before 02 July 2012 (centrally authorised products) and 21 July 2012 (nationally authorised products) and for which the frequency and dates of submission of PSURs are not laid down as a condition to the marketing authorisation or determined otherwise in the list of Union reference dates, shall submit PSURs according to the following submission schedule [REG 28(2), DIR Art 107c(2)].

- at 6 months intervals once the product is authorised, even if it is not marketed;
- once a product is marketed, 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.

VII.C.3. List of European Union reference dates and frequency of submission of PSURs²⁰

VII.C.3.1. Objectives of the EU reference dates list

The Agency shall make public a list of Union reference dates (hereinafter referred to as list of EU reference dates) and frequency of submission of PSURs by means of the European medicines web-portal [DIR Art 107c(7), REG Art 26(1)(g)].

The objectives of the list of EU reference dates and frequency of submission of PSURs are:

- Harmonisation of data lock point and frequency of submission of PSURs for the same active substance and combination of active substances:

For medicinal products containing the same active substance or combination of active substances subject to different marketing authorisations, an EU reference date should be set up and the frequency and date of submission of PSURs harmonised in order to allow the preparation of a single assessment established in DIR Art 107e(1). Such information should be included in the list published by the Agency.

- Optimisation of the management of PSURs and PSURs assessments within the EU:

The list overrules the submission schedule described in DIR Art 107c(2)(b).

For active substances or combinations of active substances included in the list, marketing authorisation holders shall vary, if applicable, the condition laid down in their marketing authorisations in order to allow the submission of PSURs in accordance to the frequency and submission date as indicated in the list [DIR 107c(4) to (7)].

The periodicity is defined on the basis of a risk-based approach in order to prioritise the periodic re-evaluation of the risk-benefit balance of active substances in a way that best protects public health [Directive 2010/84/EU Preamble Recital 23].

- Single EU assessment and reassessment of the risk-benefit balance of an active substance based on all available safety data:

The list enables the harmonisation of PSUR submissions for medicinal products containing the same active substance or the same combination of active substances.

²⁰ The initial EU reference dates list was adopted by the CHMP/CMDh following consultation of the PRAC in September 2012 and was published on 01 October 2012.

A single EU PSUR assessment provides a mechanism for evaluating the totality of available data on the benefits and risks of an active substance or combination of active substances. The effective application of work sharing principles is important in avoiding duplication of efforts and in prioritising the use of limited resources in the best interests of European citizens.

VII.C.3.2. Description of the EU reference dates list

The Union reference date of medicinal products containing the same active substance or the same combination of active substances shall be [DIR Art 107c(5)]:

- the date of the first marketing authorisation in the EU of a medicinal product containing that active substance or that combination of active substances; or
- if the date of first marketing authorisation cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

The list of EU reference dates and frequency of submission of PSURs consists of a comprehensive list of substances and combinations of active substances in alphabetical order, for which PSURs, where required, shall be submitted in accordance with the EU reference date and the frequency as determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC) [DIR Art 107c(4) and (6)]. The list should be updated in line with the “list of all medicinal products for human use authorised in the Union” as referred to in REG Art 57(1)(b).

The EU reference dates list should contain the following information:

- the EU reference dates;
- the frequencies of submission of PSURs;
- the data lock points of the next submissions of PSURs;
- the date of publication (on the European Medicines web-portal) of the frequency for PSURs submission and data lock point for each active substance and combination of active substances. Any change to the dates of submission and frequency on PSURs specified in the marketing authorisation shall take effect 6 months after the date of such publication [DIR Art 107c(7)].

Where specificity is deemed necessary, the list should include the scope of the PSUR and related EU single assessment procedure (see VII.C.3.3.) such as:

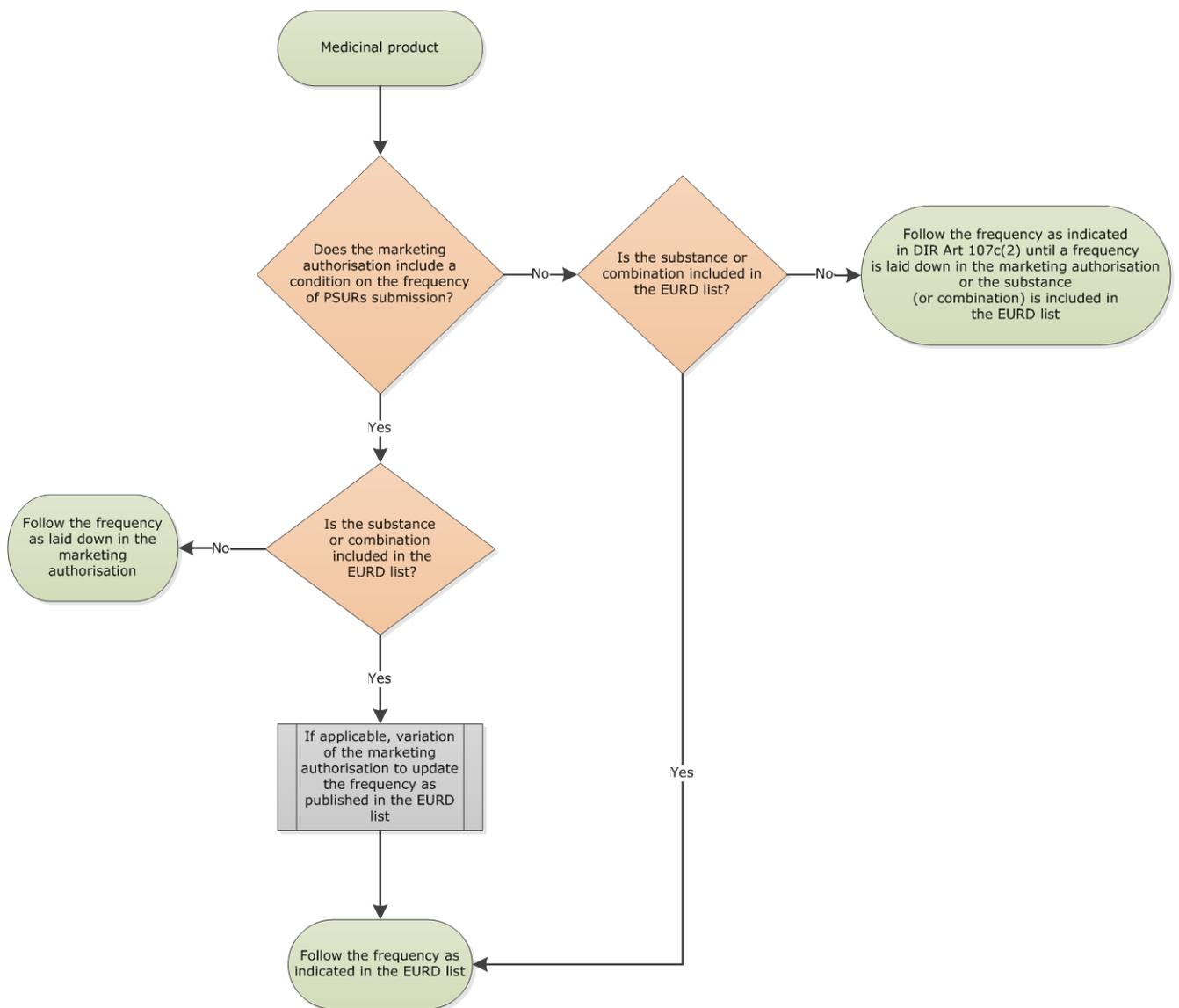
- whether or not it should cover all the indications of the substance or combination of active substances;
- whether or not it should cover all the formulations/routes of administration of the products containing a substance or combination of active substances;
- whether generic, well-established use, traditional herbal and homeopathic medicinal products shall submit a PSUR due to a request from a competent authority or due to concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted [DIR Art 107c(2) second subparagraph] (see VII.C.3.3.2.).

VII.C.3.3. Application of the list of EU reference dates to submission of PSURs

VII.C.3.3.1. Submission of PSURs for medicinal products: general requirement

Figure VII.3. presents the various potential scenarios for the submission of a PSUR as a general requirement.

Figure VII.3. Conditions for PSURs submission as general requirement



The data lock points included in the list of EU reference dates enable the synchronisation of PSURs submission for products subject to different marketing authorisations and permit the EU single assessment. These data lock points are fixed on a certain date of the month, and should be used to determine the submission date (which has legal status) of the PSUR. Marketing authorisation holders can request to amend those dates in accordance with section VII.C.3.5.2.

Unless otherwise specified in the list of EU reference dates and frequency of submission, or agreed with competent authorities in Member States or the Agency, as appropriate, a single PSUR shall be prepared for all medicinal products containing the same active substance and authorised for one marketing authorisation holder. The PSUR shall cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorised under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen shall be presented in a separate section of the PSUR and any safety concerns shall be addressed accordingly [IR Art 34(6)].

For medicinal products containing an active substance or a combination of active substances not included in the EU reference dates list, PSURs shall be submitted according to the PSUR frequency defined in the marketing authorisation or if not specified, in accordance with the submission schedule specified in DIR Art 107c(2) and REG Art 28(2).

VII.C.3.3.2. Submission of PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products

By way of derogation, generics (authorised under DIR Art 10(1)), well-established use (authorised under DIR Art 10a), homeopathic (authorised under DIR Art 14) and traditional herbal (authorised under DIR Art 16a) medicinal products are exempted from submitting PSURs except in the following circumstances [DIR Art 107b(3)]:

- the marketing authorisation provides for the submission of PSURs as a condition;
- PSURs is (are) requested by a competent authority in a Member State on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted (e.g. when the “reference” medicinal product is no longer marketed). The assessment reports of the requested PSURs shall be communicated to the PRAC, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the CMDh or CHMP accordingly, in order to apply the procedures laid down in DIR Art 107c(4) and 107e.

In order to facilitate and optimise the PSUR EU single assessment process, to avoid duplications of requests for PSURs and to provide transparency and predictability for the marketing authorisation holders, the legislative provision laid down in DIR 107b(3)(b) is applied by specifying in the list of EU reference dates, the substances for which PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products are required. This specification is based on the request made by a competent authority in a Member State during the creation or maintenance of the list of EU reference dates and on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance.

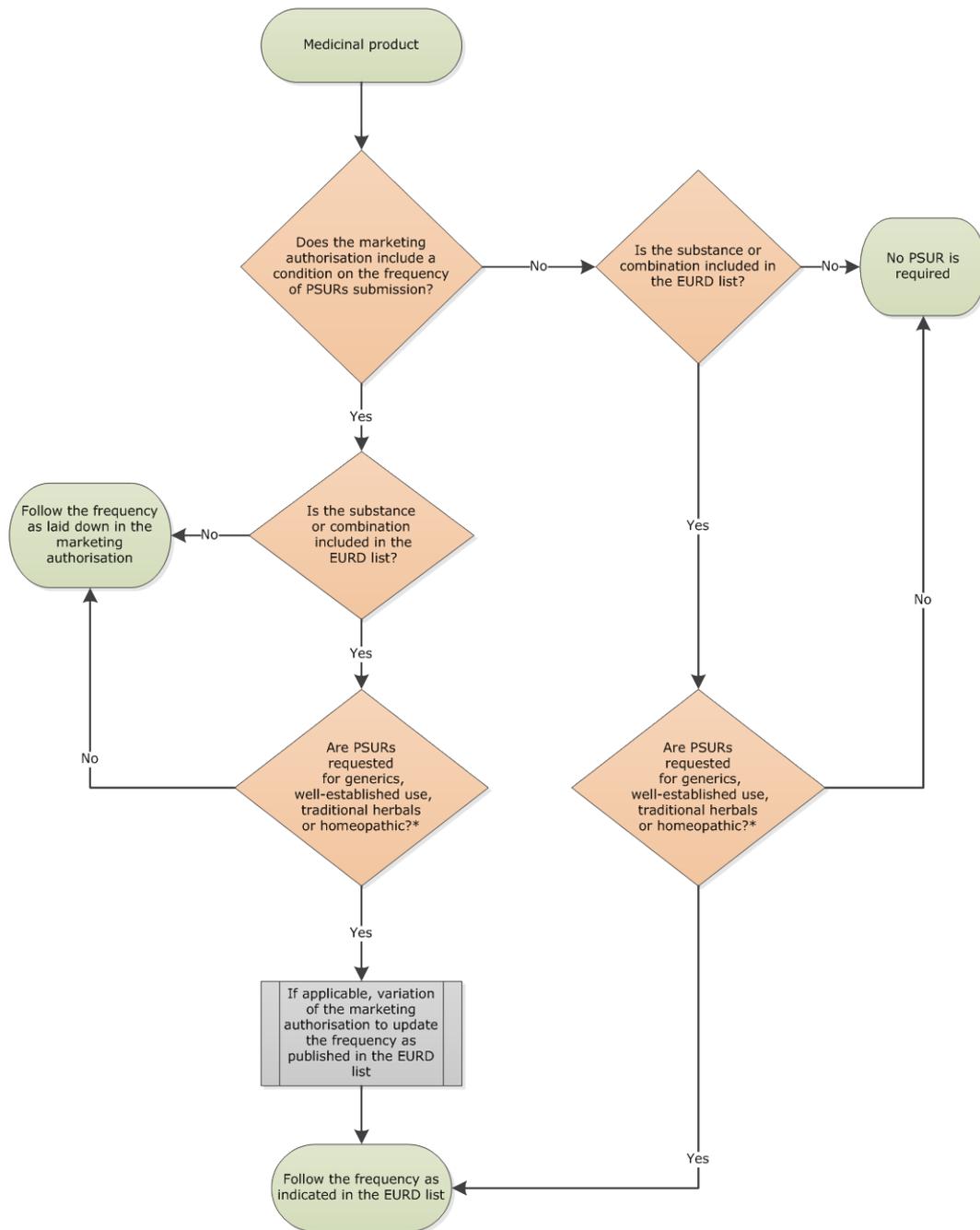
The harmonised frequency for the submission of the reports and the EU reference dates are determined by the CHMP and/or CMDh after consultation of the PRAC.

The application of the list of EU reference dates for the submission of PSURs for generic, well-established use, traditional herbal and homeopathic medicinal products does not undermine the right of a competent authority in a Member State to request the submission of PSURs at any time under the provision laid down in [DIR Art 107c(2) second subparagraph].

For products where PSURs are no longer required to be submitted routinely, it is expected that marketing authorisation holders will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts on the risk-benefit balance or the product information (See [Module VI](#) and [Module IX](#)).

[Figure VII.4](#) presents the various potential scenarios as regard the submission of a PSUR for generic, well-established use, traditional herbal and homeopathic medicinal products:

Figure VII.4. Conditions for PSURs submission for generic, well-established use, traditional herbal and homeopathic medicinal products.



* Whether marketing authorisation holders for generics, well-established use, traditional herbal and homeopathic medicinal products are requested to submit PSURs following a request of a competent authority in a Member State due to concerns relating to pharmacovigilance data or lack of PSUR submission.

VII.C.3.3.3. Submission of PSURs for fixed dose combination products

Unless otherwise specified in the list of EU reference dates and frequency of submission, if the substance that is the subject of the PSUR is also authorised as a component of a fixed combination medicinal product, the marketing authorisation holder shall either submit a separate PSUR for the combination of active substances authorised for the same marketing authorisation holder with cross-references to the single-substance PSUR(s), or provide the combination data within one of the single-substance PSURs [IR Art 34(7)].

VII.C.3.3.4. Submission of PSURs on demand of a competent authority in a Member State

Marketing authorisation holders shall submit PSURs immediately upon request from a competent authority in a Member State [DIR Art 107c(2)]. To facilitate the EU assessment and avoid duplication of requests, the competent authorities in the Member States should normally make use of the list of EU reference dates to request the submission of PSURs, however in especial circumstances competent authorities in Member States can directly request the submission of a PSUR. When the timeline for submission has not been specified in the request, marketing authorisation holders should submit the PSUR within 90 calendar days of the data lock point.

VII.C.3.4. Criteria used for defining the frequency of submission of PSURs

When deviating from the PSUR submission schedule defined in DIR Art 107c(2)(b), the frequencies of submission of PSURs and the corresponding data lock points should be defined on a risk-based approach by the CHMP where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure or by the CMDh otherwise, after consultation with the PRAC.

The following prioritisation criteria should be taken into account when defining the frequency of submission for a given active substance or combination of active substances:

- information on risks or benefits that may have an impact on the public health;
- new product for which there is limited safety information available to date (includes pre- and post-authorisation experiences);
- significant changes to the product (e.g. new indication has been authorised, new pharmaceutical form or route of administration broadening the exposed patient population);
- vulnerable patient populations/poorly studied patient populations, missing information (e.g. children, pregnant women) while these populations are likely to be exposed in the post-authorisation setting;
- signal of/potential for misuse, medication error, risk of overdose or dependency;
- the size of the safety database and exposure to the medicinal product;
- medicinal products subjected to additional monitoring.

Any change in the criteria listed above for a given active substance or combination of active substances may lead to an amendment of the list of EU reference dates (e.g. increase of the frequency for PSUR submission).

VII.C.3.5. Maintenance of the list of EU reference dates

VII.C.3.5.1. General principles

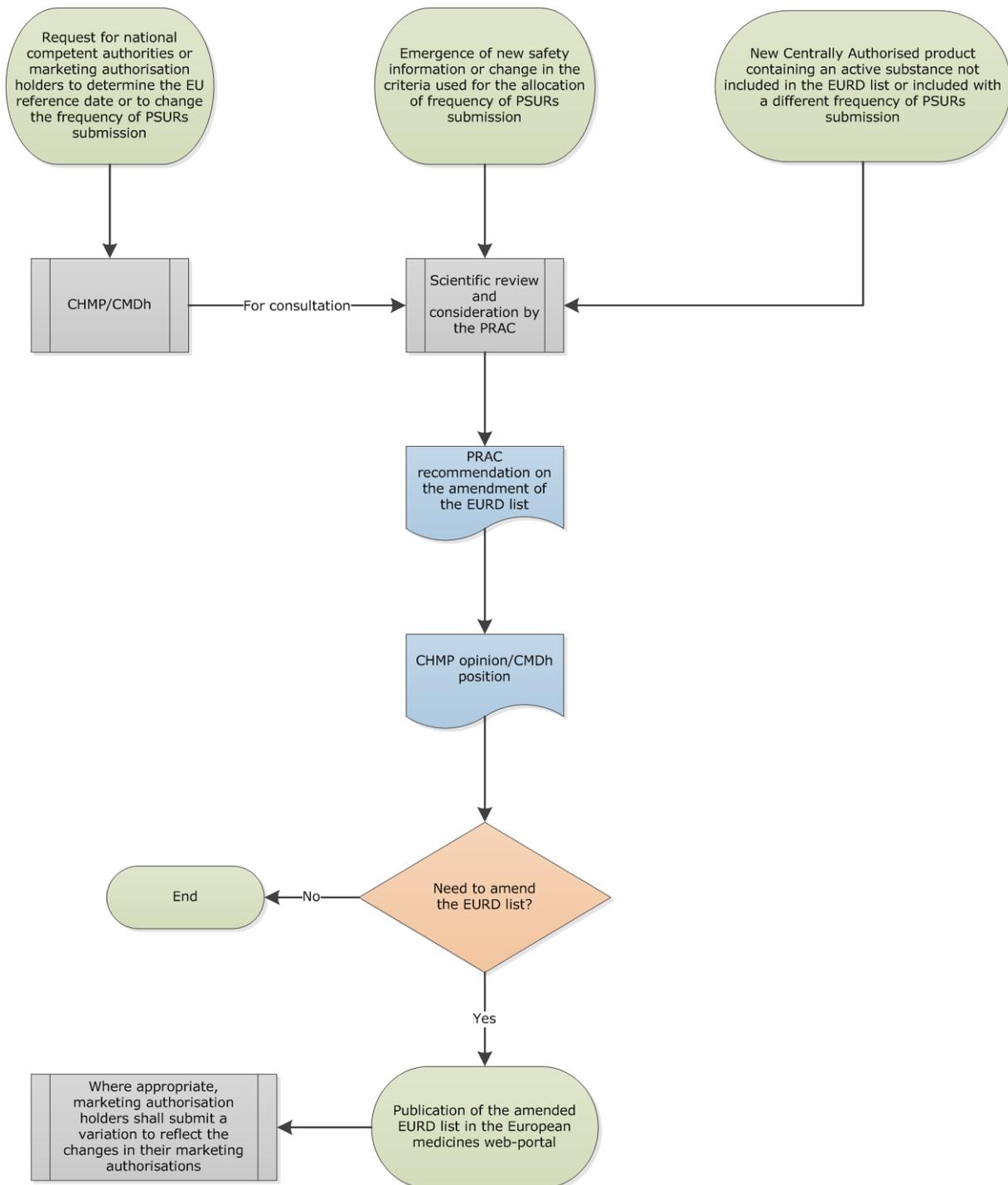
The maintenance of the list of EU reference dates should facilitate regulatory responsiveness to public health concerns identified within the EU and therefore the list will be subject to changes to reflect the decisions taken (e.g. by the Agency's committees following signal detection).

The information included in the list such as the active substances and combinations of active substances, the frequencies of submission of PSURs and data lock points may need to be updated when considered necessary by the CHMP or CMDh after consultation with the PRAC. Changes to the list may be applied on one of the following grounds:

- emergence of new information that might have an impact on the risk-benefit balance of the active substances or combinations of active substances, and potentially on public health;
- any change in the criteria used for the allocation of frequency for PSUR submission and defined under VII.C.3.4.;
- a request from the marketing authorisation holders as defined under DIR Art 107c(6);
- active substance newly authorised.

Figure VII.5. provides a general overview of the maintenance of the list of EU reference dates and frequency of submission of PSURs:

Figure VII.5. Maintenance of the list of EU reference dates and frequency of submission of PSURs



VII.C.3.5.2. Requests from marketing authorisation holders to amend the list of EU reference dates

Marketing authorisation holders shall be allowed to submit a request to the CHMP or the CMDh, as appropriate, to determine the Union reference dates or to change the frequency of submission of PSURs on one of the following grounds [DIR Art 107c(6)]:

- for reasons relating to public health;
- in order to avoid a duplication of the assessment;
- in order to achieve international harmonisation.

The request and its grounds should be considered by the PRAC and the CHMP if it concerns at least one marketing authorisation granted in accordance with the centralised procedure or the CMDh otherwise, which will either approve or deny the request.

The list will then be amended accordingly when appropriate and published on the European medicines web-portal (see section VII.C.3.6.).

For details about how to submit requests for amendments to the list, refer to the EU reference dates cover note and the related template published on the European medicines web-portal²¹

VII.C.3.6. Publication of the list

Upon its establishment and adoption by the CHMP and CMDh following PRAC consultation, the list of EU reference dates and frequency of submission of PSURs is published on the European medicines web-portal.

In case of amendments, the updated list should be published following its adoption by the CHMP or the CMDh. It is expected to be updated monthly.

VII.C.3.7. Amendment of the marketing authorisation according to the list of EU reference dates

Any changes to the dates and frequencies of submission of PSURs specified in the list take effect six months after the date of the publication on the European medicines web-portal. Where appropriate, marketing authorisation holders shall submit the relevant variation in order to reflect the changes in their marketing authorisation [DIR 107c(6)], unless the marketing authorisation contains a direct cross reference to the list of EU reference dates.

VII.C.4. Processes for PSUR Assessment in the EU network

The competent authorities in the Member States shall assess PSURs to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of the medicinal product [DIR Art 107d].

For purely nationally authorised medicinal products authorised in one Member State, the assessment of PSURs is conducted by the competent authority in the Member State where the product is authorised (see VII.C.4.1.).

For medicinal products authorised in more than one Member State, containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holders and for which the frequency and dates of submission of PSURs have been

²¹ <http://www.emea.europa.eu>

harmonised in the list of EU reference dates, an EU single assessment of all PSURs is conducted with recommendation from the PRAC in accordance with the procedure described in VII.C.4.2.1. and VII.C.4.2.2..

Further to assessment of the PSUR and opinion from the CHMP or position from the CMDh, as applicable, following the recommendation from the PRAC, the competent authorities in Member States, or the European Commission for centrally authorised products, shall take the necessary measures to vary, suspend or revoke the marketing authorisation(s), in accordance with outcome of the assessment [DIR Art 107g(2)] [REG Art 28(4) and (5)] (see VII.C.4.2.3. and VII.C.4.2.4.).

The outcome of the PSUR assessment results in a legally binding decision or position in case of any action to vary, suspend, revoke the marketing authorisations of the medicinal products containing the concerned active substance or combination of active substances, on the basis of the position of the CMDh or the opinion of the CHMP following the recommendations from the PRAC. Furthermore, marketing authorisation holders are reminded of their obligation to keep their marketing authorisation up to date in accordance with REG Art 16(3) and DIR Art 23(3). The recommendations are therefore implemented in a harmonised and timely manner for all products within the scope of the procedure across the EU.

Amendments to the SmPC, package leaflet and labelling as a result of the PSUR assessment should be implemented without subsequent variation submission for centrally authorised products and through the appropriate variation for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures.

When the proposals for the product information include new adverse reactions in section 4.8 (“Undesirable effects”) of the SmPC, or modifications in the description, frequency and severity of the existing reactions, marketing authorisation holders should provide in the relevant sections of the PSUR appropriate information to allow the adequate description and classification of the frequency of the adverse reactions. If other sections of the SmPC (e.g. SmPC section 4.4 “Special warnings and precautions for use”) are considered to be updated, clear proposals should be provided for the competent authorities in the Member States to consider during the PSUR assessment²². The proposals should be included in the PSUR regional appendix (VII.C.5.).

Harmonisation of the entire product information in all the Member States where the product is authorised is not one of the objectives of the PSUR assessment procedure. Instead, the outcome of the assessment should incorporate the new safety warnings and key risk minimisation recommendations, arising from the assessment of the data in the PSUR, to be included in the relevant sections of the product information.

VII.C.4.1. PSURs for purely nationally authorised medicinal products

It is the responsibility of the competent authority in the Member State where the product is authorised to evaluate the PSURs for these medicinal products and the assessment is conducted in accordance with the national legislation.

Listings of individual cases may be requested in the context of the PSUR assessment procedure for adverse reactions of special interest and should be provided by the marketing authorisation holder within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual case safety reports, (including information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases), where necessary for the scientific evaluation. Information on the context or rationale for the request should generally be provided.

²² See “Guideline on Summary of Product Characteristics” as published on the Website of the European Commission in the Notice to Applicants, Volume 2C: <http://ec.europa.eu/health/files/eudralex>

Following the assessment of PSURs, the competent authority in the Member State should consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary. They should vary, suspend or revoke the marketing authorisation when applicable according to the appropriate procedure at national level.

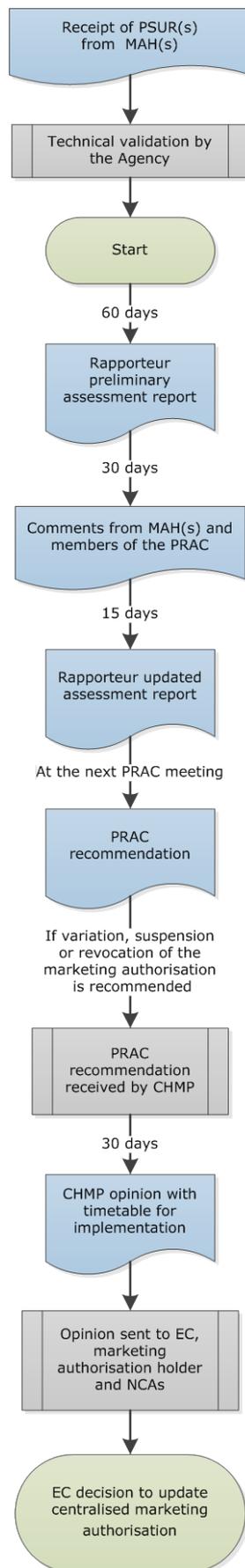
The assessment report and conclusions of the competent authority in the Member State should be provided to the marketing authorisation holder.

VII.C.4.2. Medicinal products authorised in more than one Member State

VII.C.4.2.1. Assessment of PSURs for a single centrally authorised medicinal product

This section describes the assessment of PSURs where only one centrally authorised medicinal product is involved according to the procedure set up in Article 28 of Regulation (EC) No 726/2004 (see figure VII.6.).

Figure VII.6. PSUR assessment procedure for a single centrally authorised medicinal product



The assessment of PSURs for a single centrally authorised medicinal product is coordinated by the Agency and shall be conducted by a Rapporteur appointed by the PRAC [REG Art 28(3)] (hereinafter referred to as "PRAC Rapporteur").

Upon receipt, the Agency should perform a technical validation of the report to ensure that the PSUR application is in a suitable format.

Listings of individual cases from EudraVigilance database may be retrieved to support the PSUR assessment.

Further to the above verifications, the procedure starts in accordance with the official starting dates published on the Agency's website. The detailed procedural timetables are published as a generic calendar on the Agency's website.

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

During the assessment, additional listings of individual cases may be requested by the PRAC Rapporteur through the Agency for adverse reactions of special interest and should be provided by the marketing authorisation holder(s) within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual cases safety reports, (including information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases), where necessary for the scientific evaluation. Information on the context or rationale for the request should generally be provided.

During the drafting of the assessment report, the PRAC Rapporteur shall closely collaborate with the CHMP Rapporteur [REG Art 28(3)].

The PRAC Rapporteur shall prepare an assessment report and send it to the Agency and to the members of the PRAC [REG Art 28(3)] within 60 days of the start of the procedure.

The Agency shall send the PRAC Rapporteur's preliminary assessment report to the marketing authorisation holder [REG Art 28(3)].

By Day 90, the marketing authorisation holder and members of the PRAC may send comments on the PRAC Rapporteur's preliminary assessment report to the Agency and the PRAC Rapporteur. Those comments should also include responses to outstanding issues or questions raised by the PRAC Rapporteur in the preliminary assessment report and which can be addressed within the timeframe of the comments phase.

Following receipt of comments, the PRAC Rapporteur shall prepare an updated assessment report [REG Art 28(3)] within 15 days (i.e. by Day 105). The updated assessment report is made available to the members of the PRAC and should be forwarded to the marketing authorisation holder by the Agency

An oral explanation to the PRAC can be held at the request of the PRAC or the marketing authorisation holder in case of recommendation for a revocation or suspension of the marketing authorisation, a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The PRAC shall adopt the updated assessment report with or without further changes at its next meeting [REG Art 28(3)], together with a recommendation on the maintenance of the marketing authorisation or the need to vary, suspend or revoke the marketing authorisation. The PRAC recommendation may also highlight the need to conduct a post-authorisation safety study, request an update of the RMP, review of safety issues and/or close monitoring of events of interest.

Divergent positions of PRAC members and the grounds on which they are based shall be reflected in the recommendation issued by the PRAC [REG Art 28(3)].

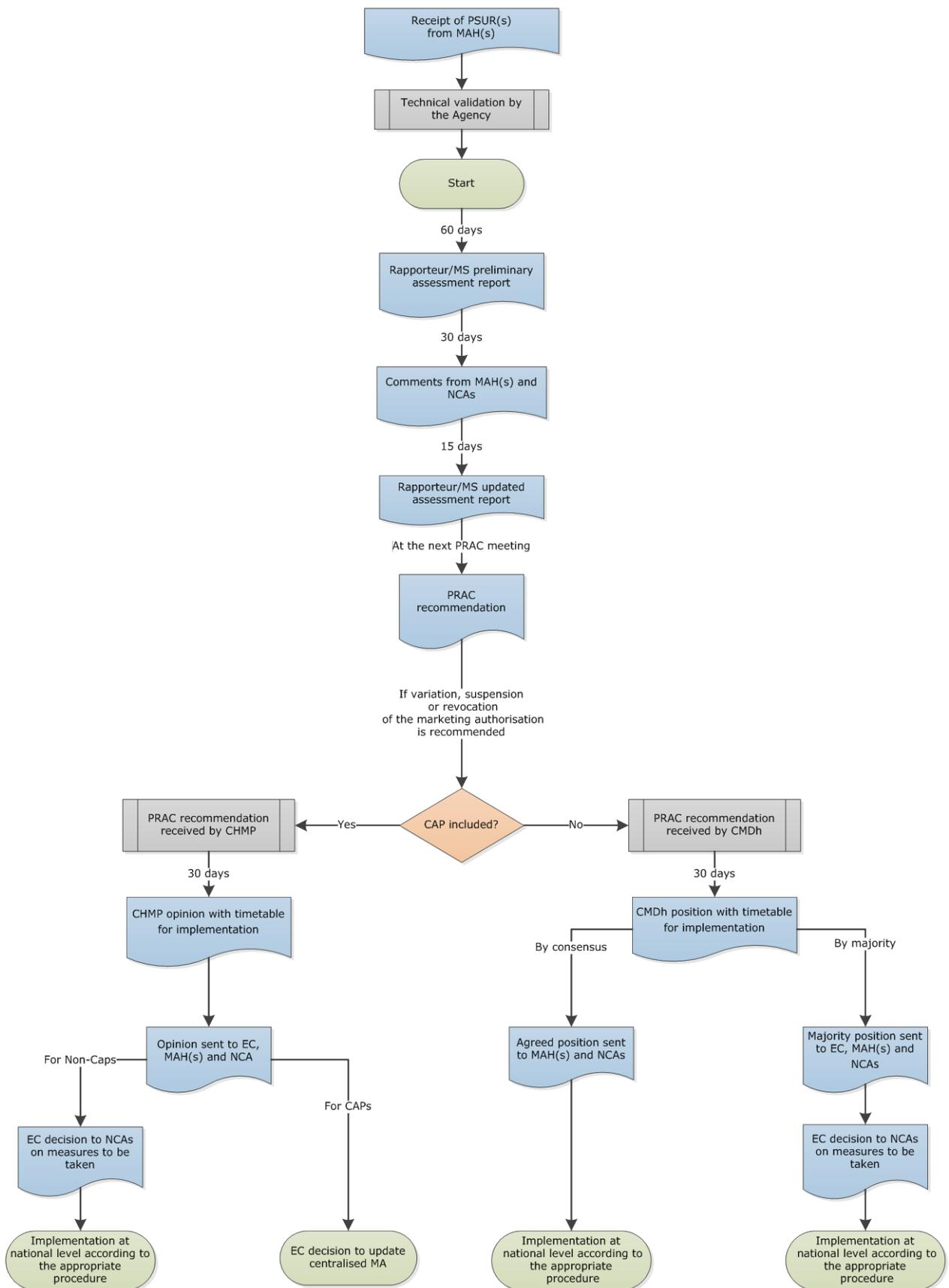
The Agency shall include the PRAC recommendation and adopted assessment report in the repository, and forward both to the marketing authorisation holder [REG Art 28(3)].

Further to adoption at the PRAC meeting, in case of any regulatory action is recommended, the assessment report and PRAC recommendation are sent to the CHMP for adoption of an opinion for the centrally authorised product concerned as described in VII.C.4.2.3..

VII.C.4.2.2. Assessment of PSURs for medicinal products subject to different marketing authorisations containing the same active substance (EU single assessment)

This section describes the assessment of PSURs for medicinal products subject to different marketing authorisations, authorised in more than one Member State, containing the same active substance or the same combination of active substances whether or not held by the same marketing authorisation holder and for which the frequency and dates of submission of PSURs have been harmonised in the list of EU reference dates. This could include a mixture of centrally authorised products, products authorised through the mutual recognition, decentralised and national procedures. [DIR Art 107e to 107g] (so-called PSUR “EU single assessment” procedure).

Figure VII.7. PSUR assessment procedure for “EU single assessment”



The assessment of PSURs for medicinal products, also called “EU single assessment”, shall be conducted by [DIR Art 107e(1)]:

- a “Member State” appointed by the CMDh where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure;
- a “Rapporteur” appointed by the PRAC, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure (hereinafter referred to as “PRAC Rapporteur”).

The PSUR EU single assessment procedure is coordinated by the Agency. Upon receipt, the Agency should perform a technical validation of the reports to ensure that the PSURs applications are in a suitable format.

Upon establishment of the list of all medicinal products for human use authorised in the EU referred to in REG Art 57, the Agency should ensure that all marketing authorisation holder(s) of the given substance have submitted PSUR(s), as required. In the event where a PSUR has not been submitted, the Agency should contact the concerned marketing authorisation holder(s). However, this will not preclude the start of the single assessment procedure for other PSUR(s) of the same active substance.

Listings of individual cases from EudraVigilance database may be retrieved to support the PSURs assessment.

Further to the above verifications, the procedure starts in accordance with the official starting dates published on the Agency's website. The detailed procedural timetables are published as a generic calendar on the Agency's website.

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

Further to the start of procedure, the PRAC Rapporteur or Member State conducts the single assessment of all PSURs submitted for the given active substance.

During the assessment, additional listings of individual cases may be requested by the PRAC Rapporteur or Member State through the Agency for adverse drug reactions of special interest and should be provided by the marketing authorisation holder(s) within an established timeframe to be included in the request. This may be accompanied by a request for an analysis of individual cases safety reports, (including information on numbers of cases, details of fatal cases and as necessary, analysis of non-serious cases), where necessary for the scientific evaluation. Information on the context or rationale for the request should generally be provided.

The PRAC Rapporteur or Member State shall prepare an assessment report and send it to the Agency and to the Member States concerned [DIR Art 107e(2)] within 60 days of the start of the procedure. This preliminary assessment report should be circulated to the members of the PRAC.

The Agency shall send the PRAC Rapporteur's/Member State preliminary assessment report to the concerned marketing authorisation holder(s) [DIR Art 107e(2)]. This assessment report should be circulated amongst all the marketing authorisation holders whose medicinal product(s) are part of the EU single assessment.

By Day 90, the marketing authorisation holder(s), Member States and members of the PRAC as applicable may send comments on the PRAC Rapporteur's/Member State's preliminary assessment report to the Agency and the PRAC Rapporteur/Member State, as applicable. Those comments should also include responses to outstanding issues or questions raised by the PRAC Rapporteur/Member State in the preliminary assessment report and which can be addressed within the timeframe of the comments phase.

Following receipt of comments, the PRAC Rapporteur/Member State shall prepare an updated assessment report [DIR Art 107e (3)] within 15 days (i.e. by Day 105). The updated assessment report is forwarded to the members of the PRAC and should be circulated by the Agency amongst all the marketing authorisation holders whose medicinal product(s) are part of the EU single assessment.

An oral explanation to the PRAC can be held at the request of the PRAC or the marketing authorisation holder in case of recommendation for a revocation or suspension of the marketing authorisation, a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The PRAC shall adopt the updated assessment report with or without further changes at its next meeting [DIR Art 107e(3)], together with a recommendation on maintenance of the marketing authorisation or the need to vary, suspend or revoke the marketing authorisation. The PRAC recommendation may also highlight the need to conduct a post-authorisation safety study (see **Module VIII**), request an update of the RMP (see **Module V**), review of safety issue and/or close monitoring of events of interest.

Divergent positions of PRAC members and the grounds on which they are based shall be reflected in the recommendation issued by the PRAC [DIR Art 107e(3)].

The Agency shall include the PRAC recommendation and adopted assessment report in the repository, and forward both to the marketing authorisation holder(s) [DIR Art 107e(3)].

Further to adoption at the PRAC meeting, in case of any regulatory action is recommended, the assessment report and PRAC recommendation are sent to:

- the CHMP where at least one centrally authorised product is included in the single assessment, for adoption of an opinion as described in **VII.C.4.2.3.**;
- the CMDh where no centrally authorised product is included in the single assessment, for agreement of a position as described in **VII.C.4.2.4.**.

VII.C.4.2.3. Single assessment including at least one centrally authorised product leading to a CHMP opinion

The CHMP acknowledges receipt of the PRAC recommendation and assessment report, in case of any regulatory action, at their next meeting following the PRAC adoption. Within 30 days from receipt, the CHMP shall consider the PRAC assessment report and recommendation and adopt an opinion on the maintenance, variation, suspension, revocation of the marketing authorisation(s) concerned [DIR 107g(3)].

An oral explanation to the CHMP can be held at the request of the CHMP or the marketing authorisation holder(s) only in case of differences with the PRAC recommendation where CHMP considers the possibility of adopting an opinion on the suspension or revocation of the marketing authorisation(s), a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The opinion will contain the following:

- the final assessment report and recommendation adopted by the PRAC;
- detailed explanation of the scientific grounds for differences with the PRAC recommendation, if applicable [DIR Art 107g(3)];
- in the case of a CHMP opinion to vary the marketing authorisation(s):
 - the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation;

- for centrally authorised products, revised product information and if applicable, conditions imposed to the marketing authorisation holder and where appropriate, the conditions or restrictions imposed to the Member States for the safe and effective use of the medicinal product, in accordance with the provision provided in DIR Art 127a;
- for nationally authorised products, including those authorised through the mutual recognition and decentralised procedures, an annex indicating the new safety warnings and key risk minimisation recommendations to be included in the relevant sections of the product information as applicable.
- in the case of a CHMP opinion to suspend the marketing authorisation(s), the scientific conclusions together with the grounds for suspension and conditions for lifting the suspension;
- in the case of a CHMP opinion to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation;
- divergent positions of CHMP members, where applicable.

Further to adoption, the Agency should send the CHMP opinion together with its annexes and appendices to the European Commission, marketing authorisation holder(s) and competent authorities in Member States.

The final assessment conclusions and recommendations are published in the European medicines web-portal (VII.C.7.).

a. Post CHMP opinion - Centrally authorised products

Where the CHMP opinion states that the terms of the marketing authorisation(s) needs to be varied, the marketing authorisation holder(s) of centrally authorised products should provide the translations of the product information and the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation, in all EU official languages, in accordance with the translation timetable adopted by the CHMP.

Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing authorisation is necessary, the European Commission shall adopt a decision addressed to marketing authorisation holders to vary, suspend or revoke the marketing authorisation(s) of centrally authorised product(s) [DIR Art 107g(4b)].

Further to adoption, the European Commission should notify the decisions amending the terms of the marketing authorisation of centrally authorised products to the marketing authorisation holder(s).

b. Post CHMP opinion - Nationally authorised products, including those authorised through the mutual recognition and decentralised procedures

Further to receipt of a CHMP opinion stating that regulatory action to the concerned marketing authorisations is necessary, the European Commission shall adopt a decision addressed to the competent authorities in Member States concerning the measures to be taken [DIR Art 107g(a)] in respect of nationally authorised products, including those authorised through the mutual recognition and decentralised procedures.

Further to the receipt of the decision from the European Commission, the competent authorities in Member States shall take the necessary measures to vary, suspend or revoke the marketing authorisation(s) within 30 days [DIR Art 107g(4)].

VII.C.4.2.4. Single assessment not including centrally authorised product leading to a CMDh position

The CMDh acknowledges receipt of the PRAC recommendation and assessment report, in case of any regulatory action, at their next meeting following the PRAC adoption.

Within 30 days from receipt, the CMDh shall consider the PRAC assessment report and recommendation and reach a position on the maintenance, variation, suspension, revocation of the marketing authorisation(s) concerned [DIR Art 107g(1)].

An oral explanation to the CMDh can be held at the request of the CMDh or the marketing authorisation holder(s), only in case of differences with the PRAC recommendation where the CMDh considers the possibility to reach a position on the suspension or revocation of the marketing authorisation(s), a new contraindication, a restriction of the indication or a reduction of the recommended dose.

The position will contain the following:

- the final assessment report and recommendation adopted by the PRAC;
- detailed explanation of the scientific grounds for differences with the PRAC recommendation, if applicable [DIR Art 107g(2)];
- in the case of a CMDh position to vary the marketing authorisation(s), the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation and an annex indicating the new safety warnings and key risk minimisation recommendations to be included in the relevant sections of the product information, as applicable;
- in the case of a CMDh position to suspend the marketing authorisation(s), the scientific conclusions together with the grounds for suspension and conditions for lifting the suspension;
- in the case of a CMDh position to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation;
- divergent position(s) for the CMDh members, where applicable.

The final assessment conclusions and recommendations shall be published by the Agency in the European medicines web-portal [DIR Art 107I] (VII.C.7.).

If the CMDh position is reached by consensus:

The position agreed including the action to be taken is recorded by the chairperson in the minutes of the CMDh meeting where agreed.

The chairman shall send the agreed CMDh position [DIR Art 107g(2)] and its appendices to the marketing authorisation holder(s) and competent authorities in Member States.

Further to receipt of the CMDh position stating that regulatory action to the concerned marketing authorisation is necessary, the competent authorities in Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation(s) concerned in accordance with the timetable for implementation determined in the agreed position [DIR Art 107g(2)].

In case the position of the CMDh agreed that variation to the terms of marketing authorisation is required, the marketing authorisation holder(s) shall submit the relevant variation to that effect within the timetable for implementation [DIR Art 107g(2)] as appended to the agreed position.

If the CMDh position is reached by majority vote:

The majority position on the action to be taken is recorded by the chairman in the minutes of the CMDh meeting where agreed.

The majority position of the CMDh together with its annexes and its appendices, including translations in all EU official languages where applicable, shall be forwarded to the European Commission [DIR Art 107g(2)]. The position of the CMDh should also be forwarded to the competent authorities in Member States.

Further to receipt of a CMDh position stating that regulatory action to the concerned marketing authorisation is necessary, the European Commission shall adopt decision(s) [DIR Art 107g(2)] addressed to the competent authorities in Member States in order for them to vary, suspend or revoke the marketing authorisation(s) of nationally authorised product(s) which is addressed to marketing authorisation holders.

Further to receipt of the decision from the European Commission, the competent authorities in Member States shall take the necessary measures to maintain, vary, suspend or revoke the marketing authorisation(s) within 30 days [DIR Art 107g(2)].

VII.C.4.3. Relationship between PSUR and risk management plan

The general relationship between the risk management plan (RMP) and the PSUR is described in [Module V](#), while an overview of the common RMP/PSUR modules is provided in [VII.C.4.3.1.](#)

During the preparation of a PSUR, the marketing authorisation holder should consider whether any identified or potential risks discussed within the PSUR is important and requires an update of the RMP. In these circumstances, updated revised RMP including the new important safety concern should be submitted with the PSUR and assessed in parallel, following the timetable for the assessment of PSUR as described above.

If important safety concerns are identified by the national competent authorities in the Member States during the assessment of a PSUR and no updated RMP or no RMP has been submitted, recommendations should be made to submit an update or a new RMP within a defined timeline.

VII.C.4.3.1. PSUR and risk management plan – common modules

The proposed modular formats for the PSUR and the RMP aim to address duplication and facilitate flexibility by enabling common PSUR/RMP sections to be utilised interchangeably across both reports. Common sections with the above mentioned reports are identified in [Table VII.1.](#):

Table VII.1. Common sections between PSUR and RMP

PSUR section	RMP section
Section 3 – “Actions taken in the reporting interval for safety reasons”	Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”
Sub-section 5.2 – “Cumulative and interval patient exposure from marketing experience”	Part II, module SV – “Post-authorisation experience”, section “Non-study post-authorisation exposure”
Sub-section 16.1 – “Summary of safety concerns”	Part II, module SVIII – “Summary of the safety concerns” (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)
Sub-section 16.4 – “Characterisation of risks”	Part II, Module SVII – “Identified and potential

PSUR section	RMP section
	risks”
Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”	Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”

VII.C.5. EU-specific requirements for periodic safety update reports

The scientific evaluation of the risk-benefit balance of the medicinal product included in the PSUR detailed in VII.B.5. shall be based on all available data, including data from clinical trials in unauthorised indications and populations according to the provisions of DIR Art 107b and IR Art 34(1).

The EU-specific requirements should be included in the PSUR EU regional appendix.

VII.C.5.1. PSUR EU regional appendix, sub-section “Proposed product information”

The assessment of the need for amendments to the product information is incorporated within the PSUR assessment procedure in the EU. The regulatory opinion/position should include recommendations for updates to product information where needed. Marketing authorisation holders should provide the necessary supportive documentation and references within the PSUR or in this appendix to facilitate this.

Within the PSUR, the marketing authorisation holder is required to consider the impact of the data and evaluations presented within the report, on the marketing authorisation. Based on the evaluation of the cumulative safety data and the risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved SmPC(s) for the product(s) for which the PSUR is submitted [IR Art 34 (5)].

In this sub-section, the marketing authorisation holder should provide the proposals for product information (SmPC and package leaflet) based on the above mentioned evaluation. These should be based on all EU authorised indications.

A track change version of the proposed SmPCs and package leaflets based on the assessment and conclusions of the PSUR should be provided. For centrally authorised medicinal products, the proposed product information should also be submitted to Module 1.3.1 of the Electronic Common Technical Document (eCTD).

All the SmPCs and packages leaflets covered by the PSUR and in effect at the data lock point, should be reviewed to ensure that they reflect the appropriate information according to the cumulative data included and analysed in the PSUR.

Amendments to the product information should not be postponed or delayed until the PSUR submission and amendments not related to the information presented in the PSUR, should not be proposed within the PSUR procedure. It is the obligation of the marketing authorisation holder to submit a variation in accordance with the Regulation (EC) No 1234/2008 on variations to the terms of a marketing authorisation.

A brief description of ongoing procedures (e.g. variations) to update the product information should be provided in this section.

VII.C.5.2. PSUR EU regional appendix, sub-section “Proposed additional pharmacovigilance and risk minimisation activities”

Considering the provision established in IR Art 34 (5), this sub-section should include proposals for additional pharmacovigilance and additional risk minimisation activities based on the conclusions and actions of the PSUR, including a statement of the intention to submit a RMP or an updated RMP when applicable.

VII.C.5.3. PSUR EU regional appendix, sub-section “Summary of ongoing safety concerns”

In order to support the information provided in the PSUR section 16.1 “Summary of safety concerns” (see VII.B.5.16.1.), Table 1.10 (according to the current RMP template) “Summary – Ongoing safety concerns” should be included in this PSUR sub-section. This table should be extracted from the version of RMP available at the beginning of the PSUR reporting interval (see Module V).

VII.C.5.4. PSUR EU regional appendix, sub-section “Reporting of results from post-authorisation safety studies”

Findings from both interventional and non-interventional (for further guidance see Module VIII) post-authorisation safety studies (PASS) should be reported in the PSUR. While the marketing authorisation holder should inform competent authorities in Member States and the Agency as applicable about any new information that may impact on the risk-benefit balance immediately, the PSUR should provide comprehensive information on the findings of all PASS, both interventional and non-interventional, in PSUR sections 7 and 8 respectively.

Final study reports for studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures which were completed during the reporting interval should also be included as an annex to the PSUR. For such studies discontinued during the reporting interval, the reasons for stopping the study should also be explained.

If an important safety concern has been identified in the course of a study, regardless of whether it has been detected through pre-specified methods and whether the study is considered a PASS, the marketing authorisation holder and specifically the qualified person responsible for pharmacovigilance (QPPV) will have informed the relevant competent authorities in Member States immediately.

PSURs should not be used as the initial communication method either for the submission of final study reports to the competent authorities in Member States or for the notification of any new information that might influence the evaluation of the risk-benefit balance.

VII.C.5.5. PSUR EU regional appendix, sub-section “Effectiveness of risk minimisation”

Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall risk-benefit balance is optimised. In accordance with section VII.B.5.16.5., evaluation of broad global experience should be reflected in the body of the report, when provides insights into the effectiveness of risk minimisation activities in any country or region that may have utility in other countries or regions are of particular interest .

This sub-section should additionally provide an evaluation of the effectiveness of routine and/or additional risk minimisation activities specifically relevant to an EU context. This should take account of regulatory imposed obligations for implementation of risk minimisation measures in addition to the overall requirement for monitoring of safety and benefit-risk. Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities in the EU should be included when available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, then alternative activities need to be put in place. In certain cases, it may be judged that risk minimisation cannot control the risks to the extent possible to ensure a positive risk-benefit balance and that the medicinal product needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks. More extensive guidance on monitoring the effectiveness of risk minimisation activities is included in [Module XVI](#). As a principle, the marketing authorisation holder should distinguish in their evaluation between implementation success and attainment of the intended outcome.

VII.C.6. Quality systems and record management systems for PSURs in the EU network

VII.C.6.1. Quality systems and record management systems at the level of the marketing authorisation holder

Specific quality system procedures and processes shall be in place in order to ensure the update of product information by the marketing authorisation holder in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal, and on the basis of a continuous monitoring by the marketing authorisation holder of information published on the European medicines web-portal [IR Art 11(1)(f)].

It is the responsibility of the marketing authorisation holder to check regularly the list of EU reference dates and frequency of submission published in the European medicines web-portal to ensure compliance with the PSUR reporting requirements for their medicinal products (see [VII.C.3.](#)).

Systems should be in place to schedule the production of PSURs according to:

- the list of EU reference dates and frequency of PSURs submission; or
- the conditions laid down in the marketing authorisation; or
- the standard PSUR submission schedule established according to DIR Art 107c(2) for products authorised before 2 July 2012 (for centrally authorised products) and 21 July 2012 (for nationally authorised products) as applicable (without any conditions in their marketing authorisation or not included in the list of EU references dates and frequency of submission or not affected by the derogation established in [DIR Art 107b(3)]); or
- ad hoc requests for PSURs by a competent authority in a Member State or the Agency.

For those medicinal products where the submission of an RMP is not required, the marketing authorisation holder should maintain on file a specification of important identified risks, important potential risks and missing information in order to support the preparation of the PSURs.

The marketing authorisation holder should have procedures in place to follow the requirements established by the Agency for the submission of PSURs.

The QPPV shall be responsible for the establishment and maintenance of the pharmacovigilance system [DIR Art 104(e)] and therefore should ensure that the pharmacovigilance system in place enables the

compliance with the requirements established for the production and submission of PSURs. In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV in relation to PSURs should include:

- ensuring the necessary quality, including the correctness and completeness, of the data submitted in the PSURs;
- ensuring full response according to the timelines and within the procedure agreed (e.g. next PSUR) to any request from the competent authorities in Member States and the Agency related to PSURs;
- awareness of the PSUR and assessment report conclusions, PRAC recommendations, CHMP opinions, CMDh positions and European Commission decisions in order to ensure that appropriate action takes place.

The record retention times for product-related documents in **Module I** also apply to PSURs and source documents related to the creation of PSURs, including documents related to actions taken for safety reasons, clinical trials and post-authorisation studies, relevant benefit information and documents utilised for the calculation of patient exposure.

VII.C.6.2. Quality systems and record management systems at the level of the European Medicines Agency

The application of the Agency's quality system (see **Module I**) should support compliance by the Agency when fulfilling its tasks and responsibilities for the management of PSUR procedures and EU single assessments.

The Agency should have in place a process to technically validate the completeness of PSUR submissions.

Line listings and summary tabulations from the EudraVigilance database utilised to support the PSUR assessment should be created using reports by means of the EudraVigilance data analysis system.

Effective communication and circulation of PSURs and related documents is crucial for the successful completeness of the procedure; therefore processes have to be in place for the circulation of documents between the Agency, marketing authorisation holders, the Commission and the competent authorities in Member States. Where applicable, the procedures should establish the necessity for quality checks with the aim to remove any information of a personal or commercially confidential nature.

Written procedures should reflect the different steps to follow for the maintenance of the list of EU references dates and frequency of submission of PSURs published by the Agency in the European medicines web-portal (see **VII.C.3.**).

Prior to the publication of summaries of PSUR assessment reports in the European medicines web-portal (see **VII.C.7.**) the appropriate personnel at the Agency should adhere to the procedures established for web publication of documents produced by the Agency or competent authorities in the Member States.

All records related to PSURs created by the Agency's staff members, experts or consultants are the property of the Agency and all PSURs and related documents received are in the custody of the Agency. Both types of PSURs records (created or received by the Agency) are subject to the Agency's overall control via the PSUR repository set up according to the provisions laid down in REG Art 25a.

The Agency's policy on records management (EMA/590678/2007)²³, provides the basis for a consistent, sustainable and efficient records management program and it has been developed in accordance with the commonly recognised international standard for records management, "ISO 15489-1:2001 Information and documentation – Records management"²⁴. According to the records classification stated by the Agency's policy, PSURs would be considered business, legal, evidential and research/historical value records.

The record retention times for product-related documents in **Module I** also apply to PSUR- system related documents (e.g. standard operating procedures) and PSUR -related documents (e.g. PSURs, assessment reports, the data retrieved from the EudraVigilance database or other data used to support the PSUR assessment).

VII.C.6.3. Quality systems and record management systems at the level of the competent authorities in Member States

Each competent authority in the Member States shall have in place a pharmacovigilance system [DIR Art 101] for the surveillance of medicinal products and for receipt and evaluation of all pharmacovigilance data including PSURs. For the purpose of operating its tasks relating to PSURs in addition to the pharmacovigilance system the national competent authorities in Member States should implement a quality system (see **Module I**).

Competent authorities in the Member States should monitor marketing authorisation holders for compliance with regulatory obligations for PSURs. Additionally, competent authorities should exchange information in cases of non-compliance and take appropriate regulatory actions as required.

No PSUR assessment at EU level is foreseen for purely nationally authorised products authorised in only one Member State; therefore the national competent authority in the Member State where the medicinal product is authorised should have procedures in place for the assessment of PSURs related to those medicinal products.

The procedures established by the national competent authorities in Member States for the performance of the EU single assessment of PSURs, should be in line with the procedures established by the Agency for the coordination of PSUR assessment in the EU regulatory network (see **VII.C.4.**). These procedures should establish effective communication across the EU regulatory network and the actions to be taken regarding the variation, suspension or revocation of the marketing authorisation following the PRAC recommendations, CHMP opinion, CMDh position and European Commission decision as applicable.

The procedures established by the Agency for the use of the PSUR repository to support the single assessment, should be followed by the national competent authorities in Member States.

Where tasks related to PSUR procedures are delegated to third parties, the national competent authorities in Member States should ensure that they are subject to a quality system in compliance with the obligations provided by the European legislation.

The record retention times for product-related documents in **Module I** also apply to PSUR- system related documents (e.g. standard operating procedures) and PSUR -related documents (e.g. PSURs, assessment reports, the data retrieved from the EudraVigilance database or other data used to support the PSUR assessment).

²³ www.ema.europa.eu

²⁴ www.iso.org

VII.C.7. Transparency

VII.C.7.1. Publication of PSUR-related documents on the European medicines and national medicines web-portals

The following documents shall be made publicly available by means of the European medicines web-portal [DIR Art 107I, REG Art 26(g)]:

- list of EU reference dates and frequency of submission of PSURs (see VII C.3.);
- final assessment conclusions of the adopted assessment reports;
- PRAC recommendations including relevant annexes;
- CMDh position including relevant annexes and where applicable, detailed explanation on scientific grounds for any differences with the PRAC recommendations;
- CHMP opinion including relevant annexes and where applicable, detailed explanation on scientific grounds for any differences with the PRAC recommendations;
- European Commission decision.

The version and date of publication are reflected in each document as they define the issue of the PRAC recommendations, CHMP opinions, CMDh positions and European Commission decisions at a certain point of time.

Links between the European medicines web-portal and the National medicines web-portals should be made whenever possible and relevant.

Any personal or confidential data made public by the Agency or the competent authorities in Member States as referred to in paragraphs 2 and 3 of Article 106a of Directive 2001/83/EC shall be deleted unless considered necessary in terms of protection of the public health [DIR Art 106a(4)].

VII.C.8. Renewal of marketing authorisations

Marketing authorisations need to be renewed after 5 years on the basis of a re-evaluation of the risk-benefit balance in order to continue to be valid to place the product on the market. This renewal is irrespective of whether the marketing authorisation is suspended. Further details on the procedure and the documentation requirements can be found in the current versions of the “Guideline on Processing of Renewals in the Centralised Procedure” (EMA/CHMP/2990/00) for Centralised products and the “CMDh Best Practice Guide on the processing of renewals in the MRP/DCP” (CMDh/004/2005) for other products.

No PSURs, addendum reports and summary bridging reports should be submitted within the renewal application. The clinical overview should include an addendum containing the relevant sections for the re-assessment of the risk-benefit balance of the medicinal product. These sections are identified in the above-mentioned guidelines for renewal. Marketing authorisation holders are advised to consider this GVP Module VII as guidance for the preparation of the addendum to the clinical overview.

Following the submission of a renewal application, the PRAC may be consulted for medicinal products authorised through the centralised procedure as regards safety issues. For nationally authorised products, including those authorised through the mutual recognition or decentralised procedure, the PRAC may also be consulted upon request by a competent authority in a Member State on the basis of safety concerns.

Conditional marketing authorisations should be renewed annually [REG Art 14(7)]. Further details on the procedure and the documentation to be submitted can be found in the “Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of regulation (EC) no 726/2004” (EMA/509951/2006).

VII.C.9. Transition and interim arrangements

VII.C.9.1. Submission and availability of documents before the Agency’s repository is in place

The Agency shall, in collaboration with the competent authorities in Member States and the European Commission set up and maintain a repository for PSURs and the corresponding assessment reports so that they are fully and permanently accessible to European Commission, the competent authorities in Member States, the PRAC, the CHMP and the CMDh [REG Art 25a].

The repository shall undergo an independent audit before the functionalities are announced by the Agency’s management board [REG Art 25a].

As established in the transitional provisions introduced in Directive 2010/84/EU Art 2(7), until the Agency can ensure the functionalities agreed for the repository, marketing authorisation holders under the obligation to submit PSURs irrespective of whether the medicinal product is authorised in one or more Member States and irrespective of whether the active substance or combination of active substances is on the EU reference date list shall submit the PSURs to all competent authorities in Member States in which the medicinal products are authorised. For the substances or combination of active substances subject to the EU single assessment, and for which an EU reference date has been established, the PSURs should be also sent to the Agency.

The competent authorities in Member States requirements for the submission of PSURs during this transitional period are published in the Agency web-site²⁵.

From 12 months after the functionalities of the repository have been established and have been announced by the Agency, the marketing authorisation holders shall submit the PSURs electronically to the Agency regardless of the authorisation procedure of the medicinal product [DIR Art 107b(1)]. The competent authorities in Member States shall ensure that this obligation applies as required [DIR Art 2(7)].

Once the structured electronic format “ePSUR”, based on content agreed in the ICH-E2C(R2), becomes available, marketing authorisation holders will have the possibility to submit PSURs and related documents automatically via an electronic gateway.

Until the repository is in place, the relevant documents should be circulated as follows:

- The preliminary assessment report created by the PRAC Rapporteur/Member State within 60 days of the start of the procedure should be circulated to the Agency and the members of the PRAC through a dedicated mailbox. The Agency should send the report to the concerned marketing authorisation holder(s);
- members of the PRAC should circulate their comments through a dedicated mailbox by Day 90 on the PRAC Rapporteur/Member State preliminary assessment report;

²⁵ www.ema.europa.eu

- comments by the marketing authorisation holders(s) by Day 90 on the PRAC Rapporteur/Member State preliminary assessment report, should be submitted to the Agency, PRAC Rapporteur and all members of the PRAC, according to the instructions for submission published by the Agency;
- updated PRAC Rapporteur/Member State assessment report created within 15 days (i.e. by Day 105) should be circulated to the Agency and members of the PRAC through a dedicated mailbox. The Agency should forward the updated PRAC Rapporteur/Member State assessment report to the marketing authorisation holders concerned.

Further to adoption, the Agency should send the CHMP opinion together with its annexes and appendices to the European Commission, marketing authorisation holder(s) and competent authorities in Member States, through secure email until the repository is in place.

VII.C.9.2. Quality systems and record management systems at the level of the competent authorities in Member States

Special considerations should be taken for the management of the PSURs submitted to the concerned competent authorities in Member States until the Agency can ensure the functionalities agreed for the PSUR repository and 12 months after the establishment of the repository according to the transitional provisions.

VII.C.9.3. Publication of the EU list of union references dates and start of the EU- PSUR single assessment procedure

As stated in VII.C.3.6., the list of EU reference dates and frequency of submission should be published in the European medicines web-portal, nevertheless, the EU single assessment procedure for substances included only in nationally authorised products, detailed in VII.C.4.2.2., and VII.C.4.2.4. will be delayed until funds are available.

VII.APPENDICES

VII.Appendix 1. Examples of tabulations for estimated exposure and adverse events/reactions data

Marketing authorisation holders can modify these examples tabulations to suit specific situations, as appropriate.

Table VII.2. Estimated cumulative subject exposure from clinical trials

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials.

Treatment	Number of Subjects
Medicinal product	
Comparator	
Placebo	

Table VII.3. Cumulative subject exposure to investigational drug from completed clinical trials by age and sex

Age range	Number of subjects		
	Male	Female	Total

Data from completed trials as of [date]

Table VII.4. Cumulative subject exposure to investigational drug from completed clinical trials by racial/ethnic group

Racial/ethnic group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

Data from completed trials as of [date]

Table VII.5. Cumulative exposure from marketing experience

Indication	Sex		Age (years)				Dose		Formulation		Region					
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	EU	Japan	Colombia	US/Canada	Other
Overall																
Depression																
Migraine																

Table VII.5 includes cumulative data obtained from day/month/year throughout day/month/year, where available

Table VII.6. Interval exposure from marketing experience

Indication	Sex		Age (years)				Dose			Formulation		Region				
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	EU	Japan	Colombia	US/Canada	Other
Depression																
Migraine																

Table VII. 6 includes interval data obtained from day/month/year throughout day/month/year

Table VII.7. Cumulative tabulation of serious adverse events from clinical trials

System Organ Class	Investigational medicinal product	Blinded	Active comparator	Placebo
Preferred Term				
<u>Blood and lymphatic system disorders</u>				
Anaemia				
Bone marrow necrosis				
<u>Cardiac disorders</u>				
Tachycardia				
Ischaemic cardiomyopathy				

Table VII.8. Numbers of adverse reactions by preferred term from post-authorisation sources*

SOC MedDRA PT	Spontaneous, including competent authorities (worldwide) and literature				Non-interventional post-marketing study and reports from other solicited sources **		
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
<SOC 1>							
<PT>							
<PT>							
<PT>							
<SOC 2>							
<PT>							
<PT>							
<PT>							
<PT>							

* Non-interventional post-authorisation studies, reports from other solicited sources and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, competent authorities (worldwide), and scientific literature)

** This does not include interventional clinical trials.

VII. Appendix 2. Example of tabular summary of safety signals that were ongoing or closed during the reporting interval

Table VII.9. The tabular summary below is a fictitious example of tabular summary of safety signals ongoing or closed during the reporting interval

Reporting interval: DD-MMM-YYYY to DD-MMM-YYYY

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	MMM/YYYY	Ongoing	MMM/YYYY	meta-analysis (published trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
SJS	MMM/YYYY	Closed	MMM/YYYY	Sporadic case reports	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 reports within 6 months of authorisation; plausible time to onset and no possible alternative causes.	Targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologists and literature searches	RSI updated with a warning and precaution DHPc sent Effectiveness survey planned 6 months post DHPc. RMP updated

Explanatory notes:

Signal term:

- A brief descriptive name of a medical concept for the signal. This may evolve and be refined as the signal is evaluated. The concept and scope may or may not be limited to specific MedDRA term(s), depending on the source of signal.

Date detected:

- Month and year the marketing authorisation holder became aware of the signal.

Status:

- Ongoing: Signal under evaluation at the data lock point of the PSUR. Anticipated completion date, if known, should be provided.
- Closed: Signal for which evaluation was completed before the data lock point of the PSUR.

Note: A new signal of which the marketing authorisation holder became aware during the reporting interval may be classified as closed or ongoing, depending on the status of the signal evaluation at the end of the reporting interval of the PSUR.

Date closed:

- Month and year when the signal evaluation was completed.

Source of signal:

- Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous reports, clinical trial data, scientific literature, and non-clinical study results, or information request or inquiries from a competent authority (worldwide).

Reason for evaluation and summary of key data:

- A brief summary of key data and rationale for further evaluation.

Action(s) taken or planned:

State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the data lock point, these should be listed, otherwise leave blank for ongoing signals.

Appendix L: Post-Authorisation Safety Studies

19 April 2013
EMA/813938/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module VIII – Post-authorisation safety studies (Rev 1)

Draft of first version finalised by the Agency in collaboration with Member States	19 January 2012
Draft agreed by ERMS FG	24 January 2012
Draft adopted by Executive Director	20 February 2012
Released for public consultation	21 February 2012
End of consultation (deadline for comments)	18 April 2012
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Revised draft agreed by ERMS FG	21 June 2012
Revised draft adopted by Executive Director as final	22 June 2012
Date for coming into effect	2 July 2012
Draft Revision 1* finalised by the Agency in collaboration with Member States	21 March 2013
Draft Revision 1 agreed by ERMS FG	27 March 2013
Draft Revision 1 adopted by Executive Director as final	19 April 2013
Date for coming into effect of Revision 1	25 April 2013

*Note: Revision 1 contains the following:

- Clarifications of the text following questions received from stakeholders regarding
 - scope of the guidance to EU and non-EU studies: page 5, section VIII.B.1.;
 - classification of a post-authorisation study as a PASS according to its main aim: page 6, section VIII.B.3.;
 - study registration (study registration not limited to studies conducted in the EU and updates of study record to be made preferably within two weeks): page 7, section VIII.B.4. and page 8, section VIII.B.4.;

See websites for contact details



- Increased consistency with GVP Module V regarding the four categories of studies included in the risk management plan: page 4, section VIII.A. and page 5, section VIII.B.1.;
- Amendments to make reference to published detailed guidance for the format and content of non-interventional PASS protocols and final study reports: page 8, section VIII.B.5.1., page 10, section VIII.B.5.1., page 12, section VIII.B.6.3.2., and page 15, section VIII.B.6.3.2.;
- Amendment of regulatory wording to use that adopted by the Agency or following legal advice regarding that
 - in the procedure for imposing a PASS, the PRAC may adopt an advice with an assessment report: page 17, sections VIII.C.2.a., VIII.C.2.b. and VIII.C.2.c.;
 - roles and responsibilities to marketing authorisation holders for non-interventional PASS apply to studies imposed as an obligation as a condition to the marketing authorisation: page 19, section VIII.C.4.1.;
- Editorial corrections and improvements: page 4, section VIII.A., page 5, section VIII.B.1., page 10, section 9.6., and page 19, section VIII.C.4.1..
- Update of the cross-reference to the document "Member States' requirements for transmission of PASS information " (now GVP Module VIII Addendum I).

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VIII.A. Introduction

A post-authorisation safety study (PASS) is defined in Directive 2001/83/EC (DIR) Art 1(15) as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

A PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily, or pursuant to an obligation imposed by a competent authority [DIR Art 107m(1), Regulation (EC) No 726/2004 (REG) Art 28b]. These studies shall be conducted in accordance with the following provisions:

- DIR Art 107m-q and Commission Implementing Regulation (EU) No 520/2012 (IR) Art 36-38 for PASS initiated, managed or financed by a marketing authorisation holder pursuant to an obligation imposed by a competent authority; these studies include:
 - studies imposed as an obligation in accordance with REG Art 10 and Art 10a and with DIR Art 21a and Art 22a (category 1 of studies in Module V);
 - studies imposed as a specific obligation in the framework of a marketing authorisation granted under exceptional circumstances (category 2 of studies in Module V);
- DIR Art 107m for PASS initiated, managed or financed by a marketing authorisation holder voluntarily, namely those that have not been imposed as an obligation; they include those required in the risk management plan (RMP) to investigate a safety concern or to evaluate the effectiveness of risk minimisation activities (category 3 of studies in Module V) and, depending on their objective (see VIII.B.3.), some studies that may provide safety information of less significance (category 4 of studies of Module V).

This Module concerns PASS which are clinical trials or non-interventional studies and does not address non-clinical safety studies.

A PASS is non-interventional if the following requirements are cumulatively fulfilled [Volume 10 of The Rules Governing Medicinal Products in the European Union, Questions and Answers, Version 9.0, August 2011, Question 1.9]¹:

- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by its scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort or other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

If a PASS is a clinical trial, the provisions of Directive 2001/20/EC and of Volume 10 of The Rules Governing Medicinal Products in the European Union¹ shall be followed.

The purposes of this Module are to:

- provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by marketing authorisation holders voluntarily or pursuant to an obligation imposed by a competent authority (VIII.B.);
- describe procedures whereby competent authorities may impose to a marketing authorisation holder an obligation to conduct a clinical trial or a non-interventional study (VIII.C.2.), and the impact of this obligation on the risk management system (VIII.C.3);
- describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results (VIII.C.4.) and for changes to the marketing authorisation following results (VIII.C.5.).

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

VIII.B. Structures and processes

VIII.B.1. Scope

The guidance in VIII.B. applies to non-interventional PASS which are initiated, managed or financed by a marketing authorisation holder and conducted in the European Union (EU). This guidance should also be used for studies conducted outside the EU which have been imposed or required by a EU competent authority (categories 1, 2 and 3 of studies defined in Module V).

Where applicable, legal requirements which are applicable to studies conducted pursuant to an obligation are recommended to studies conducted voluntarily in order to support the same level of transparency, scientific standards and quality standards for all PASS. This applies, for example, to the format of study protocols, abstracts and final study reports and to the communication of study information to the Agency and national competent authorities. Where relevant, a distinction is made in the text between situations where the provision of the guidance represents a legal requirement or a recommendation.

This guidance apply to studies initiated, managed or financed by a marketing authorisation holder as well as those conducted by a third party on behalf of the marketing authorisation holder.

This guidance applies to studies that involve primary collection of safety data directly from patients and health care professionals and those that make secondary use of data previously collected from patients and health care professionals for another purpose.

VIII.B.2. Terminology

Date at which a study commences: date of the start of data collection.

Start of data collection: the date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts [IR Art 37]. Simple counts in a database to support the development of the study protocol, for example to inform the sample size and statistical precision of the study, are not part of this definition.

¹ <http://ec.europa.eu/health/documents/eudralex/vol-10/>

End of data collection: the date from which the analytical dataset is completely available [IR Art 37].

Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

Substantial amendment to the study protocol: amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, to the study population, to the sample size, to the definitions of the main exposure, outcome and confounding variables and to the analytical plan.

VIII.B.3. Principles

In accordance with DIR Art 1(15), a post-authorisation study should be classified as a PASS when the main aim for initiating the study includes any of the following objectives:

- to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;
- to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);
- to evaluate the risks of a medicinal product after long-term use;
- to provide evidence about the absence of risks;
- to assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
- to measure the effectiveness of a risk minimisation activity.

Whereas the PASS design should be appropriate to address the study objective(s), the classification of a post-authorisation study as a PASS is not constrained by the type of design chosen if it fulfils the criteria as set in DIR Art 1(15). For example, a systematic literature review or a meta-analysis may be considered as PASS depending on their aim.

Relevant scientific guidance should be considered by marketing authorisation holders and investigators for the development of study protocols, the conduct of studies and the writing of study reports, and by the Pharmacovigilance Risk Assessment Committee (PRAC) and national competent authorities for the evaluation of study protocols and study reports. Relevant scientific guidance includes the ENCePP Guide on Methodological Standards in Pharmacoepidemiology,² the ENCePP Checklist for Study Protocols², the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population for studies conducted in children,³ and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP)⁴.

For studies that are funded by a marketing authorisation holder, including studies developed, conducted or analysed fully or partially by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the marketing authorisation holder and investigators should ensure that the study meets its regulatory

² http://www.encepp.eu/standards_and_guidances/index.html

³ EMEA/CHMP/PhVWP/235910/2005; available on

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003764.pdf

⁴ http://www.pharmacoepi.org/resources/guidelines_08027.cfm

obligations while permitting their scientific expertise to be exercised throughout the research process. In the research contract, the marketing authorisation holder should consider the provisions of the ENCePP Code of Conduct,⁵ and address the following aspects:

- rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
- rights and obligations of the investigator(s) and marketing authorisation holder;
- clear assignment of tasks and responsibilities;
- procedure for achieving agreement on the study protocol;
- provisions for meeting the marketing authorisation holder's pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable;
- intellectual property rights arising from the study and access to study data;
- storage and availability of analytical dataset and statistical programmes for audit and inspection;
- communication strategy for the scheduled progress and final reports;
- publication strategy of interim and final results.

Non-interventional post-authorisation safety studies shall not be performed where the act of conducting the study promotes the use of a medicinal product [DIR Art 107m(3)]. This requirement applies to all studies and to all activities performed in the study, including for studies conducted by the personnel of the marketing authorisation holder and by third parties on behalf of the marketing authorisation holder.

Payments to healthcare professionals for participating shall be restricted to compensation for time and expenses incurred [DIR Art 107m(4)].

VIII.B.4. Study registration

In order to support transparency on non-interventional PASS conducted voluntarily or pursuant an obligation and to facilitate exchange of pharmacovigilance information between the Agency, Member States and marketing authorisation holders, the marketing authorisation holder should make study information (including for studies conducted outside the EU) available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency and accessible through the European medicines web-portal.⁶ The study protocol should be entered in the register before the start of data collection. Updates of the study protocol in case of substantial amendments, progress reports where applicable, and the final study report should be entered in the register (preferably within two weeks after their finalisation). Study information should normally be submitted in English. If the study protocol or the study report is written in another language, the marketing authorisation should facilitate access to study information by including an English translation of the title, the abstract of the study protocol and the abstract of the final study report.

Where prior publication of the protocol could threaten the validity of the study (for example, in a case-control study where prior knowledge of the exposure of interest could lead to information bias) or the protection of intellectual rights, a study protocol with redactions made by the MAH may be entered into the register prior to the start of data collection. These redactions should be justified and kept to the

⁵ http://www.encepp.eu/code_of_conduct/index.html

⁶ http://www.encepp.eu/encepp_studies/indexRegister.shtml

minimum necessary for the objective aimed by the redaction process. Whenever a redacted study protocol is published prior to the start of data collection, the title page of the protocol should include the mention "Redacted protocol" and the complete study protocol should be made available to the Agency and national competent authorities upon request. The complete study protocol should be entered in the register (preferably within two weeks after the end of data collection).

VIII.B.5. Study protocol

All post-authorisation safety studies must have a written study protocol before the study commences. The study should follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. EU and, where present, national requirements shall be followed for ensuring the well-being and rights of the participants [DIR Art 107m(2)]. The marketing authorisation holder may be required by the national competent authority to submit the protocol to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)].

For PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.4 for the submission of the study protocol.

Member States' requirements for transmission of the study protocol are specified in **Module VIII Addendum I**. For PASS concerning centrally-authorized products, the study protocol should also be transmitted to the Agency.

In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) or his/her delegate (see Module I) should be involved in the review and sign-off of study protocols conducted in the EU. Where applicable, the marketing authorisation holder's pharmacovigilance contact person at national level should be informed of any study sponsored or conducted by the marketing authorisation holder in that Member State and have access to the protocol.

VIII.B.5.1. Format and content of the study protocol

The study protocol should include the following information:

1. **Title:** informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version. If the study protocol has been registered in the EU PAS Register, subsequent versions of the protocol should mention on the title page "EU PAS Register No:" with the registration number.
2. **Marketing authorisation holder:** name and address of the marketing authorisation holder.
3. **Responsible parties:** names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the Agency and national competent authorities upon request.
4. **Abstract:** stand-alone summary of the study protocol including the following sub-sections:
 - Title with subtitles including version and date of the protocol and name and affiliation of main author
 - Rationale and background
 - Research question and objectives

- Study design
 - Population
 - Variables
 - Data sources
 - Study size
 - Data analysis
 - Milestones
5. **Amendments and updates:** any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.
6. **Milestones:** table with planned dates for the following milestones:
- Start of data collection
 - End of data collection
 - Study progress report(s) as referred to in Article 107m(5) of Directive 2001/83/EC
 - Interim report(s) of study results, where applicable, in line with phases of data analyses
 - Final report of study results

Any other important timelines in the conduct of the study should be presented.

7. **Rationale and background:** short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.
8. **Research question and objectives:** research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.
9. **Research methods:** description of the research methods, including:
- 9.1. **Study design:** overall research design and rationale for this choice.
 - 9.2. **Setting:** study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.
 - 9.3. **Variables:** outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.
 - 9.4. **Data sources:** strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and

effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.

- 9.5. **Study size:** any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.
- 9.6. **Data management:** data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.
- 9.7. **Data analysis:** the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorise, analyse and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.
- 9.8. **Quality control:** description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.
- 9.9. **Limitations of the research methods:** any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalisability, and random error. The likely success of efforts taken to reduce errors should be discussed.
10. **Protection of human subjects:** safeguards in order to comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.
11. **Management and reporting of adverse events/adverse reactions:** procedures for the collection, management and reporting of individual cases of adverse reactions and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted. For studies where reporting is not required (see Module VI), this should be stated.
12. **Plans for disseminating and communicating study results,** including any plans for submission of progress reports and final reports.
13. **References.**

The format of the study protocol should follow the Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies published by the Agency⁷.

Feasibility studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medical events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol with a summary of their methods and results. The full report should be made available

⁷ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf

to the Agency and national competent authorities upon request. Feasibility studies that are part of the research process should be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study.

An annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

VIII.B.5.2. Substantial amendments to the study protocol

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, the national competent authorities and the Agency should be informed immediately and the study shall subsequently be conducted in accordance with Directive 2001/20/EC and Volume 10 of The Rules Governing Medicinal Products in the European Union.

For PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.4 for the submission of substantial amendments to the study protocol.

Member States' requirements for transmission of substantial amendments to the study protocol are specified in **Module VIII Addendum I**. For PASS concerning centrally-authorized products, substantial amendments to the study protocol should also be transmitted to the Agency.

VIII.B.6. Reporting of pharmacovigilance data to competent authorities

VIII.B.6.1. Data relevant to the risk-benefit balance of the product

The marketing authorisation holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned [DIR Art 107m(7)]. Any new information that may affect the risk-benefit balance of the medicinal product should be communicated immediately in writing as an Emerging Safety Issue to competent authorities of the Member States in which the product is authorised and to the Agency via email (P-PV-emerging-safety-issue@ema.europa.eu). Information affecting the risk-benefit balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data.

This communication should not affect information on the results of studies which should be provided by means of periodic safety update reports (PSURs) (see Module VII) and in RMP updates (see Module V), where applicable.

VIII.B.6.2. Reporting of adverse reactions/adverse events

Adverse reactions/adverse events should be reported to competent authorities in accordance with the provisions of Module VI. Procedures for the collection, management (including a review by the marketing authorisation holder if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol. If appropriate, reference can be made to the Pharmacovigilance System Master File (see Module II) but details specific to the study should be described in this section. For study designs where expedited reporting is not required, this should be stated in the study protocol.

VIII.B.6.3. Study reports

VIII.B.6.3.1 Progress reports

Progress reports may be requested by a national competent authority [DIR Art 107m(5)]. They may also be requested by the PRAC, and by the Agency for PASS concerning centrally-authorised products. Requests for progress reports may be made before the study commences or any time during the study conduct. They may be guided by the communication of risk-benefit information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product.

Upon request from a national competent authority, progress reports shall be submitted to the competent authorities of the Member States in which the study is conducted [DIR Art 107m(5)]. Member States' requirements for transmission of progress reports are specified in [Module VIII Addendum I](#). For PASS concerning centrally-authorised products, progress reports should also be transmitted to the Agency.

The timing of the progress reports should be agreed with the relevant competent authorities and specified in the study protocol when they have been agreed before the study commences. Study progress should also be reported in any periodic safety update reports (PSURs) (see Module VII) and risk management plan (RMP) updates (see Module V), where applicable.

The content of the progress report should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients or number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may also include any interim report of study results. After review of the report, additional information may be requested.

VIII.B.6.3.2. Final study report

The final study report should be submitted as soon as possible within 12 months of the end of data collection.

For PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.4 as regards submission of the final study report.

Member States' requirements for transmission of the final study report are specified in [Module VIII Addendum I](#). For PASS concerning centrally-authorised products, the final study report should also be transmitted to the Agency.

If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

The final study report should include the following information:

1. **Title:** title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of main author. If the study has been registered in the EU PAS Register, the final study report should mention on the title page "EU PAS Register No:" with the registration number.
2. **Abstract:** stand-alone summary in the format presented below.
3. **Marketing authorisation holder:** name and address of the marketing authorisation holder.

4. **Investigators:** names, titles, degrees, addresses and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the Agency and national competent authorities upon request.
5. **Milestones:** planned and actual dates for the following milestones:
 - Start of data collection
 - End of data collection or date of early termination, if applicable, with reasons for termination
 - Study progress report(s)
 - Interim report(s) of study results, where applicable
 - Final report of study results
 - Any other important milestone applicable to the study, including date of protocol approval by an Institutional Review Board/Independent Ethics Committee if applicable, and date of study registration in the EU PAS Register.
6. **Rationale and background:** short description of the safety concern(s) that led to the study being initiated or imposed, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.
7. **Research question and objectives:** research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.
8. **Amendments and updates to the protocol:** list of any substantial amendment and update to the initial study protocol after the start of data collection, including a justification for each amendment or update.
9. **Research methods:**
 - 9.1. **Study design:** key elements of the study design and the rationale for this choice.
 - 9.2. **Setting:** setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.
 - 9.3. **Subjects:** any source population and eligibility criteria of study subjects. Sources and methods of selection of participants should be provided, including, where relevant methods for case ascertainment, as well as number of and reasons for dropouts.
 - 9.4. **Variables:** all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.
 - 9.5. **Data sources and measurement:** for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.
 - 9.6. **Bias:** any efforts to assess and address potential sources of bias.

- 9.7. **Study size:** study size, rationale for any sample size calculation and any method for attaining projected study size.
- 9.8. **Data transformation:** transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.
- 9.9. **Statistical methods:** description of:
- main summary measures
 - statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies
 - any methods used to examine subgroups and interactions
 - how missing data were addressed
 - any sensitivity analyses
 - any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.
- 9.10. **Quality control:** mechanisms to ensure data quality and integrity.
10. **Results:** presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals. This section should include the following sub-sections:
- 10.1. **Participants:** numbers of study subjects at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed, and reasons for non-participation at any stage. In the case of a systematic review or meta-analysis, number of studies screened, assessed for eligibility and included in the review with reasons for exclusion at each stage.
- 10.2. **Descriptive data:** characteristics of study participants, information on exposures and potential confounders and number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).
- 10.3. **Outcome data:** numbers of participants across categories of main outcomes.
- 10.4. **Main results:** unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period.
- 10.5. **Other analyses:** other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.
- 10.6. **Adverse events and adverse reactions:** summary of all adverse events/adverse reactions reported in the study, in line with requirements described in Module VI. For certain study designs such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this should be stated.

11. Discussion:

- 11.1. **Key results:** key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, impact of the results on the risk-benefit balance of the product.
- 11.2. **Limitations:** limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed.
- 11.3. **Interpretation:** interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.
- 11.4. **Generalisability:** the generalisability (external validity) of the study results.

12. References.

13. **Other information:** any additional or complementary information on specific aspects not previously addressed.

The format of the final study report should follow the Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies published by the Agency⁸.

The abstract of the final study report should include a summary of the study methods and findings presented in the following format:

1. Title, with subtitles including date of the abstract and name and affiliation of main author;
2. Keywords (not more than five keywords indicating the main study characteristics);
3. Rationale and background;
4. Research question and objectives;
5. Study design;
6. Setting;
7. Subjects and study size, including dropouts;
8. Variables and data sources;
9. Results;
10. Discussion (including, where relevant, an evaluation of the impact of study results on the risk-benefit balance of the product);
11. Marketing authorisation holder;
12. Names and affiliations of principal investigators.

VIII.B.7. Publication of study results

For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&mid=WC0b01ac05800250b3

be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

VIII.B.7.1. Regulatory submission of manuscripts accepted for publication

In order to allow national competent authorities to review in advance the results and interpretations to be published, the marketing authorisation holder should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

VIII.B.8. Data protection

Marketing authorisation holders and investigators shall follow relevant national legislation and guidance of those Member States where the study is being conducted [DIR Art 107m(2)]. The legislation on data protection must be followed in accordance with Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

For PASS imposed as an obligation, the marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected [IR Art 36]. This provision should also be applied to PASS voluntarily initiated, managed or financed by the marketing authorisation holder.

VIII.B.9. Quality systems, audits and inspections

The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection [IR Art 36]. This provision should also be applied to PASS voluntarily initiated, managed or financed by the marketing authorisation holder.

VIII.B.10. Impact on the risk management system

Non-interventional PASS imposed as an obligation or required to investigate a safety concern of the RMP (category 3 of studies in Module V) should be described in the RMP Part III (see Module V). Protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until submission of the final study report to the competent authorities. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan.

Other non-interventional PASS which are not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product (category 4 of studies in Module V) should be listed in the RMP section III "Summary table of additional pharmacovigilance activities.

For studies imposed as an obligation, see also VIII.C.3.

VIII.C. Operation of the EU network

VIII.C.1. Scope

Provisions of VIII.C. refer specifically to post-authorisation safety studies initiated, managed or financed by marketing authorisation holders pursuant to obligations imposed by a competent authority. Sections VIII.C.2. and VIII.C.3. apply to both interventional and non-interventional PASS. Sections VIII.C.4. and VIII.C.5. apply to non-interventional PASS.

VIII.C.2. Procedure for imposing post-authorisation safety studies

In the EU, the conduct of any post-authorisation safety study (PASS) can be imposed during the evaluation of the initial marketing authorisation application or during the post-authorisation phase by the Agency or the national competent authority whenever there are concerns about the risks of an authorised medicinal product. This obligation shall be duly justified based on benefit-risk considerations, shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study [DIR Art 22a, REG Art 10a]. The request may also include recommendations on key elements of the study (e.g. study design, setting, exposure(s), outcome(s), study population). An overview of study designs and databases frequently used in post-authorisation safety studies is provided in VIII.Appendix 1.

a. Request for a post-authorisation safety study as part of the initial marketing authorisation application

A marketing authorisation may be granted by the competent authority subject to the conduct of a PASS [DIR Art 21a, REG Art 10]. If the need for a PASS is identified for a centrally authorised product or a nationally authorised product authorised through the mutual recognition or the decentralised procedure, the PRAC may adopt an advice with an assessment report to the Committee for Medicinal Products for Human Use (CHMP) or to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) as applicable.

b. Request for a post-authorisation safety study during a post-authorisation regulatory procedure

The need for a PASS could be identified by the Agency or a national competent authority during a post-authorisation regulatory procedure, for example, an extension or a variation to a marketing authorisation or a renewal procedure. If the need for a PASS is identified for a centrally authorised product or a nationally authorised product through the mutual recognition or the decentralised procedure, the PRAC may adopt an advice with an assessment report to the CHMP or the CMDh as applicable.

c. Request for a post-authorisation safety study due to an emerging safety concern

After the granting of the marketing authorisation, the Agency or a national competent authority, where applicable, may impose on the marketing authorisation holder an obligation to conduct a post-authorisation safety study if there are concerns about the risk of the authorised medicinal product [DIR Art 22a, REG Art 10a], for example following evaluation of a safety signal (see Module IX). If the need for a PASS is identified for a centrally authorised product or a nationally authorised product through the mutual recognition or the decentralised procedure, the PRAC may adopt an advice with an assessment report to the CHMP or the CMDh as applicable.

d. Joint post-authorisation safety studies

If safety concerns apply to more than one medicinal product, the Agency or the national competent authority shall, following consultation with the PRAC, encourage the marketing authorisation holders concerned to conduct a joint PASS [DIR Art 22a, REG Art 10a]. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the marketing authorisation holders should contain the justification for the request of a joint study and the elements of the study design that support a joint protocol. Upon request from the marketing authorisation holders, the national competent authority or the Agency may organise a pre-submission meeting in order to provide suggestions for a joint study proposal and facilitate agreement in developing a joint protocol. If a joint protocol is not voluntarily agreed and different proposals are submitted, the national competent authority or Agency may define, in consultation with the PRAC, either a common core protocol or key elements (for example, the study design, the study population and the definition of exposure and outcomes) which each marketing authorisation holder will have to implement in the study protocol to be submitted to the national competent authority or the PRAC in accordance with DIR Art 107n(1).

e. Written observations in response to the imposition of an obligation

Within 30 days of receipt of the written notification of the obligation, the marketing authorisation holder may request the opportunity to present written observations in response to the imposition of the obligation [DIR Art 22a(2), REG Art 10a(2)]. The national competent authority or the Agency shall specify a time limit for the provision of these observations. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority or the European Commission shall withdraw or confirm the obligation. When the obligation is confirmed, the marketing authorisation shall be subject to variation to include the obligation as a condition and the risk management plan (RMP), where applicable, shall be updated accordingly [DIR Art 22a(3), REG Art 10a(3)] (see Module V).

VIII.C.3. Impact on the risk management system

All post-authorisation safety studies imposed as a condition to the marketing authorisation will be described in the RMP (see Module V and VIII.B.10.) and their results provided in the PSUR following completion of the final report, where applicable (see Module VII).

All relevant sections/modules of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimisation plan and the summary of activities, as appropriate. A copy of the study protocol approved by the competent authority should be provided annex 6 of the RMP.

When a RMP does not exist, a new RMP should be developed referring to the post-authorisation safety study.

VIII.C.4. Regulatory supervision of non-interventional post-authorisation safety studies

Non-interventional PASS conducted pursuant to obligations imposed by a competent authority are supervised and assessed by the PRAC, unless the PASS was requested by a national competent authority of a single Member State according to DIR Art 22a and conducted only in that Member State, in which case national oversight procedures apply [DIR Art 107n(1)].

VIII.C.4.1. Roles and responsibilities of the marketing authorisation holder

Following the imposing of the obligation to conduct a non-interventional PASS as a condition to the marketing authorisation, the marketing authorisation holder shall develop a study protocol and submit it to the national competent authority or the PRAC for review [DIR Art 107n(1)] as appropriate. When the PRAC is involved in the oversight of the study, the marketing authorisation holder shall submit the study protocol to the PRAC and to the Agency.

The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial, in which case Directive 2001/20/EC shall apply. If the study is a non-interventional study (see VIII.A.), the marketing authorisation holder shall ensure that the study meets the requirements applicable to non-interventional PASS set out in DIR Art 107m-q, in IR Art 36-38, in Module VIII.B and in requirements specific to the requested PASS. The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified (see VIII.B.8. and VIII.B.9.).

The marketing authorisation holder shall develop the study protocol following the format of IR Art 38 and should consider the recommendations set out in VIII.B.5.1. The study may commence only when the written endorsement from the national competent authority or the PRAC, as appropriate, has been issued. When a letter of endorsement has been issued by the PRAC, the marketing authorisation holder shall forward the protocol to the competent authority of the Member State(s) in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol [DIR Art 107n(3)]. EU and national requirements shall be followed to ensure the well-being and rights of participants in the study [DIR Art 107m(2)].

Prior to submission of the protocol, the marketing authorisation holder may submit a request to the Agency for a pre-submission meeting with the Agency and the PRAC rapporteur in order to clarify specific aspects of the requested study (such as study objectives, study population, definition of exposure and outcomes) and to facilitate the development of the protocol in accordance with the objectives determined by the PRAC.

After a study has been commenced, the marketing authorisation holder shall submit any substantial amendments to the protocol, before their implementation, to the national competent authority or to the PRAC, as appropriate (see VIII.B.2. for the definition of a substantial amendment). When the PRAC is involved in the oversight of the study, the marketing authorisation holder shall submit the amended study protocol to the PRAC and to the Agency.

The marketing authorisation holder may be requested to submit the study progress reports to the competent authorities in which the study is conducted [DIR Art 107m(5)].

Upon completion of the study, the marketing authorisation holder shall submit a final study report, including a public abstract, to the national competent authority or to the PRAC as soon as possible and not later than 12 months after the end of data collection, unless a written waiver has been granted by the national competent authority or the PRAC, as appropriate [DIR Art 107p(1)]. The final study report shall follow the format of IR Art 38, with consideration to the recommendations set out in VIII.B.6.3.2. The public abstract shall follow the format of IM Art 38.

When the PRAC is involved in the oversight of the study, the marketing authorisation holder shall submit the final study report to the PRAC and to the Agency. When the PRAC is responsible for regulatory supervision of the PASS, the marketing authorisation holder should request the waiver in writing to the Agency at least three months before the due date for the submission of the report. The request should include a justification for the waiver. The request should be assessed by the PRAC

rapporteur and granted or rejected by the PRAC on the basis of the justification and timeline submitted by the marketing authorisation holder.

The marketing authorisation holder shall submit the study protocol, the abstract of the final study report and the final study report in English except for studies to be conducted in only one Member State that requests the study according to DIR Art 22a. For the latter studies, the marketing authorisation holder shall provide an English translation of the title and abstract of the study protocol as well as an English translation of the abstract of the final study report [IR Art 36].

VIII.C.4.2. Roles and responsibilities of the PRAC and national competent authority

When the PRAC is involved in the oversight of the study, the PRAC will nominate a PRAC rapporteur responsible for the supervision of the PASS. The PRAC rapporteur should write a protocol assessment report, including a list of questions if appropriate, and submit it for review and approval by the PRAC.

If the study proves to be interventional, the PRAC rapporteur should not provide an assessment report but should issue an explanatory statement to the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

Within 60 days from submission of the draft protocol, the national competent authority or the PRAC shall issue a letter endorsing the draft protocol, a letter of objection or a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC. The letter of objection shall set out in detail the grounds for the objection in any of the following cases:

- it is considered that the conduct of the study promotes the use of a medicinal product;
- it is considered that the design of the study does not fulfil the study objectives [DIR Art 107n(2)].

In case of submission of an amended study protocol, the national competent authority or the PRAC, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection [DIR Art 107o]. The PRAC will provide the marketing authorisation holder with a letter of endorsement or objection to the protocol amendment within 30 days of submission. The letter of objection will provide a timeline by which the marketing authorisation holder should resubmit an amended version of the protocol.

In cases where the PRAC has assessed the final study results, the PRAC will produce an assessment report, including a list of questions as appropriate. If the PRAC addresses a list of questions to the marketing authorisation holder, the PRAC conclusion on the study results, including their recommendations to the CHMP or CMDh, as applicable (see VIII.C.5.), will be issued once the marketing authorisation holder has addressed the questions posed.

VIII.C.4.3. Roles and responsibilities of the Agency

The Agency shall provide scientific secretariat to the PRAC.

Upon receipt of the study protocol and of the final study report submitted by the marketing authorisation holder the Agency will provide the PRAC rapporteur with a summary of the study protocol and of the final study report.

The Agency will inform the marketing authorisation holder in writing and within the appropriate timelines of the decisions of the PRAC with respect to the assessment of the following:

- Study protocol;

- Study protocol amendments;
- Final study report;
- Waiver request for the submission of the final study protocol.

When the marketing authorisation holder submit a request to the Agency for a pre-submission meeting the Agency will be responsible for a timely set up of the meeting with the Agency and the PRAC rapporteur.

The Agency shall make public on the European medicines web-portal protocols and public abstracts of results of the post-authorisation safety studies referred to in DIR Art 107n and 107p.

VIII.C.5. Changes to the marketing authorisation following results from a non-interventional post-authorisation safety study

The marketing authorisation holder shall evaluate whether the study results have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities or the Agency an application to vary the marketing authorisation [DIR Art 107p(2)]. In such case, the variation should be submitted to the national competent authority or the Agency with the final study report within 12 months of the end of data collection. Where applicable, the PRAC and the CHMP or the CMDh will coordinate the assessment of the study results within the variation procedure.

Following the review of the final study report, the PRAC may recommend variation, suspension or revocation of the marketing authorisation [DIR Art 107q(2), REG Art 28b(2)]. The recommendation by the PRAC shall mention any divergent positions and the grounds on which they are based [DIR Art 107q(1)].

For centrally authorised products, or substances for which at least one centrally-authorized product exists, recommendations for the variation, suspension or revocation of the marketing authorisation made by the PRAC shall be transmitted to the CHMP which shall adopt an opinion taking into account the recommendation. The CHMP opinion shall be transmitted to the European Commission. The Commission shall adopt a decision in accordance with REG Art 10. When the opinion of the CHMP differs from the recommendation of the PRAC, the CHMP shall attach to its opinion a detailed explanation [REG Art 28b(2)].

For nationally authorised products including those authorised through the mutual recognition or the decentralised procedure and for substances where no centrally-authorized product exists, the Member States represented within the CMDh shall agree a position taking into account the PRAC recommendation and include a timetable for the implementation of this agreed position. When a consensus agreement is reached, the chairman of the CMDh shall record the agreement and send the agreed position to the marketing authorisation holder and Member States who should adopt necessary measures to vary, suspend or revoke the marketing authorisation in line with the implementation timetable of the CMDh. In case a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics (SmPC) and package leaflet within the determined timetable for implementation. In case a consensus agreement cannot be reached, the position of the majority of the Member States represented within the CMDh should be forwarded to the Commission who shall apply the procedure laid down in DIR Art 33 and 34. Where the agreement reached by the Member States represented within the CMDh or the position of the majority of Member States differs from the recommendation of the PRAC, the CMDh shall attach to the agreement or majority position a detailed explanation of the scientific grounds for differences together with the recommendation [DIR Art 107q(2)].

More urgent action may be required in certain circumstances, for example, based on interim results included in progress reports (see also VIII.B.6.3.1).

VIII.Appendix 1. Methods for post-authorisation safety studies

VIII.App1.1. Study designs

Post-authorisation safety studies may adopt different designs depending on their objectives. A brief description of the main types of studies, as well as the types of data resources available, is provided hereafter. However, this Appendix is not intended to be exhaustive and should be complemented with other information sources, such as the ENCePP Guide for Methodological Standards.

VIII.App1.1.1. Active surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain more completely the number of adverse events in a given population via a continuous organised process. An example of active surveillance is the follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this product may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system. Automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may also provide an efficient active surveillance system.

VIII.App1.1.1.1. Intensive monitoring schemes

Intensive monitoring is a system of record collation in designated areas, e.g. hospital units or by specific healthcare professionals in community practice. In such cases, the data collection may be undertaken by monitors who attend ward rounds, where they gather information concerning undesirable or unintended events thought by the attending physician to be causally related to the medication. Monitoring may also be focused on certain major events that tend to be drug-related such as jaundice, renal failure, haematological disorders, bleeding. The major strength of such systems is that the monitors may document important information about the events and exposure to medicinal products. The major limitation is the need to maintain a trained monitoring team over time.

Intensive monitoring may be achieved by reviewing medical records or interviewing patients and/or physicians/pharmacists in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, collection of information on the use of a medicinal product, such as the potential for abuse, may be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Intensive monitoring with sentinel sites is most efficient for those medicinal products used mainly in institutional settings such as hospitals, nursing homes, and haemodialysis centres. Institutional settings may have a greater frequency of use for certain products and may provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may provide an efficient active surveillance system.

VIII.App1.1.1.2. Prescription event monitoring

In prescription event monitoring, patients may be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical

events, and reasons for discontinuation can be included in the questionnaire [VIII.App 1. References 6-7]. Limitations of prescription event monitoring include incomplete physician response and limited scope to study products which are used exclusively in hospitals. More detailed information on adverse events from a large number of physicians and/or patients may be collected.

VIII.App1.1.1.3. Registries

A registry is an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry).

Disease/outcome registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations may help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition or from outside the registry, or for a case-only design (see VIII.App 1.1.2.4.).

Exposure registries address populations exposed to medicinal products of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a medicinal product has a special impact on this group of patients. Some exposure registries address exposures to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Simple cohort studies may measure incidence, but, without a comparison group, cannot evaluate any association between exposures and outcomes. Nonetheless, they may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan drug indicated for a specific condition.

VIII.App1.1.2. Observational studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports, active surveillance programmes or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies, based on primary data collection or secondary use of existing data.

VIII.App1.1.2.1. Cross-sectional study (survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. A drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed, which limits its use for etiologic research unless the exposures do not change over time. These studies are best used to examine the prevalence of a disease at one time-point or to examine trends over time, when data for serial time-points can be captured. These studies may also be used to examine the crude association between exposure and outcome in ecologic analyses.

VIII.App1.1.2.2. Cohort Study

In a cohort study, a population-at-risk for an event of interest is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each

patient. A patient might be exposed to a medicinal product at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving exposure to medicinal product(s), comparison cohorts of interest are selected on the basis of medication use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events may also be investigated using the same data source in a cohort study. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a product of interest (such as an orphan drug) or to study very rare outcomes. The identification of patients for cohort studies may come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

VIII.App1.1.2.3. Case-control study

In a case-control study, cases of disease (or events) are identified and patients without the disease or event of interest at the time of selection, are then selected as controls from the source population that gave rise to the cases. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease among the exposed as compared to the non-exposed. Patients may be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (the elderly, children, pregnant women, etc.). Existing large population-based databases are a useful and efficient means of providing needed exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicinal product (or products) and one specific rare adverse event, as well as to identify risk factors for adverse events (or actually, effect-modifiers). Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study may also provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

When the source population for the case-control study is a well-defined cohort, it is then possible to select a random sample from it to form the control series. The name "nested case-control study" has been coined to designate those studies in which the control sampling is density-based (e.g. the control series represents the person-time distribution of exposure in the source population). The case-cohort is also a variant in which the control sampling is performed on those persons who make up the source population regardless of the duration of time they may have contributed to it.

A case-control approach could also be set up as a permanent scheme to identify and quantify risks (case-control surveillance). This strategy has been followed for rare diseases with a relevant aetiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders.

VIII.App1.1.2.4. Other designs

Other designs have been proposed to assess the association between intermittent exposures and short-term events, including the self-controlled case-series, the case-crossover and the case-time-control studies. In these designs, only cases are used and the control information is obtained from past

person-time experience of the cases themselves. One of the important strengths of these designs is that those confounding variables that do not change within individuals are automatically matched.

VIII.App1.1.3. Clinical trials

When significant risks are identified from pre-approval clinical trials, further clinical trials might be called for to evaluate the mechanism of action for the adverse reaction. If the study is a clinical trial, provisions of Directive 2001/20/EC shall apply. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing may also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicinal product in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies may include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolise medicinal products differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

VIII.App1.1.3.1. Large simple trials

A large simple trial is a specific form of clinical trial where large numbers of patients are randomised to treatment but data collection and monitoring is kept to the minimum, consistent with the aims of the study. This design may be used in pharmacovigilance to elucidate the risk-benefit profile of a medicinal product outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event. The use of the term 'simple' refers to data structure and not data collection. It is used in relation to situations in which a small number of outcomes are measured and the term may not adequately reflect the complexity of the studies undertaken. These studies qualify as clinical trials.

VIII.App1.1.4. Drug utilisation studies

Drug utilisation studies (DUS) describe how a medicinal product is, prescribed and used in routine clinical practice in large populations, including elderly patients, children, pregnant women or patients with hepatic or renal dysfunction, who are often excluded by randomized clinical trials. Stratification by age, gender, concomitant medication and other characteristics allows a comprehensive characterization of treated patients, including the distribution of those factors that may influence clinical, social, and economic outcomes. From these studies, denominator data may be derived for use in determining rates of adverse reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions. DUS may be used to examine the relationship between recommended and actual clinical practice. These studies may help to monitor use in everyday medical practice and medication error and to determine whether a medicinal product has potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing.

VIII.App1.2. Data sources

Pharmacoepidemiological studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders and other variables, through interview of appropriate subjects (e.g. patients, relatives) or by consulting the paper-based medical records. However, the advent of automated healthcare databases has remarkably increased the efficiency of pharmacoepidemiologic research. There are two main types of automated databases, those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. These datasets may include millions of patients and allow for large studies. They may not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data, and paper-based medical records should be consulted to ascertain and validate test results and medical diagnoses. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmacoepidemiological studies or in their validation phase.

Marketing authorisation holders should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results). External validity should also be taken into account. As far as feasible the data source chosen to perform the study should include the population in which the safety concern has been raised. In case another population is involved, the marketing authorisation holder should evaluate the differences that may exist in the relevant variables (e.g. age, sex, pattern of use of the medicinal product) and the potential impact on the results. In the statistical analysis, the potential effect of modification of such variables should be explored.

With any data source used, the privacy and confidentiality regulations that apply to personal data should be followed.

**Appendix M: Member States' Requirements
for Transmission of Information on
Non-interventional Post-authorisation
Safety Studies**

19 April 2013
EMA/395730/2012 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module VIII Addendum I – Member States' requirements for transmission of information on non-interventional post-authorisation safety studies (Rev 1)

Date for coming into effect of first version	2 July 2012
Date for coming into effect of Revision 1*	25 April 2013

*Note: Revision 1 contains the following:

- Specification in explanatory note no 4 that the notification to all Member States is made by the Agency;
- Renaming of the document as Module VIII Addendum I (instead of Annex to Module VIII) in order to avoid confusion with GVP Annexes which are applicable to all GVP Modules.

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

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The tables below specify Member States' (MS) requirements for the transmission of information on post-authorisation safety studies initiated, managed or financed by marketing authorisation holders (MAHs) voluntarily or pursuant to an obligation.

These requirements are based on Directive 2001/83/EC Art 107 m-q and the GVP Module VIII. They do not cover the situation of studies conducted in only one Member State that requests the study according to Article 22a, in which case the MAH shall submit the draft protocol and the other study information to the national competent authority of the Member State in which the study is conducted.

These tables cover the requirements for transmission of information to national regulatory authorities, not to ethics committees, national review boards or other bodies in place according to national legislation.

Table VIII Add I.1. Studies imposed as an obligation by a competent authority

	Study protocols, updated study protocols following substantial amendments, final study reports ¹		Progress reports if requested ¹
	Direct transmission by MAH to MS ²	Transmission by MAH to MS via PRAC ³	Direct transmission by MAH to MS ²
Member States where the study is conducted	All		All
Member States acting as Rapporteur or RMS for the medicinal product **		All	All
Member States where the medicinal product is authorised, but not acting as Rapporteur of RMS for the medicinal product **		All	DE

¹ Study information should also be entered and maintained in the EU PAS Register.

² Final study protocols, substantial amendments to study protocol, any progress reports, abstracts of final study report and final study reports to be transmitted by marketing authorisation holders to Member States according to national procedures.

³ Information to be transmitted by marketing authorisation holders to the Agency and all PRAC members in the context of the oversight of post-authorisation safety studies by the PRAC as described in Directive 2001/83/EC Art 107 n-p.

** even if study not conducted in the Member State

Table VIII Add I.2. Studies initiated, managed or financed voluntarily by MAHs

	Study protocols, updated study protocols following substantial amendments, progress reports if requested and final study reports	
	Transmission by MAH via notification from EU PAS Register ⁴	Additional transmission by MAH to MS ⁵
Member States where the study is conducted	All	AT, BG, CZ, DE, ES, IT, NL, PT, RO
Member States acting as Rapporteur or RMS for the medicinal product **	All	DE, DK, NL, PT, RO
Member States where the medicinal product is authorised but not acting as Rapporteur or RMS for the medicinal product **	All	DE, RO

⁴ Notification message sent by the European Medicines Agency to all EU Member States with a link to the study record

⁵ Information to be transmitted by marketing authorisation holders to Member States according to national procedures.

** even if study not conducted in the Member State

Appendix N: Signal Management

22 June 2012
EMA/827661/2011

Guideline on good pharmacovigilance practices (GVP)

Module IX – Signal management

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	19 January 2012
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Revised draft adopted by Executive Director as final	22 June 2012
Date for coming into effect	2 July 2012

See websites for contact details

European Medicines Agency www.ema.europa.eu
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IX.A. Introduction

The Report of the Council for International Organisations of Medical Sciences Working group VIII *Practical Aspects of Signal Detection in Pharmacovigilance* (CIOMS, Geneva 2010) defines a signal as *information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.*

For the purpose of this Module, only new information related to adverse effects will be considered.

In order to suggest a new potentially causal association or a new aspect of a known association, any signal should be validated taking into account other relevant sources of information.

The signal management process can be defined as the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed. The signal management process shall include all steps from initial signal detection; through their validation and confirmation; analysis and prioritisation; and signal assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made [IR Art 21(1)].

In the European Union, the signal management process concerns all stakeholders involved in the safety monitoring of medicinal products including patients, healthcare professionals, marketing authorisation holders, regulatory authorities, scientific committees and decision-making bodies (such as competent authorities in the Member States and the European Commission (EC)).

Whereas the EudraVigilance database will be a major source of pharmacovigilance information, the signal management process covers signals arising from outside the EudraVigilance database or not directly supported by the EudraVigilance database. For the purpose of monitoring data in EudraVigilance database, only signals related to an adverse reaction shall be considered [IR Art 19(1)].

Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004, Directive 2010/84/EU amending Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC include provisions for signal management in the European Union.

In this Module, all applicable legal requirements are referenced as explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

The objectives of this Module are:

- to provide general guidance and requirements on structures and processes involved in signal management (section IX.B.);
- to describe how these structures and processes are applied in the setting of the EU pharmacovigilance and regulatory network (section IX.C.).

IX.B. Structures and processes

IX.B.1. Sources of data and information

The sources for identifying new signals are diverse. They potentially include all scientific information concerning the use of medicinal products including quality, non-clinical, clinical, pharmacovigilance and pharmacoepidemiological data. Specific sources for signals include spontaneous adverse drug reaction (ADR) reporting systems, active surveillance systems, non-interventional studies, clinical trials, scientific literature and other sources of information.

Signals from spontaneous reports may be detected from monitoring of individual case safety reports (ICSRs), ADR databases, articles from the scientific literature or review of information provided by marketing authorisation holders in the context of regulatory procedures (e.g. variations, renewals, post-authorisation commitments, periodic safety update reports (PSURs), Risk Management Plan (RMP) updates or from other activities related to the on-going benefit-risk monitoring of medicinal products.

Spontaneous reports of ADRs may also be notified to poison centres, teratology information services, vaccine surveillance programmes, reporting systems established by marketing authorisation holders, and any other structured and organised data collection schemes allowing patients and healthcare professionals to report suspected adverse reactions related to medicinal products. Competent authorities should liaise with other institutions or organisations managing such reporting system so as to be informed of these suspected adverse reactions.

Due to the increase in volume of spontaneous reports of (ADRs), the introduction of electronic safety reporting by patients and healthcare professionals and the mandatory electronic transmission of case reports from marketing authorisation holders to competent authorities, signal detection is now increasingly based on periodic monitoring of large databases such as the EudraVigilance database.

Signals may arise from a wide range of different study types, including quality, non-clinical, interventional and non-interventional studies, systematic reviews and meta-analyses. Interventional trials and observational studies may, by design, recruit and follow-up a defined population of subjects who may experience ADRs. Review of aggregated data and statistical analyses may also point to an elevated risk of an adverse event to be further investigated as a signal.

Published results of relevant studies should be identified by marketing authorisation holders by screening the scientific literature. For general guidance on performing literature searches, refer to [Module VI](#).

Marketing authorisation holders should regularly screen internet or digital media under their management or responsibility as specified in [Module VI](#), for potential reports of suspected ADRs, which may characterise a new signal. Marketing authorisation holders and competent authorities should seek further information related to suspected ADRs they become aware of from any source. Suspected serious ADRs should be confirmed if possible through other data sources such as EudraVigilance.

IX.B.2. Methodology for signal detection

As a general principle, signal detection should follow a recognised methodology, which may vary depending on the type of medicinal product it is intended to cover. Vaccines may for example require other methodological strategies.

The detection of signals shall be based on a multidisciplinary approach. Signal detection within the EudraVigilance database shall be complemented by statistical analysis where appropriate [IR Art 19(2)].

In order to determine the evidentiary value (i.e. the supporting evidence) of a signal a recognised methodology shall be applied taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure-response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data [IR Art 20(1)].

Different factors may be taken into account for the prioritisation of signals, namely whether the association or the active substance/medicinal product is new, the strength of the association, the seriousness of the reaction involved and the documentation of the reports in the EudraVigilance database [IR Art 20(2)].

IX.B.3. The signal management process

IX.B.3.1. Introduction

The signal management process covers all steps from detecting signals to recommending action(s) as follows:

- signal detection;
- signal validation;
- signal analysis and prioritisation;
- signal assessment;
- recommendation for action;
- exchange of information.

Although these steps generally follow a logical sequence, the wide range of sources of information available for signal detection may require some flexibility in the conduct of signal management e.g.:

- when signal detection is primarily based on a review of individual case safety reports (ICSRs), this activity may include validation and preliminary prioritisation of any detected signal;
- when a signal is detected from results of a study, it is generally not possible or practical to assess each individual case, and validation may require collection of additional data;
- recommendation for action (followed by decision in accordance with the applicable legislation) and exchange of information are components to be considered at every step of the process.

For the purpose of this guidance, signals originating from the monitoring of data from spontaneous reporting systems are considered as the starting point of the signal management process. The same principles should apply for data originating from other sources.

IX.B.3.2. Signal detection

Detailed guidance on methods of signal detection may be found in the Report of CIOMS Working group VIII [Practical Aspects of Signal Detection in Pharmacovigilance](#) (CIOMS, Geneva 2010) and in the [Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System](#) (Doc. Ref. EMEA/106464/2006 rev. 1).

Whichever methods are employed for the detection of signals, the same principles should apply, namely:

- the method used should be appropriate for the data set; for example, the use of complex statistical tools may not be appropriate for smaller data sets;

- data from all appropriate sources should be considered;
- systems should be in place to ensure the quality of the signal detection activity;
- any outputs from a review of cumulative data should be assessed by an appropriately qualified person in a timely manner;
- the process should be adequately documented, including the rationale for the method and periodicity of the signal detection activity.

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

IX.B.3.2.1. Review of individual case safety reports

As specified in **Module VI**, ICSRs may originate from a spontaneous reporting system, post-authorisation studies and monitoring of literature. Even a single report of a serious or severe adverse reaction (for example, one case of toxic epidermal necrolysis, aplastic anaemia or liver transplant) may be sufficient to raise a signal and to take further action. A review of ICSRs for this purpose should consider the number of cases (after exclusion of duplicates), the patient's demographics (including age and gender), the suspected medicinal product (including dose administered, formulation) and the suspected adverse reaction (including signs and symptoms), the temporal association, the clinical outcome in relation to drug continuation or discontinuation (i.e. de-challenge / re-challenge information). An assessment of causality of a suspected association should also consider, the presence of potential alternative causes including other concomitant medications, the underlying disease, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship.

IX.B.3.2.2. Statistical analyses

Signal detection is now increasingly based on a regular periodic monitoring of large databases of spontaneous reports of ADRs. Such databases allow generation of statistical reports presenting information on adverse reactions received over a defined time period for defined active substances or medicinal products. Various methods have been developed to identify statistics of disproportionate reporting, i.e. higher reporting than expected for an suspected adverse reaction for an active substance/medicinal product of interest compared to all other active substances/medicinal products in the database, (expressed e.g. as a lower bound of the proportionate reporting ratio ≥ 1). Given the limitations of these methods, statistics of disproportionate reporting alone do not necessarily indicate that there is a signal to be further investigated or that a causal association is present.

Use of statistical tools may not be appropriate in all situations. The size of the data set, the completeness of the available information and the severity of the adverse reaction(s) should be taken into account when considering the use of statistical methods and the selection of criteria for the detection of signals.

The periodicity at which statistical reports should be generated and reviewed may vary according to the active substance/medicinal product, its indication and any known potential or identified risks. Some active substances/medicinal products may also be subject to an increased frequency of data monitoring (see **IX.C.2.**). The duration for this increased frequency of monitoring may also vary and be flexible with the accumulation of knowledge of the risk profile associated with the use of the concerned active substance/medicinal product.

IX.B.3.2.3. Combination of statistical methods and review of individual case safety reports

Statistical reports may be designed to provide tools for identifying suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical association. Such filtering tools may facilitate the selection of ICSRs to be reviewed as a first step. The thresholds used in this filtering process (for example, at least 3 cases reported) may vary according to the extent of usage of medicinal products and thus the potential public health impact.

Irrespective of the statistical method used, where statistical reports are used to automate the screening of a database, signal detection should always involve clinical judgement and the corresponding ICSRs should be individually reviewed, considering their clinical relevance (IX.B.3.2.1.).

The statistical method should therefore be a supporting tool in the whole process of signal detection and subsequent validation.

IX.B.3.3. Signal validation

Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis [IR Art 21(1)].

To validate a signal the following should be taken into account:

- Clinical relevance including, for example:
 - strength of evidence for a causal effect (e.g. number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders);
 - seriousness and severity of the reaction and its outcome;
 - novelty of the reaction (e.g. new and serious adverse reactions);
 - drug-drug interactions;
 - reactions occurring in special populations.
- Previous awareness:
 - the extent to which information is already included in the summary of product characteristics (SmPC) or patient leaflet;
 - whether the association has already been assessed in a PSUR or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.

In principle only a new signal for which there is no previous awareness should be validated. However, an already known association may give rise to a new signal if its apparent frequency of reporting, its duration, its severity or a change in the previously reported outcome (such as new fatality) suggests new information as compared with the information included in the SmPC or previously assessed by the competent authority.

- Availability of other relevant sources of information providing a richer set of data on the same association:
 - literature findings regarding similar cases;
 - experimental findings or biological mechanisms;

- screening of databases with larger datasets (e.g. EudraVigilance when the signal was sourced initially by data from national or company-specific database).

The magnitude and clinical significance of a signal may also be examined by descriptive analyses in other available data sources or by analysis of the characteristics of exposed patients and their medicinal product utilisation patterns.

Signals for which the validity is not confirmed may deserve special attention in subsequent analyses i.e. it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm the signal. For example, there might be an inadequate case documentation or a supporting evidence of a causal association only in some of the ICSRs. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases should be reviewed at appropriate time intervals to ensure that all relevant cases are considered.

Marketing authorisation holders and competent authorities should establish tracking systems to capture the outcome of the validation of signals including the reasons why signals were not validated as well as information that would facilitate further retrieval of ICSRs and validation of signals.

IX.B.3.4. Signal analysis and prioritisation

A key element of the signal management process is to promptly identify validated signals with important public health impact or that may significantly affect the benefit-risk profile of the medicinal product in treated patients. These signals require urgent attention and need to be prioritised for further management without delay. This prioritisation process should consider:

- the impact on patients depending on the severity, reversibility, potential for prevention and clinical outcome of the association;
- the consequences of treatment discontinuation on the disease and the availability other therapeutic options;
- the strength and consistency of the evidence supporting an association, e.g., biological plausibility, a high number of cases reported in a short period of time, the measure of disproportionality of reporting and rapid increase of that measure over time and identification of the signal in different settings (e.g. general practice and hospital settings), data sources or countries;
- clinical context (e.g. whether the association suggest a clinical syndrome that may include other reactions);
- the public health impact, including the extent of utilisation of the product in the general population and in special populations (e.g. pregnant women, children or the elderly) and the patterns of medicinal product utilisation (e.g. off-label use or misuse). The public health impact may include an estimation of the number of patients that may be affected by an adverse reaction and this number could be considered in relation to the size of the general population, the population with the target disease and the treated population;
- increased frequency or severity of a known adverse reaction;
- novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction occurs shortly after the marketing of a new medicinal product;
- if a marketing authorisation application for a new active substance is still under evaluation.

In some circumstances, priority can also be given to signals identified for medicinal products or events with potential high media and pharmacovigilance stakeholder interest in order to communicate the result to the public and healthcare professionals as early as possible.

The outcome of signal prioritisation should include a recommendation of the time frame for the management of the signal.

The outcome of the signal prioritisation process should be entered in the tracking system, with the justification for the priority attributed.

IX.B.3.5. Signal assessment

The objective of signal assessment is to further evaluate a validated signal so as to identify the need for additional data collection or for any regulatory action. It consists of an assessment of the available pharmacological, non-clinical and clinical data and information from other sources. This review should be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports, expert consultation, and information held by marketing authorisation holders and competent authorities. When information is drawn from a range of sources, the strengths and limitations of each source should be considered in order to assess the contribution they can provide to the overall evaluation of the signal in terms of a recommendation for action. Summarising information from different data sources also requires the choice of an internationally agreed case definition (e.g. Brighton collaboration case definition for vaccines). If no such definition exists, an operational definition should be developed.

Signals may need to be assessed at a broader level e.g. at the therapeutic or system organ class level or at the level of a Standardised MedDRA¹ Query (i.e. SMQ). The search for information to assess the significance of a signal may also need to be extended to other products of the class and to other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of a reaction (e.g. QT prolongation and torsades de pointes) or to clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure).

Gathering information from various sources may take time. For a new signal of a serious or severe adverse reaction, measures should be taken at any stage in the management of a signal including detection, if the information already available supports the conclusion that there is a potential risk that needs to be prevented or minimised in a timely manner.

IX.B.3.6. Recommendation for action

Signal assessment results in a recommendation that either no further action is required at this point in time or a further action is needed. Although the recommendation for action normally takes place in a logical sequence after signal assessment based on the extent of the information, the need for action should be considered throughout the signal management process. For example, the first case of an adverse reaction indicating a manufacturing defect may require immediate recall of a product batch. The review of available information at the signal validation or signal prioritisation stages may similarly conclude that the evidence is sufficiently strong to introduce temporary measures. In such situations, it is still necessary to proceed with a formal assessment of the signal to confirm or not the safety issue in order to extend or lift the temporary measures.

The recommendation for action may include a request for:

- immediate measures including the possibility of suspending the marketing authorisation of the medicinal product;

¹ MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- additional information to be provided by the marketing authorisation holder, e.g. in order to confirm if a conclusion is valid for all indications and patient groups;
- periodic review of the signal, for example through PSURs (see [Module VII](#));
- additional investigations or risk minimisation activities;
- an update of the product information through a regulatory procedure;
- conduct of a post-authorisation safety study (see [Module VIII](#)).

Whenever actions are requested of a marketing authorisation holder, the request should specify a timeframe by which they should be completed, including provision of progress reports and interim results, proportionate to the severity and public health impact of the signal.

IX.B.3.7. Exchange of information

Information on validated signals, Emerging Safety Issues and the outcome of signal assessments should be exchanged between competent authorities and marketing authorisation holders.

Marketing authorisation holders should communicate signals that may have implications for public health and the benefit-risk profile of a product immediately to the competent authorities as an Emerging Safety Issue (see [Module VI](#)), and when appropriate this should include proposals for action.

The outcomes of signal assessment involving new or changed risks and risks that have an impact on the benefit-risk balance of the concerned active substance/medicinal products should be communicated to the public including health care professionals and patients (see [IX.C.6.](#)) as well as to the concerned marketing authorisation holders.

IX.B.4. Quality requirements

IX.B.4.1. Tracking

All validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps should be recorded and tracked systematically. Tracking systems should be used for documentation and should also include signals, for which the validation process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association. All records need to be archived [IR Art 24(1)] (see [Module I](#)).

IX.B.4.2. Quality systems and documentation

An essential feature of a signal management system is that it is clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are standardised, that these tasks are conducted by people with appropriate expertise and are clear to all parties involved and that there is provision for appropriate control and, when needed, improvement of the system. Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to all signal management processes (see [Module I](#)). Detailed procedures for this quality system should be developed, documented and implemented. The organisational roles and responsibilities for the activities and maintenance of documentation, quality control and review, and for ensuring corrective and preventive action need to be assigned and recorded. This should include the responsibilities for quality assurance auditing of the signal management system, including auditing of sub-contractors. Data and document confidentiality (per the applicable regulations), security and validity (including integrity when transferred) should be guaranteed.

Through their tracking system, all parties should keep an audit trail of their signal management activities and of the relevant queries and their outcomes, including how signals have been detected, validated, confirmed and assessed [IR Art 24(2)].

Documentation may be requested from the marketing authorisation holders demonstrating compliance with these provisions and reviewed before and after marketing authorisation.

Staff should be specifically trained in signal management activities in accordance with their roles and responsibilities. The training system and location of the training records should be documented, and curricula vitae and job descriptions should be archived.

IX.C. Operation of the EU network

IX.C.1. Roles and responsibilities

Within the context of the operation of the EU regulatory network, the marketing authorisation holders, the Agency and national competent authorities should continuously monitor the data available in the EudraVigilance database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the benefit-risk balance. A recognised signal detection methodology should be applied and detected signals should be validated, as appropriate.

The Agency and national competent authorities shall cooperate in the monitoring of the data available in the EudraVigilance database [IR Art 18(1)].

Regarding medicinal products authorised in accordance with Regulation (EC) No 726/2004 (centrally authorised products (CAPs)) the Agency shall be assisted in the monitoring of data in EudraVigilance by the rapporteur appointed by the PRAC in accordance with Article 62(1) of that Regulation [IR Art 22(5)].

For medicinal products authorised in accordance with Directive 2001/83/EC in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation has been granted in accordance with Directive 2001/83/EC, Member States may agree within the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), in collaboration with the PRAC, to appoint a lead Member State for the monitoring of data in the EudraVigilance database and for validation and confirmation of signals on behalf of the other Member States. The lead Member State may be supported by a co-leader, which shall assist the lead Member State in the fulfilment of its tasks. Any such appointment shall be reviewed at least every four years [IR Art 22(1)]. When appointing a lead Member State, and as appropriate a co-leader, the CMDh in collaboration with the PRAC, may take into account whether any Member State is acting as reference Member State, in accordance with Article 28(1) of Directive 2001/83/EC, or as a rapporteur for the assessment of periodic safety update reports in accordance with Article 107(e) of that Directive [IR Art 22(2)].

All Member States shall remain responsible for monitoring the data in the EudraVigilance database in accordance with Article 107h(1)(c) and Article 107h(3) of Directive 2001/83/EC [IR Art 22(4)].

The national competent authorities and the Agency shall validate and confirm any signal that has been detected by them in the course of their continuous monitoring of the data in EudraVigilance database [IR Art 21(4)].

For medicinal products or active substances where a rapporteur has been appointed by the PRAC, this rapporteur should confirm validated signals. For medicinal products or active substances where a lead Member State has been appointed, this lead Member State should confirm validated signals.

Confirmation by the PRAC rapporteur or the lead Member State means communication through the European Pharmacovigilance Issues Tracking Tool (EPITT) (see IX.C.5.) that the signal is valid. A justification should be provided when the signal is not confirmed. All confirmed signals shall be transmitted to the PRAC. For such medicinal products or active substances for which a lead Member State has been appointed, the lead Member State should validate and confirm as a single step the signals it has detected. For such medicinal products or active substances where a lead Member State has not been appointed, the national competent authority should validate and confirm as a single step the signals it has detected.

IX.C.1.1. Roles and responsibilities of the Agency

The Agency:

- shall make public on the European medicines web-portal a list of active substances/medicinal products and the authority (lead Member State, co-lead Member State or the Agency) responsible for their monitoring in EudraVigilance [IR Art 22(3)];
- following consultation with the PRAC may publish a list of medical events that have to be taken into account for the detection of a signal [IR Art 19(2)];
- shall support the monitoring of the data in the EudraVigilance database by providing national competent authorities with access to:
 - data outputs and statistical reports allowing a review of all adverse reactions reported to EudraVigilance in relation with an active substance or a medicinal product;
 - customised queries supporting the evaluation of individual case safety reports and case series;
 - customised grouping and stratification of data enabling the identification of patient groups with a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse reaction;
 - statistical signal detection methods [IR Art 23];
- shall ensure appropriate support for the monitoring of the data in EudraVigilance by marketing authorisation holders [IR Art 23];
- should prepare a technical document establishing common requirements for signal detection and describing EudraVigilance data outputs and statistical reports;
- shall administer the European Pharmacovigilance Issues Tracking Tool (EPITT) for validated signals that require further assessment [IR Art 21(5)];
- shall take the lead for EudraVigilance data monitoring, signal detection and signal validation for CAPs and for active substances contained in several medicinal products, where at least one marketing authorisation has been granted in accordance with Regulation (EC) 726/2004;
- shall enter validated signals it has detected into EPITT;
- should validate (including, if appropriate, in the EudraVigilance database) and enter into EPITT any other signal communicated by a third party (e.g. regulatory authority from outside the EU), involving a CAP or an active substance for which the EudraVigilance data monitoring is performed by the Agency;
- shall confirm in collaboration with the Member States as soon as possible and no later than 30 days from its receipt any validated signal communicated by marketing authorisation holders involving a CAP or an active substance for which the EudraVigilance data monitoring is performed by the

Agency. In this context, where the validity of the signal is not confirmed, special attention shall be paid to any follow-up information which may allow for the signal's confirmation [IR Art 21(3)], see IX.B.3.3;

- shall transmit confirmed signals to the PRAC for initial analysis and prioritisation in accordance with Article 28a(2) of Regulation (EC) No 726/2004 [IR Art 21(5)];
- shall forthwith inform the concerned marketing authorisation holder(s) of the conclusions of the PRAC of the assessment of any confirmed signal [IR Art 21(6)];
- shall keep an audit trail of its signal detection activities [IR Art 24(1)].

IX.C.1.2. Roles and responsibilities of the lead Member State

The lead Member State:

- shall take the lead for EudraVigilance data monitoring, signal detection, signal validation and signal confirmation for active substances/medicinal products for which it has been appointed the lead;
- shall confirm signals that have been detected and validated by a national competent authority for these substances/medicinal products;
- shall enter into EPITT signals it has detected, validated and confirmed itself for these substances/medicinal products
- should validate (including, if appropriate, in the EudraVigilance database) and enter into EPITT any other signal communicated by a third party (e.g. regulatory authority from outside the EU) for these substances/medicinal products;
- shall confirm as soon as possible and no later than 30 days from its receipt any validated signal communicated by marketing authorisation holders for these substances/medicinal products. In this context, where the validity of the signal is not confirmed, special attention shall be paid to any follow-up information which may allow for the signal's confirmation [IR Art 21(3)], see IX.B.3.3.;
- shall keep an audit trail of their signal detection activities [IR Art 24 (1)].

IX.C.1.3. Roles and responsibilities of the national competent authorities

The national competent authorities shall specifically monitor data originated in their territory [IR Art 18(4)], including data arising from sources mentioned in IX.B.1.

If a lead Member State or the Agency has been appointed for the monitoring of an active substance/medicinal product, the national competent authorities:

- should enter validated signals it has detected into EPITT for the lead Member State or the rapporteur appointed by the PRAC to confirm.

If no lead Member State or the Agency has been appointed for the monitoring of an active substance/medicinal product, the national competent authorities:

- shall monitor the data of the EudraVigilance database for substances/medicinal products authorised in their territory;
- shall validate and confirm any signal they have detected from EudraVigilance for substances/medicinal products authorised in their territory;
- shall enter validated and confirmed signal they have detected into EPITT for substances/medicinal products authorised in their territory;

- shall confirm as soon as possible and no later than 30 days from its receipt any validated signal communicated by a marketing authorisation holder for an active substance/medicinal product authorised in their territory. In this context, where the validity of the signal is not confirmed, special attention shall be paid to any follow-up information which may allow for the signal's confirmation [IR Art 21(3)], see IX.B.3.3.

The national competent authorities shall keep an audit trail of their signal detection activities [IR Art 24 (1)].

IX.C.1.4. Roles and responsibilities of the Pharmacovigilance Risk Assessment Committee

The Pharmacovigilance Risk Assessment Committee (PRAC):

- shall prioritise validated and confirmed signals for further assessment [REG Art 28a];
- should nominate a rapporteur for the assessment of the validated and confirmed signals with a time frame for the assessment;
- shall transmit to the CHMP or to the CMDh, as appropriate, any recommendations for action following the signal assessment;
- shall perform a regular review of the signal management methodology to be used and publish recommendations as appropriate [IR Art 20 (3)];
- should review at least every four years the lead and the co-lead Member States responsible for the monitoring of the data in EudraVigilance [IR Art 22(1)];
- should review the list of medical events that have to be taken into account for the detection of a signal before their publication by the Agency [IR Art 19(2)].

IX.C.1.5. Roles and responsibilities of marketing authorisation holder

The marketing authorisation holder should continuously monitor the safety of its medicinal products and inform the authorities of any changes that might have an impact on the marketing authorisation.

The marketing authorisation holder:

- shall monitor the data in EudraVigilance to the extent of their accessibility [IR Art 18(2)]. See also EudraVigilance access rights for stakeholder group III in the EudraVigilance Access Policy for Medicines for Human Use². The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information [IM Art 18(3)];
- shall validate any signal detected from EudraVigilance and shall forthwith inform the responsible competent authority for signal detection in line with the list as published by the Agency [IR Art 21(2)]. For the validation step, the elements of information presented in IX.B.3.3. should be taken into account;
- should notify in writing as an Emerging Safety Issue to the competent authorities in Member States where the medicinal product is authorised and to the Agency via email (P-PV-emerging-safety-issue@ema.europa.eu) (see also Module VI), any safety issue arising from its signal detection

² EudraVigilance access policy for medicines for human use published on 23 August 2011
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108538.pdf

activity which could have a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health;

- should collaborate with the PRAC for the assessment of the signals by providing additional information upon request;
- should keep an audit trail of its signal detection activities.

IX.C.2. Periodicity of data monitoring in EudraVigilance

National competent authorities and the Agency shall ensure the continuous monitoring of data in the EudraVigilance database with a frequency proportionate to the identified risk, the potential risk and the need for additional information [IR Art 18(3)]. The monitoring should be based on a periodic review of statistical outputs (e.g. reaction monitoring reports) to determine whether there are new or changed risks in the safety profile of an active substance/medicinal product. The statistical outputs should contain ADRs in a structured hierarchy (e.g. MedDRA hierarchy) by active substance(s)/medicinal product(s) and allow filters and thresholds to be applied on several fields as appropriate.

The baseline frequency for reviewing the statistical outputs from EudraVigilance should be once-monthly. An increase to the baseline frequency of data monitoring in EudraVigilance may be decided by the lead Member State, the national competent authority or the Agency if justified by the identified or potential risks of the product or by the need for additional information. The PRAC should be informed of the decision and the justification.

For products subject to additional monitoring (see **Module X**), the frequency for reviewing the statistical outputs should be every 2 weeks until the end of additional monitoring. A 2-week frequency for reviewing the statistical outputs may also be applied for any other product taking into account the following criteria:

- any product considered to have an identified or potential risk that could impact significantly on the benefit-risk balance or have implications for public health. This may include risks associated with significant misuse, abuse or off-label use. The product may be moved back to baseline frequency of monitoring if risks are not confirmed;
- any product for which the safety information is limited due to low patient exposure during drug development, including products authorised under conditional approval or under exceptional circumstances, or for which there are vulnerable or poorly studied patient populations or important missing information (e.g. children, pregnant women, renal-impaired patients) while post-marketing exposure is likely to be significant;
- any product that contains active substances already authorised in the EU but is indicated for use in a new patient population or with a new route of administration;
- any product for which the existing marketing authorisation has been significantly varied (e.g. changes to indication, posology, pharmaceutical form or route of administration), thereby modifying the exposed patient population or the safety profile.

Confirmation of a signal arising from the EudraVigilance data monitoring activities does not necessarily imply that the product has to be more frequently monitored and a risk proportionate approach should be applied.

More frequent monitoring than every 2 weeks should be based on a proposal from the lead Member State, national competent authority or the Agency. It should be targeted to a safety concern of interest especially during public health emergencies (e.g. pandemics) and may be applied in the context of

customised queries or near real-time alerts³ conducted in the EudraVigilance Data Analysis System (EVDAS).

IX.C.3. Signal analysis, prioritisation and assessment by the Pharmacovigilance Risk Assessment Committee (PRAC)

When the Agency or national competent authority validating or confirming a signal considers urgent action is required before the next PRAC meeting it should trigger the Rapid Alert procedure (see Module XII). All other signals that have been detected, validated and confirmed by the Agency or a national competent authority should be sent to the PRAC for consideration at its next meeting. In its consideration of a signal, the PRAC should agree on a prioritisation based on the individual patient and public health impact of the potential change to the benefit-risk balance. Depending on the prioritisation, an analysis of the need for further assessment or for any immediate recommendation for action should be made, taking into account the time frame proposed by the Agency or the national competent authority that detected the signal.

When PRAC considers a signal as a high priority at a given meeting, a recommendation on the action(s) required should be made during the same meeting and appropriate procedure(s) should be initiated by the Agency and/or national competent authorities in conjunction with the marketing authorisation holder

When it considers that further signal assessment is needed, the PRAC should nominate a rapporteur and should define a timeframe for this assessment taking into account the prioritisation of the signal.

The rapporteur for the signal assessment should transmit to the PRAC an assessment stating whether there may be new risks, whether risks have changed or whether there is a change in the benefit-risk balance in relation to the concerned active substance or medicinal product. The assessment should also include a proposed recommendation for action(s), if appropriate. The PRAC can also conclude that no action is required at EU level at this time point.

Following review of the rapporteur's assessment report, the PRAC should make a recommendation for action(s), stating the reasons on which it is based. The recommendation should include an implementation timetable for completion of any actions requested of the marketing authorisation holder commensurate with the extent and seriousness of the matter in accordance with Article 107h(2) of Directive 2001/83/EC and Article 28a(2) of Regulation (EC) 726/2004.

IX.C.4. Processes for EU regulatory follow-up

The recommendation for action of the PRAC should be sent to the CHMP in the case of an active substance that is centrally authorised and to the CMDh in the case of an active substance that is nationally authorised including authorisation through the mutual recognition or decentralised procedure.

The CHMP or CMDh may decide on any or a combination of the following actions:

- the marketing authorisation holder should conduct further evaluation of data and provide the results of that evaluation according to a defined timeline;
- the marketing authorisation holder should submit an *ad-hoc* PSUR;
- the marketing authorisation holder should sponsor a post-authorisation study according to an agreed protocol and submit the final results of that study;

³ EVDAS automated data processing and network transmission takes usually 1 day

- the marketing authorisation holder should be requested to submit a RMP or an updated RMP;
- the marketing authorisation holder should take any measures that are required for ensuring the safe and effective use of the medicinal product;
- the marketing authorisation should be varied, suspended, revoked or not renewed;
- the Member States or the Commission should initiate as appropriate, the procedure provided for in Article 31 or in Section 4, Urgent Union Procedure or in Article 31 where appropriate, of Directive 2001/83/EC;
- urgent safety restrictions should be imposed in accordance with Article 22 of Regulation (EC) 1234/2008;
- an inspection should take place in order to verify that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive 2001/83/EC;
- the medicinal product should be included in the list of medicinal products that are subject to additional monitoring within the scope defined in Article 23 of Regulation (EC) 726/2004.

Where recommended by the PRAC and agreed by the CHMP or the CMDh as appropriate, a procedure should be initiated with a timetable in which the marketing authorisation should be varied, suspended, revoked or not renewed where applicable.

IX.C.5. Record management in the EU regulatory network

The Agency and the national competent authorities shall keep an audit trail of all their signal management activities relating to EudraVigilance and of the relevant queries and their outcomes.

Any signal that has been detected and validated by the Agency or a national competent authority in line with the processes described in section IX.B. should be entered into the web-based European Pharmacovigilance Issues Tracking Tool (EPITT) administered by the Agency. All subsequent evaluations, timelines, decisions, actions, plans, reporting and all other key steps should be recorded and tracked systematically in EPITT by the Agency or the national competent authority in line with the guidance document *Exchange of Information Relating to Signals through EPITT by the EU Regulatory Network* (EMA/383041/2011).

IX.C.6. Transparency

Article 26(1) of Regulation (EC) 726/2004 states that the Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised in the EU. This information will include the conclusions of the PRAC following the assessment of signals and any recommendations.

Appendix O: Additional Monitoring

19 April 2013
EMA/169546/2012

Guideline on good pharmacovigilance practices (GVP) Module X – Additional monitoring

Draft finalised by the Agency in collaboration with Member States	25 May 2012
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Date for coming into effect	25 April 2013

See websites for contact details

European Medicines Agency www.ema.europa.eu
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X.A. Introduction

Pharmacovigilance is a vital public health function with the aim of rapidly detecting and responding to potential safety hazards associated with the use of medicinal products.

A medicinal product is authorised on the basis that, its benefit-risk balance is considered to be positive at that time for a specified target population within its approved indication (s). However, not all risks can be identified at the time of initial authorisation and some of the risks associated with the use of a medicinal product emerge or are further characterised in the post-authorisation phase of the product's lifecycle. . To strengthen the safety monitoring of medicinal products, the 2010 EU Pharmacovigilance legislation, further amended in 2012, has introduced a framework for enhanced risk proportionate post-authorisation data collection for medicinal products, including the concept of additional monitoring for certain medicinal products.

As defined in Article 23 of Regulation (EC) No 726/2004 (REG) and Article 11 of Directive 2001/83/EC (DIR), the Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring (hereafter referred to as "the list"). These medicinal products will be readily identifiable by an inverted equilateral black triangle ▼ as stipulated in the Implementing Regulation (EU) No 198/2013. That triangle will be followed by an explanatory statement in the summary of product characteristics (SmPC) as follows:

"This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions."

A similar statement will also be included in the package leaflet. This explanatory statement should encourage healthcare professionals and patients to report all suspected adverse reactions.

The pharmacovigilance provisions of Regulation (EC) No 726/2004 and of Directive 2001/83/EC have been recently amended by Regulation (EU) No 1027/2012 and Directive 2012/26/EU respectively. These amendments have impacted on the content and the scope of Article 23 of the REG and will be applicable for centrally authorised products on 5 June 2013. This GVP takes into account the new provisions relating to the list of products which require additional monitoring.

Post-authorisation spontaneous Adverse Drug Reactions (ADR) reports remain a cornerstone of pharmacovigilance. Data from ADR reports is a key source of information for signal detection activities (see [Module IX](#)). Increasing the awareness of healthcare professionals and patients of the need to report suspected adverse drug reactions and encouraging their reporting is therefore an important means of monitoring the safety profile of a medicinal product.

The concept of additional monitoring originates primarily from the need to enhance the ADR reporting rates for newly authorised products for which the safety profile might not be fully characterised or for products with newly emerging safety concerns that also need to be better characterised. The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and thereby informing the safe and effective use of medicinal products.

This Module is divided in two sections:

- [X.B.](#) provides general principles for assigning additional monitoring status to medicinal products and on communication and transparency aspects.
- [X.C.](#) describes the operation of the EU network regarding the supervision of additional monitoring status, the communication strategy and the impact on pharmacovigilance activities.

X.B. Structures and processes

X.B.1. Principles for assigning additional monitoring status to a medicinal product

All medicines are authorised on the basis that the benefit of treatment is considered to outweigh the potential risks. To come to this conclusion for a marketing authorisation, data from clinical trials conducted during the development of a medicine are assessed. However, adverse reactions which occur rarely or after a long time may become apparent only once the product is used in a wider population and/or after long term use. In addition, the benefits and risks of a medicine may have been evaluated in conditions which may differ from those in everyday medical practice, e.g. clinical trials might exclude certain types of patients with multiple co-morbidities or concomitant medications. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. Marketing authorisation holders and competent authorities continuously monitor medicinal products for any information that becomes available and assess whether it impacts on the benefit-risk profile of the medicinal product. However, for certain medicinal products enhanced post-authorisation data collection is needed to ensure that any new safety hazards are identified as promptly as possible and that appropriate action can be initiated immediately. Therefore, in order to strengthen the monitoring of certain medicinal products and in particular to encourage the spontaneous reporting of ADRs, the concept of additional monitoring has been introduced.

Additional monitoring status can be assigned to a medicinal product at the time of granting a marketing authorisation or in some cases at later stages of the product life cycle for a medicinal product for which a new safety concern has been identified. The additional monitoring status is particularly important when granting marketing authorisation for medicinal products containing a new active substance and for all biological medicinal products, which are priorities for pharmacovigilance. Competent authorities may also require additional monitoring status for a medicinal product which is subject to specific obligations e.g. the conduct of a Post-Authorisation Safety Study (PASS) or restrictions with regards to the safe and effective use of the medicinal product.

X.B.2. Communication and transparency

The additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions without creating undue alarm. This can be achieved for example by highlighting the need to better characterise the safety profile of a new medicinal product by identifying additional risks but placing those potential risks in the context of the known benefits for this product. A publicly available list of medicinal products with additional monitoring status should be kept up to date by the Agency. In addition, healthcare professionals and patients should be enabled to easily identify those products through their product labelling. The publication of the list together with appropriate communication should encourage healthcare professionals and patients to report all suspected adverse drug reactions for all medicinal products subject to additional monitoring.

X.C. Operation of the EU network

X.C.1. Criteria for including a medicinal product in the additional monitoring list

X.C.1.1. Mandatory scope

According to Article 23(1) of Regulation (EC) No 726/2004 (REG), it is mandatory to include the following categories of medicinal products in the list:

- medicinal products authorised in the EU that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- any biological medicinal product not covered by the previous category and authorised after 1 January 2011;
- products for which a PASS was requested at the time of marketing authorisation (point (cb) of Article 9(4) of Regulation (EC) No 726/2004 and point (b) of Article 21a of Directive 2001/83/EC);
- products authorised with specific obligations on the recording or suspected adverse drug reactions exceeding those referred to in Chapter 3 of Directive 83/2001/EC (point (cb) of Article 9(4) of Regulation (EC) No 726/2004 and point (c) of Article 21a of Directive 2001/83/EC);
- products for which a PASS was requested following the grant of marketing authorisation (Article 10a(1) of Regulation (EC) No 726/2004 and point (a) of Article 22a (1) of Directive 2001/83/EC);
- products which were granted a conditional marketing authorisation (Article 14(7) of Regulation (EC) No 726/2004);
- products authorised under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004 and Article 22 of Directive 2001/83/EC).

X.C.1.2. Optional scope

As set out in Article 23(2) of Regulation (EC) No 726/2004 there is the possibility to include in the list medicinal products subject to conditions, not falling under the mandatory scope. This can be done at the request of the European Commission or a national competent authority, as appropriate, following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC).

As reflected in Article 23(2) of Regulation (EC) No 726/2004 the situations that could form the basis for a request for inclusion in the list are:

- When a marketing authorisation is granted subject to one or more of the following:
 - conditions or restrictions with regard to the safe and effective use of the medicinal product [REG Art 9(4)(c), DIR Art 21a(d)];
 - measures for ensuring the safe use of the medicinal product to be included in the risk management system [REG Art 9(4)(ca), DIR Art 21a(a)];
 - an obligation to conduct a post-authorisation efficacy study [REG Art 9(4)(cc)DIR Art 21a(f)];
 - the existence of an adequate pharmacovigilance system [DIR Art 21a(e)].

The scope of Article 23(2) of Regulation (EC) No 726/2004 does not only include medicinal products which are authorised or for which conditions are established after entry into force of the new pharmacovigilance legislation but also medicinal products which were authorised or made subject to

conditions before such date, provided they fall within one or more of the above situations for the optional scope.

Pharmacovigilance rules in general and additional monitoring specifically take into account that the full safety profile of medicinal products can only be confirmed after products have been placed on the market. Due consideration should, therefore, be given to the merit of inclusion of a medicinal product in the list in terms of increasing awareness about the safe and effective use of a medicinal product and/or providing any additional information for the evaluation of the product. In this regard, the decision to include a medicinal product subject to conditions in the list should take account of the nature and scope of the conditions or obligations placed on the marketing authorisation including their potential public health impact. The decision should also consider the usefulness of the additional monitoring status in relation to other additional pharmacovigilance activities proposed in the risk management plan, for example in relation to the objectives of PASS.

X.C.2. Criteria for defining the initial time period of maintenance in the additional monitoring list

X.C.2.1. Mandatory scope

For medicinal products containing new active substances as well as for all biological medicinal products approved after 1 January 2011 the initial period of time for inclusion is five years after the Union Reference Date (URD) referred to in Article 107c(5) of Directive 2001/83/EC.

X.C.2.2. Optional scope

The period of time for inclusion in the list of medicinal products authorised subject to conditions is decided by the European Commission or the national competent authority, as appropriate, is linked to the fulfilment of the conditions and obligations placed on the marketing authorisation.

If new conditions are imposed to the marketing authorisation during a product's lifecycle, it is envisaged that a medicinal product previously removed from the list can be added to the list again if for example the criteria stipulated in Article 23(2) of Regulation (EC) No 726/2004 are met again.

X.C.3. Roles and responsibilities

X.C.3.1. The European Commission

The European Commission decides, based on a recommendation from the PRAC:

- if a particular centrally authorised medicinal product subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 should be included in the list.

X.C.3.2. The Agency

The Agency:

- is responsible for publishing the list of medicinal products that are subject to additional monitoring on the European web-portal with an electronic link(s) to a webpage where the product information and the summary of the RMP are publicly available;
- will coordinate the gathering of information that should be sent by the competent authorities within the EU network in order to set up, maintain and publish the list;
- is responsible for removing medicinal products from the list after a pre-determined time period;

- will take into account the list of centralised medicinal products subject to additional monitoring in determining the frequency and processes of its signal detection activities;
- will inform the relevant MAH when a centralised medicinal product has been included to the list of additional monitored products;
- will support the process of consultation of the PRAC on the inclusion of medicinal products on the list.

X.C.3.3. National competent authorities

National competent authorities should:

- inform the Agency which nationally authorised medicinal products are to be included in the list and provide the electronic links to the national webpage where the product information and the summary of the RMP are publicly available;
- decide, based on a recommendation from the PRAC, if a particular nationally authorised medicinal product subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 should be subject to additional monitoring and therefore included in the list;
- make publicly available in their national web-portal the list of medicinal products authorised in their territory that are subject to additional monitoring. The list shall include an electronic link to a webpage where the product information and the summary of the RMP are publicly available;
- inform the Agency of any update that needs to be made for nationally authorised medicinal products included in the list that is published by the Agency;
- take into account the list of nationally authorised medicinal products subject to additional monitoring in determining the frequency and processes of their signal detection activities;
- inform the relevant MAH when a nationally medicinal product has been included to the list of additional monitored products.

X.C.3.4. The Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC:

- recommends, upon request of the European Commission or a national competent authority, as appropriate, if a medicinal product which is subject to conditions as set out in Article 23(2) of Regulation (EC) 726/2004 should be included in the list.

X.C.3.5. The Marketing authorisation holder

The marketing authorisation holder:

- shall include in the SmPC and Package leaflet of their medicinal products subject to additional monitoring the black triangle symbol ▼ and the standardised explanatory statement on additional monitoring;
- should include information on the status of additional monitoring in any material to be distributed to healthcare professionals and patients and should make all efforts to encourage reporting of adverse reactions, as agreed with national competent authorities;
- should provide evidence to the competent authorities concerned on the status of any conditions imposed by the national competent authorities or the European Commission;

- should submit the relevant variation to include/remove the black symbol, the statement, and the standardised explanatory sentence from the SmPC and PL, where applicable.

X.C.4. Creation and maintenance of the list

As defined in Article 23 of Regulation (EC) 726/2004 the Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring. This list will include the names and active substances of all medicinal products approved in the EU subject to additional monitoring irrespective of the approval procedure (i.e. centrally or nationally authorised). In addition, as defined in Article 106 of Directive 2001/83/EC, each Member State shall make publicly available on their national web-portal the list of medicinal product authorised in their territory that are subject to additional monitoring, and take all appropriated measures to encourage patients and health care professional to report any suspected adverse drug reactions.

X.C.4.1. Process for the creation of the list

The Agency in support of the European Commission will identify the centrally authorised products requiring additional monitoring. National competent authorities are responsible for identifying the nationally authorised products requiring additional monitoring.

Only medicinal products that fall under the mandatory scope according to Article 23(1) of Regulation (EC) 726/2004 will be automatically included in the list. For medicinal products that fall under the optional scope, consultation with the PRAC is required.

The Agency and the national competent authorities will maintain the information that is publicly available and ensure that it is up to date. While the Agency will have direct access to relevant data for centrally authorised products, for nationally authorised products, the Agency will rely on accurate and timely information provided by national competent authorities with regard to the inclusion or removal of medicinal products from the list and the provision of the electronic links to the national web-portals where the product information and the summary of the RMP are publicly available.

The Agency and the Members States will make the list available to the public.

X.C.4.2. Process for the maintenance of the list

The list will be updated monthly following each PRAC meeting, as appropriate.

X.C.4.2.1. Inclusion of medicinal products in the list

Mandatory scope

According to Article 23(1) of Regulation (EC) 726/2004 medicinal product that fall under the mandatory scope will be automatically included in the list on an ongoing basis. In case of medicinal products approved through the mutual recognition or decentralised procedures, the Reference Member State (RMS) should inform the Agency once authorisation for such products has been granted. In addition, each national competent authority included in such procedures should inform the Agency, within 15 days of granting the marketing authorisation nationally, and provide the electronic links to their national web-portal where the product information and the summary of the RMP are publicly available. The Agency will include medicinal products in the list within the next update following receipt of the European Commission decision, in case of centrally authorised products, or following receipt of the national competent authorities' notification.

Optional scope

According to Article 23(2) of Regulation (EC) No 726/2004 medicinal products that fall under the optional scope, consultation with the PRAC is required prior to inclusion in the list.

In case of mutual recognition or decentralised procedures, the RMS should be the lead and consult the PRAC as soon as relevant conditions are considered necessary and before the finalisation of the procedure.

In case of purely national procedures, the national competent authority should consult the PRAC as soon as relevant conditions are considered necessary and before the finalisation of the procedure.

The Agency will include centrally authorised products in the list within 15 days of receipt of the European Commission decision. For non-centrally authorised products, once a procedure is finalised each national competent authority should inform the Agency within 15 days on those particular medicinal products that are to be included in the list and provide the electronic links to their national web-portal where the product information and the summary of the RMP are publicly available.

X.C.5. Black symbol and explanatory statements

For medicinal products included in the list, the SmPC shall include the statement:

“This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.”,

preceded by an inverted equilateral black triangle (Implementing Regulation (EU) No 198/2013). A similar statement will also be included in the package leaflet. Once the medicinal product is included or removed from the list, the marketing authorisation holder shall update the SmPC and the package leaflet to include or remove, as appropriate, the black symbol, the statement, and the standardised explanatory statement.

If the decision to include or remove a medicinal product from the list is done during the assessment of a regulatory procedure (e.g. marketing authorisation application, extension of indication, renewal) the SmPC and the package leaflet should be updated before finalisation of the procedure in order to include or remove the black triangle symbol and explanatory statement from the product information.

If the decision to include or remove a medicinal product from the list is done outside a regulatory procedure, then the marketing authorisation holder is requested to subsequently submit a variation to update the product information of that product accordingly.

X.C.6. Transparency

Pursuant to Article 23 of Regulation 726/2004, the Agency will make publicly available the list of the names and active substances of all medicinal products approved in the EU subject to additional monitoring and the general criteria to include medicinal products in the list. The national competent authority shall also make publicly available the list of medicinal products authorised in their territory that are subject to additional monitoring.

The list will include an electronic link(s) to the relevant web-portal where the product information and the summary of the RMP are publicly available.

Appendix P: Safety Communication

22 January 2013
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Guideline on good pharmacovigilance practices (GVP)

Module XV – Safety communication

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG	12 July 2012
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See websites for contact details

European Medicines Agency www.ema.europa.eu
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XV.A. Introduction

This Module provides guidance to marketing authorisation holders, competent authorities in Member States and the European Medicines Agency on how to communicate and coordinate safety information in the EU. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions and contributing to the protection of patients' and public health (see [Module I](#)).

Safety communication is a broad term covering different types of information on medicines, including statutory information as contained in the product information (i.e. the summary of product characteristics (SmPC), package leaflet (PL) and the labelling of the packaging) and public assessment reports. Although some principles in this Module (i.e. [Section XV.B.1 and B.2.](#)) apply to all types of safety communication, the module itself focuses on the communication of 'new or emerging safety information', which means new information about a previously known or unknown risk of a medicine which has or may have an impact on a medicine's benefit-risk balance and its condition of use. Unless otherwise stated, the term 'safety communication' in this module should be read as referring to emerging safety information.

Experience so far has demonstrated the need to coordinate safety communication within the EU regulatory network. High levels of public interest are anticipated when new safety concerns arise and it is important that clear and consistent messages are provided across the EU in a timely manner. The new legislation on pharmacovigilance therefore includes a number of provisions to strengthen safety communication and its coordination¹.

Communication of important new safety information on medicinal products should take into account the views and expectations of concerned parties, including patients and healthcare professionals, with due consideration given to relevant legislation. This Module addresses some aspects of the interaction with concerned parties and supplements the specific guidance given in [Module XI](#) on public participation as well as the guidance on communication planning given in [Module XII](#).

Communication is distinct from transparency, which aims to provide public access to information related to data assessment, decision-making and safety monitoring performed by competent authorities. The new EU legislation on pharmacovigilance envisages an unprecedented level of transparency. Transparency provisions applicable to each pharmacovigilance process are provided in the relevant GVP Modules.

[Section XV.B.](#) of this Module describes principles and means of safety communication. [Section XV.C.](#) provides guidance on the coordination and dissemination of safety communications within the EU network. Both sections give particular consideration to direct healthcare professional communications (DHPCs), and provide specific guidance for preparing them. This is because of the central importance of DHPCs in targeting healthcare professionals and because of the level of coordination required between marketing authorisation holders and competent authorities in their preparation.

Throughout this Module, legal obligations are referred to as stated in the GVP Introductory Cover Note and are usually identified by the modal verb 'shall' (e.g. 'the marketing authorisation holder shall...'). When guidance is provided on how to implement legal provisions, the modal verb 'should' is used (e.g. 'the marketing authorisation holder should...')

¹ Directive 2010/84/EU amending Directive 2001/83/EC (the latter is referenced as DIR), Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (the latter is referenced as REG) and in the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC (the Implementing Regulation is referenced as IR).

XV.B. Structures and processes

XV.B.1. Objectives of safety communication

Safety communication aims at:

- providing timely, evidence-based information on the safe and effective use of medicines;
- facilitating changes to healthcare practices (including self-medication practices) where necessary;
- changing attitudes, decisions and behaviours in relation to the use of medicines;
- supporting risk minimisation behaviour;
- facilitating informed decisions on the rational use of medicines.

In addition to the above effective, high quality safety communication can support public confidence in the regulatory system.

XV.B.2. Principles of safety communication

The following principles of safety communication should be applied:

- The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process, and should be part of risk assessment (see [Module XII](#)).
- There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. competent authorities, other public bodies and marketing authorisation holders).
- Safety communication should deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.
- Safety communication should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.
- Information on risks should be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and, if available, expected time to recovery.
- Safety communication should address the uncertainties related to a safety concern. This is of particular relevance for emerging information which is often communicated while competent authorities are conducting their evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.
- Information on competing risks such as the risk of non-treatment should be included where appropriate.
- The most appropriate quantitative measures should be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; for risk comparisons, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the benefit-risk balance may also be used.

- Patients and healthcare professionals should, where possible, be consulted and messages pre-tested early in the preparation of safety communication, particularly on complex safety concerns (see [Module XII](#)).
- Where relevant safety communication should be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations.
- The effectiveness of safety communication should be evaluated where appropriate and possible (see [XV.B.7.](#)).
- Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

XV.B.3. Target audiences

The primary target audiences for safety communication issued by regulatory authorities and marketing authorisation holders should be patients and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

As primary target audiences, healthcare professionals play an essential role. Effective safety communication enables them to give clear and useful information to their patients, thereby promoting patient safety and confidence in the regulatory system. Both healthcare professionals in clinical practice and those involved in clinical trials should be provided with appropriate information on any safety concern at the same time.

Patient, consumer and healthcare professional organisations can play a role as multipliers as they can disseminate important safety information to target audiences.

The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on medicines. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from the competent authorities in addition to the information they receive from other sources, such as from the marketing authorisation holders.

XV.B.4. Content of safety communication

Taking into account the principles in [XV.B.2.](#), safety communication should contain:

- important emerging information on any authorised medicinal product which has an impact on the medicine's benefit-risk balance under any conditions of use;
- the reason for initiating safety communication clearly explained to the target audience;
- any recommendations to healthcare professionals and patients on how to deal with a safety concern;
- when applicable, a statement on the agreement between the marketing authorisation holder and the competent authority on the safety information provided;
- information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL));
- a list of literature references, when relevant or a reference to where more detailed information can be found;

- where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

The information in the safety communication shall not be misleading and shall be presented objectively [DIR Art 106a(1)]. Safety information should not include any material or statement which might constitute advertising within the scope of Title VIII of Directive 2001/83/EC.

XV.B.5. Means of safety communication

Communication tools and channels² have become more numerous and varied over time, offering the public more information than was previously possible. The use of this increasing variety of means should be considered when issuing safety communication in order to reach the target audiences and meet their growing expectations. Different communication tools and channels are discussed below in sections XV.B.5.1.-XV-B.5.9.

XV.B.5.1. Direct healthcare professional communication (DHPC)

A direct healthcare professional communication (DHPC) is defined in this document as a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorisation holder or a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals, nor are they meant as educational material for routine risk minimisation activities.

The preparation of DHPCs involves cooperation between the marketing authorisation holder and the competent authority. Agreement between these two parties should be reached before a DHPC is issued by the marketing authorisation holder. The agreement will cover both the content of the information (see XV.B.4.) and the communication plan, including the intended recipients and the timetable for disseminating the DHPC (see Module XII).

Where there are several marketing authorisation holders of the same active substance for which a DHPC is to be issued, a single consistent message should normally be delivered.

Whenever possible, it is advised that healthcare professionals' organisations or learned societies are involved as appropriate during the preparation of DHPCs to ensure that the information they deliver is useful and adapted to the target audience.

A DHPC may be complemented by other communication tools and channels and the principle of providing consistent information should apply (XV.B.2.).

A DHPC may be an additional risk minimisation measure as part of a risk management plan (see Modules V and XV).

A DHPC should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicinal product:

- suspension, withdrawal or revocation of a marketing authorisation for safety reasons;
- an important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;
- a restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.

² For the purpose of this section tools and channels are presented without distinction as they often overlap and there is no general agreement on their categorisation.

Other situations where dissemination of a DHPC should be considered are:

- new major warnings or precautions for use in the product information;
- new data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- substantiated knowledge that the medicinal product is not as effective as previously considered;
- new recommendations for preventing or treating adverse reactions or to avoid misuse or medication error with the medicinal product;
- ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC should encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimise the potential risk).

A competent authority may disseminate or request the marketing authorisation holder to disseminate a DHPC in any situation where the competent authority considers it necessary for the continued safe and effective use of a medicinal product.

XV.B.5.2. Documents in lay language

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. Lay language documents should contain the competent authority's recommendations and advice for risk minimisation for patients and healthcare professionals in relation to the safety concern, and should be accompanied by relevant background information.

Lay language documents are generally useful to members of the public who have an interest in the subject but do not have a scientific or regulatory background. Reference should be made to other communication materials on the topic to direct readers to where they can find further information.

Competent authorities publish lay language documents on their national medicines web-portals and may additionally disseminate them to relevant parties such as patients and healthcare professionals' organisations.

Whenever possible, it is advised that patients and healthcare professionals are involved during the preparation of lay language documents to ensure that the information they deliver is useful and adapted to the target audience.

XV.B.5.3. Press communication

Press communication includes press releases and press briefings which are primarily intended for journalists.

Competent authorities may send press releases directly to journalists in addition to publishing them on their websites. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with the authority's scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system.

Press releases may also be prepared and published by marketing authorisation holders. Their press releases may reflect the position of the marketing authorisation holder on a safety topic but should also make reference to any regulatory action taken by the competent authority. Relevant ongoing reviews should be mentioned in any communication by the marketing authorisation holder.

Although aimed at journalists, press releases will be read by other audiences such as healthcare professionals, patients and the general public. Reference should therefore be made to related communication materials on the topic. In cases where a DHPC is also prepared, healthcare professionals should ideally receive it prior to or around the same time of the publication or distribution of a press release so that they are better prepared to respond to patients.

Press briefings with journalists should be considered by competent authorities for safety concerns or other matters relating to the safety of medicinal products that are of high media interest or when complex or public-health-sensitive messages need to be conveyed.

XV.B.5.4. Website

A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on medicinal products. Competent authorities as well as marketing authorisation holders should ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up-to-date, with any information that is out-of-date marked as such or removed.

The new legislation on pharmacovigilance foresees the creation of an EU medicines web portal which will contain information on all medicines authorised in the EU [Article 26 of Regulation (EU) No 1235/2010]. This web portal will become a key tool for communicating up-to-date safety information to EU citizens and will contain information in all EU official languages. Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the EU medicines web-portal. [DIR Art 106a]. Until the web portal is fully established and into operation, the Agency's website will be acting as an interim platform to convey this important up-to-date safety information.

XV.B.5.5. Other web-based communications

Online safety information may also be disseminated via other web tools. When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised. Communication practices should take into account emerging communication tools used by the various target audiences.

XV.B.5.6. Bulletins and newsletters

Bulletins and newsletters provide at regular intervals new information about medicines and their safety and effectiveness. Competent authorities can reach a large audience with these tools by using web-based and other available means.

XV.B.5.7. Inter-authority communication

When one competent authority takes regulatory action on a particular safety concern, other competent authorities usually need to respond to enquiries or communicate on the same issue. The use of inter-authority communication material, such as lines-to-take should be considered. Lines-to-take are documents specifically prepared by a competent authority to assist its own staff and those of co-operating authorities in responding to external enquires or communicating on a specific safety issue.

XV.B.5.8. Responding to enquiries from the public

Competent authorities and marketing authorisation holders should have systems in place for responding to enquiries about medicines from individual members of the public. Responses should take

into account the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by competent authorities. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

In this respect, Article 86(2) and Article 98(1) of Directive 2001/83/EC apply to marketing authorisation holders.

XV.B.5.9. Other means of communication

In addition to those discussed above, there are other tools and channels such as publications in scientific journals and journals of professional bodies.

Some tools and channels may be used in the context of risk management; risk minimisation measures often include specific programmes for risk communication. Tools used in such programmes, such as patient alert cards or healthcare professional safety guidance, are outside the scope of this module and are described in more detail in [Module XVI](#).

XV.B.6. Effectiveness of safety communication

Safety communication is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. Adequate mechanisms should be introduced in order to measure the effectiveness of the communication based on clear objectives. Measuring effectiveness allows lessons to be learned and helps in making decisions on prioritising and adapting tools and practices to meet the needs of the target audiences. A research-based approach will normally be appropriate in order to establish that safety communications have met the standard of [XV.B.2](#). This approach may measure different outcomes, including behaviour, attitudes, and knowledge. When evaluating the effectiveness of safety communication, the scope of the evaluation may be broadened to include factors other than the performance of the individual tools used in the safety communication (see [Module XVI](#)).

In the case of DHPCs, the marketing authorisation holder should be responsible for evaluating the dissemination of the DHPCs they prepare and should inform the competent authorities of the outcome and of any difficulties identified (e.g. problems related to the list of recipients or the timing and mechanism of dissemination). Appropriate action should be taken as needed to correct the situation or prevent similar problems in the future.

XV.B.7. Quality system requirements for safety communication

In accordance with the quality system requirements in [Module I](#), procedures should be in place to ensure that safety communications comply with the principles in [XV.B.2](#), as appropriate.

In particular, the communications should be subject to quality controls to ensure their accuracy and clarity. For this purpose review procedures with allocated responsibilities should be followed and documented.

XV.C. Operation of the EU regulatory network

XV.C.1. Coordination of safety announcements in the EU

In the EU, patients and healthcare professionals increasingly look at competent authorities as providers of important information on medicines. For safety communication to be effective, adequate

coordination and cooperation is required within the EU regulatory network³. A good level of coordination of safety communication is of particular importance so that healthcare professionals and patients receive consistent information on regulatory decisions in the EU.

When issuing safety announcements, competent authorities may make use of the different tools and channels described in XV.B.5. Prior to the publication of a safety announcement, the Member States, the Agency or the European Commission shall inform each other not less than 24 hours in advance, unless urgent public announcements are required for the protection of public health [DIR Art 106a(2)].

For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements [DIR Art 106a(3)].

For practical reasons, considering the potential for overlap between transparency measures and active communications and in order to focus on those topics of major health relevance, not all safety information made public by a Member State or the Agency will be subject to systematic exchange and coordination. Only safety announcements that relate to the following and that pertain to active substances contained in medicinal products authorised in more than one Member State require coordination within the EU regulatory network:

- the suspension, withdrawal or revocation of a marketing authorisation due to changes to its benefit-risk balance;
- the start or finalisation of an EU referral procedure for safety reasons;
- restriction of indication or treatment population or the addition of a new contraindication;
- dissemination of a DHPC agreed by relevant competent authorities of a Member State or the Agency (see XV.C.2.1.);
- other emerging safety concerns judged by a national competent authority or the Agency to be likely to give rise to public or media interest in more than one Member State (e.g. a publication of important safety findings in a (scientific) journal, safety-related regulatory action taken in a Member State or in a country outside the EU).

XV.C.1.1. Process for exchange and coordination of safety announcements

A competent authority of a Member State or the Agency shall inform the EU regulatory network prior to the publication of a safety announcement that pertains to active substances contained in medicinal products authorised in more than one Member State and that refer to any of the situations identified in XV.C.1. It shall include a timetable for the information being made public [DIR Art 106a(3)]. Whenever possible the safety announcement shall be sent to the network under embargo no less than 24 hours in advance of publication [DIR Art 106a (2)], in order to allow the members of the EU regulatory network to prepare or plan their own communication if necessary. Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message [DIR Art 106a(3)].

The Agency should decide for each case, on the basis of the public health relevance and urgency of the safety concern, the population and number of Members States affected and the potential for media attention, whether further action in addition to the dissemination of the safety announcement is needed, such as:

³ i.e. the competent authorities in the Member States, the Agency and the European Commission.

- the preparation of lines-to-take (see XV.B.5.7.) which should be disseminated to the EU regulatory network. The lines-to-take document should help the EU regulatory network to respond to any request for information which may follow the publication of the safety announcement;
- the preparation of an Agency safety announcement in addition to that of the Member State, which should also be disseminated under embargo to the EU regulatory network together with a timetable for its publication.

The Agency should prepare lines-to-take documents and any Agency safety announcement together with the Member State(s) who originated the process and the PRAC Lead Member State or the PRAC Rapporteur, as appropriate. The PRAC, as well as the CHMP or CMDh, should also be consulted as necessary.

Coordination of safety announcements should be done in cooperation with the concerned marketing authorisation holder(s). Whenever possible, the Agency and the competent authorities in Member States should provide any safety announcement prior to its publication to the concerned marketing authorisation holder(s), together with the timetable for the information being made public. Any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health [DIR Art 106a (4)].

The exchange and coordination of safety announcements within the EU regulatory network should make use of the EU Early Notification System (ENS). The ENS was developed for use by the Agency to provide advance notice to competent authorities in Member States and the European Commission of safety information on centrally authorised products. This system should also be used by competent authorities in Member States for the purpose of exchanging and coordinating safety announcements.

The ENS includes the Heads of Medicines Agencies (HMA), the members of the PRAC, CHMP, CMDh, the operational contact points for safety announcements at the competent authority in Member States, the European Commission and the Agency. Operational contact points should ensure that any information exchanged via the system reaches in a timely manner the relevant staff within each competent authority, including relevant staff working within the communications departments.

Safety announcements from the EU regulatory network should be shared with international partners in accordance with the guidance provided in Module XIV, subject to embargo and any specific confidentiality arrangements in place.

As a complement to the coordination of safety announcements within the EU regulatory network, competent authorities in Member States and the Agency should interact with concerned stakeholders in the EU (mainly patients' and healthcare professionals' organisations), who can play a key role in reviewing and disseminating information to the end users (patients and healthcare professionals). It is recommended that national competent authorities and the Agency keep up-to-date contact details of relevant patients, and healthcare professionals' organisations.

XV.C.1.2. Exchange of safety information produced by third parties

There are situations where emerging safety information is to be published or has been published by a party other than a competent authority of a Member State or the Agency (e.g. scientific journals, learned societies). Competent authorities should bring to the attention of the EU regulatory network any such safety information that they become aware of, together with the timing of the publication if known. Where necessary and after evaluation of the information, the Agency should prepare and disseminate a lines-to-take document or an Agency safety announcement to address the information from the third party (see XV.C.1.1.).

In the context of collaboration with authorities outside the EU, the Agency or a competent authority of a Member State may become aware of safety announcements to be published by these authorities (see [Module XIV](#)). In these cases the Agency should, as necessary, prepare and disseminate lines-to-take or safety announcements within the EU regulatory network. In all cases, the terms of any relevant confidentiality agreements with non-EU regulatory authorities and the embargoes on the information received should be respected.

XV.C.1.3. Requirements for the marketing authorisation holder in the EU

As soon as a marketing authorisation holder in the EU intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, the marketing authorisation holder shall be required to inform the competent authorities in Member States, the Agency and the European Commission [DIR Art 106a]. This should apply to announcements intended for the EU as well as outside the EU (when they concern products authorised in the EU or those for which an opinion under Article 58 of Regulation (EC) 726/2004 has been given). Informing the authorities at the same time as the public (i.e. without advance notice to the authorities) should only occur exceptionally and under justified grounds. Whenever possible, the information should be provided under embargo at least 24 hours prior to its publication.

The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading [DIR Art 106a].

Whenever a marketing authorisation holder becomes aware that a third party (see [XV.C.1.2.](#)) intends to issue communication that could potentially impact the benefit-risk balance of a medicinal product authorised in the EU, the marketing authorisation holder should inform the relevant competent authorities in Member States and the Agency and make every effort to share the content of the communications with the relevant authorities.

XV.C.1.4. Consideration for third parties

Third parties (e.g. scientific journals, learned societies, patients' organisations) are encouraged to inform the Agency and the competent authorities in Member States of any relevant emerging information on the safety of medicines authorised in the EU and, if publication is planned, to share the information ahead of publication.

XV.C.1.5. Languages and translations

Consistent messages should reach the public across the EU in a timely manner and in the official languages of the Member States as specified by the Member States where the medicinal product is placed on the market.

For the purpose of coordination, the Agency shall use English to inform the EU regulatory network of any safety announcement. When informing the Agency, the competent authorities in Member States are encouraged to provide English translations of their safety announcements for the purpose of initiating the coordination process. In the absence of a full text translation, an English summary should be provided.

XV.C.2. Direct healthcare professional communications in the EU

In the EU, a direct healthcare professional communication (DHPC) (see [XV.B.5.1.](#)) is usually disseminated by one or a group of marketing authorisation holders for the respective medicinal

product(s) or active substance(s), either at the request of a national competent authority or the Agency, or on the marketing authorisation holder's own initiative. The marketing authorisation holder should seek the agreement of the relevant national competent authorities or the Agency regarding the content of a DHPC (and communication plan) prior to dissemination.

XV.C.2.1. Processing of DHPCs

The situations when a DHPC is necessary or should be considered are provided in [XV.B.5.1](#). When drafting a DHPC, the template (see [Annex II](#)) and the guidance provided in the annotations in the template should be followed as appropriate.

The roles and responsibilities of the competent authorities in a Member State, the Agency and marketing authorisation holders in the preparation and processing of DHPCs depend on the route of authorisation of the medicinal products concerned:

- for centrally authorised products and for products subject to an EU referral procedure for safety reasons, the relevant marketing authorisation holders should submit the draft DHPC and communication plan (including the intended recipients and the timetable for disseminating the DHPC) to the Agency, which should coordinate the review process by its scientific committees (i.e. PRAC and CHMP) and CMDh.
- for products authorised through the mutual recognition or decentralised procedure, the marketing authorisation holder should submit the draft DHPC and communication plan to the Reference Member State, which should co-ordinate the process with the marketing authorisation holder, while keeping the Concerned Member States informed of any proposed action.
- for nationally authorised products not authorised through the mutual recognition or decentralised procedure, the marketing authorisation holder should submit the draft DHPC and any communication plan to the competent authorities of the Member States where the products are authorised.

The marketing authorisation holder should allow a minimum of two working days for comments. However, whenever possible more time should be allowed. The timing may be adapted according to the urgency of the situation.

The Agency will coordinate the review of DHPCs within its scientific committees/groups as appropriate (i.e. involvement of PRAC, and finalisation by CHMP or CMDh) The PRAC should always be involved in the review of DHPCs related to a safety concern being discussed at the PRAC and the DHPC should form part of the PRAC assessment (see [Module XII](#)). The Agency may also request advice from the PRAC on issues related to other safety communications.

Once the content of a DHPC and communication plan from the MAH are agreed by national competent authorities or the Agency, the national competent authorities or the Agency should exchange the final DHPC and communication plan using the early notification system (see [XV.C.1.1](#)), and the Agency should coordinate any subsequent safety announcement as appropriate using the process described in [XV.C.1.1](#). The early notification system is only used if the DHPC concerns an active substance authorised in more than one Member State.

In cases where an authority outside the EU requests the dissemination of a DHPC in their territory for a product also authorised in the EU, the marketing authorisation holder should notify the relevant competent authorities in the EU. This is part of the legal requirement under which the marketing authorisation holder shall notify the competent authorities of any new information which may impact the benefit-risk balance of a medicinal product [REG Art 16(2) and DIR 23(2)]. The need for any

subsequent communication, e.g. a DHPC, in the EU should be considered and agreed on a case-by-case basis.

A flow chart describing the processing of DHPCs is provided in [Figure XV.1](#) at the end of the Module.

XV.C.2.2. Translation of DHPCs

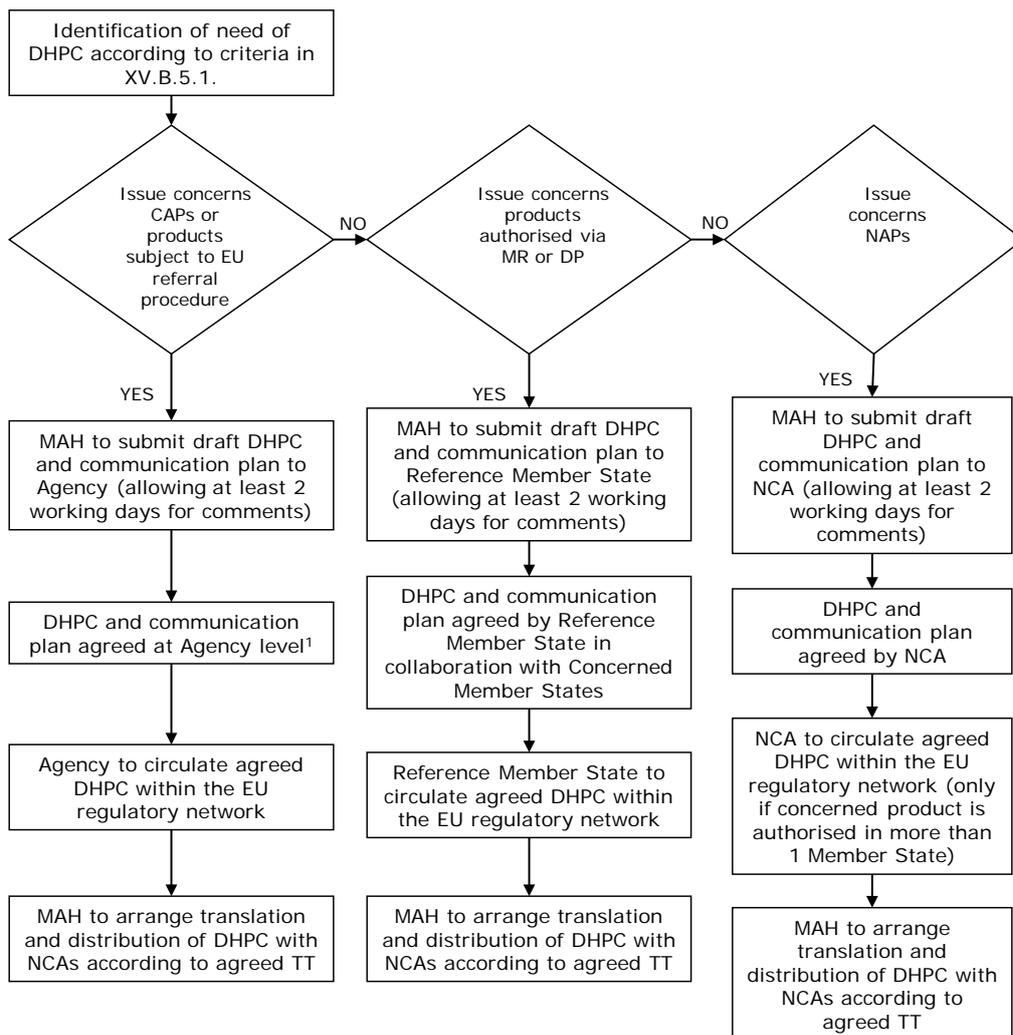
For centrally authorised products, products subject to an EU referral procedure for safety reasons and, in most cases, for products authorised through the mutual recognition or decentralised procedure, the working language for preparing the DHPCs will normally be English.

Once the text of the DHPC is agreed, the marketing authorisation holder should prepare translations in the official languages of the Member States, as specified by the Member States where the DHPC is to be distributed. The draft translations should be submitted to the Member States for a language review within a reasonable timeframe (no more than two working days).

For centrally authorised products and products subject to an EU referral procedure for safety reasons, the relevant marketing authorisation holder should provide the Agency with a complete set of all final EU official language versions as well as any additional related communication documents.

XV.C.2.3. Publication of DHPCs

The competent authorities may publish the final DHPC. The timing for such publication should be aligned to that of the dissemination of DHPC in the Member States. The competent authorities may also issue an additional safety announcement, and disseminate the DHPC to relevant healthcare professionals' organisations as appropriate.



¹ The Agency will coordinate the review of DHPC within its scientific committees (i.e. PRAC and CHMP) and CMDh.

Figure VX.1: Flow chart for the processing of Direct Healthcare Professional Communications (DHPCs) in the EU

Appendix Q: Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators

15 April 2014
EMA/204715/2012 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators (Rev 1)

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- Amendment on page 3 to update the definition of Risk minimisation measure in accordance with revision 1 of GVP Module V on risk management system.

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

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XVI.A. Introduction

Risk minimisation measures are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. Planning and implementing risk minimisation measures and assessing their effectiveness are key elements of risk management.

The guidance provided in this Module should be considered in the context of the wider GVP guidance, in particular in conjunction with [Module V](#).

Risk minimisation measures may consist of routine risk minimisation or additional risk minimisation measures. Routine risk minimisation is applicable to all medicinal products, and involves the use of the following tools, which are described in detail in [Module V](#):

- the summary of product characteristics (SmPC);
- the package leaflet;
- the labelling;
- the pack size and design;
- the legal (prescription) status of the product.

Safety concerns of a medicinal product are normally adequately addressed by routine risk minimisation measures (see [Module V](#)). In exceptional cases however, routine risk minimisation measures will not be sufficient for some risks and additional risk minimisation measures will be necessary to manage the risk and/or improve the risk-benefit balance of a medicinal product. This module provides particular guidance on the use of additional risk minimisation measures, including the selection of tools and the evaluation of their effectiveness. In specific circumstances, however, the effectiveness evaluation may also apply to routine risk minimisation measures associated with safety concern(s) which are described in the SmPC/PIL (e.g. the SmPC provides guidance for clinical actions beyond routine standards of clinical care for either the risk itself or management of the target population).

On the basis of the safety concerns described in the safety specification (see [GVP Module V](#)), the appropriate risk minimisation measures should be determined. Each safety concern needs to be individually considered and the selection of the most suitable risk minimisation measure should take into account the seriousness of the potential adverse reaction(s) and its severity (impact on patient), its preventability or the clinical actions required to mitigate the risk, the indication, the route of administration, the target population and the healthcare setting for the use of the product. A safety concern may be addressed using more than one risk minimisation measure, and a risk minimisation measure may address more than one safety concern.

Directive 2001/83/EC indicates that the marketing authorisation holder shall “monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a” (DIR Art 104 (2) (d)). The Directive and Regulation (EC) No 726/2004 also include provisions for the Agency and the national competent authorities to monitor the outcome of risk minimisation measures which are contained in the risk management plans (RMPs) or measures that are laid down as conditions.

This Module provides guidance on the principles for:

- The development and implementation of additional risk minimisation measures, including examples of risk minimisation tools;
- The evaluation of the effectiveness of risk minimisation measures.

Part XVI.B. describes the development, implementation and co-ordination of risk minimisation measures and the general principles of the evaluation of their effectiveness. Part XVI.C. considers the application of those measures and principles in the setting of the EU regulatory network.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

XVI.B. Structures and processes

XVI.B.1. General principles

Risk minimisation measures aim to optimise the safe and effective use of a medicinal product throughout its life cycle. The risk-benefit balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimising benefit, through targeted patient selection and/or exclusion and through treatment management (e.g. specific dosing regimen, relevant testing, patient follow-up). Risk minimisation measures should therefore guide optimal use of a medicinal product in medical practice with the goal of supporting the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring.

The majority of safety concerns are addressed by routine risk minimisation measures (see [Module V](#)). Exceptionally, for selected important risks, routine risk minimisation may be considered insufficient and additional risk minimisation measures may be deemed to be necessary. In determining if additional risk minimisation activities are needed, safety concerns should be prioritised in terms of frequency, seriousness, severity, impact on public health and preventability. Careful consideration should then be given to whether the goal can be reached with routine minimisation activities, and, if not considered feasible, which additional minimisation measure(s) is (are) the most appropriate. Additional risk minimisation measures should focus on the most important, preventable risks and the burden of imposing additional risk minimisation should be balanced with the benefit for patients.

A variety of tools are currently available for additional risk minimisation. This field is continuously developing, and new tools are likely to be developed in the future. Technology advances, such as interactive web-based tools may gain prominence in the future in addition to the paper-based educational materials.

Successful implementation of additional risk minimisation measures requires contributions from all impacted stakeholders, including marketing authorisation applicants or holders, patients and healthcare professionals. The performance of these measures in healthcare systems requires assessment to ensure that their objectives are fulfilled and that the measures in place are proportionate taking account of the risk-benefit balance of the product and the efforts required of healthcare professionals and patients to implement the measures. It is therefore important to ensure that additional risk minimisation measures, including assessment of their effectiveness, do not introduce undue burden on the healthcare delivery system, the marketing authorisation holders, the regulators, and, most importantly, on the patients. To this aim, they should have a clearly defined objective relevant to the minimisation of specific risks and/or optimisation of the risk-benefit balance. Clear objectives and defined measures of success with milestones need to guide the development of additional risk minimisation measures and close monitoring of both their implementation and ultimate effectiveness is necessary. The nature of the safety concern in the context of the risk-benefit balance of the product, the therapeutic need for the product, the target population and the required clinical actions for risk minimisation are factors to be considered when selecting risk minimisation tools and an implementation strategy to accomplish the desired public health outcome. The evaluation of effectiveness should facilitate early corrective actions if needed and may require modification over

time. It is recognised that this is an evolving area of medical sciences with no universally agreed standards and approaches. Therefore, it is important to take advantage of any relevant elements of methodology from pharmacoepidemiology and other disciplines, such as social/behavioural sciences and qualitative research methods.

The introduction of additional risk minimisation should be considered as a “programme” where specific tools, together with an implementation scheme and evaluation strategy are developed. The description of risk minimisation measures, an integral part of the RMP (see Module V), should therefore give appropriate consideration to the following points:

- Rationale: When additional risk minimisation measure(s) are introduced a rationale should be provided for those additional measures;
- Objectives: Each proposed additional risk minimisation measure(s) should include defined objective(s) and a clear description of how and which safety concern is addressed with the proposed additional risk minimisation measure(s);
- Description: This section of the RMP should describe the selected additional risk minimisation measures, including tools that will be used and key elements of content;
- Implementation: This section of the RMP should provide a detailed proposal for the implementation of additional risk minimisation measures (e.g. setting and timing or frequency of intervention, details of the target audience, plan for the distribution of educational tools; how the action will be coordinated where more than one marketing authorisation holder is involved);
- Evaluation: This section of the RMP should provide a detailed plan with milestones for evaluating the effectiveness of additional risk minimisation measures in process terms and in terms of overall health outcome measures (e.g. reduction of risk).

XVI.B.2.Risk minimisation measures

Risk minimisation measures aim to facilitate informed decision making to support risk minimisation when prescribing, supplying and/or using a medicinal product. While routine measures are applied to every medicinal product (see details in Module V) additional risk minimisation activities should only be introduced when they are deemed to be essential for the safe and effective use of the medicinal product (see also XVI.C.1.) and should be developed and provided by suitably qualified people.

Additional risk minimisation measures may differ widely in purpose, design, target audience and complexity. These measures might be used to guide appropriate patient selection with the exclusion of patients where use is contraindicated, to support on-treatment monitoring relevant to important risks and/or management of an adverse reaction once detected. Additionally, specific measures may be developed to minimise the risk of medication error and/or to ensure appropriate administration of the product where it is not feasible to achieve this through the product information and labelling alone.

Section XVI.B.2. describes additional risk minimisation measures that may be considered in addition to the routine measures, including:

- Educational programmes;
- Controlled access programmes;
- Other risk minimisation measures.

XVI.B.2.1. Educational programme

Educational programmes are based on targeted communication with the aim to supplement the information in the summary product characteristics (SmPC) and package leaflet. Any educational material should focus on actionable goals and should provide clear and concise messages describing actions to be taken in order to prevent and minimise selected safety concerns.

The aim of an educational programme is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimising risk. Educational materials should therefore be built on the premise that there is an actionable recommendation for targeted education and that applying this measure is considered essential for minimising an important risk and/or for optimisation of the risk-benefit balance. In the context of an educational programme, the tools can have several different target audiences, can address more than one safety concern and can be delivered using a combination of tools and media (e.g. paper, audio, video, web, in-person training). Ideally, educational materials should be available in a range of formats so as to ensure that access is not limited by disability or access to the internet. When feasible the appropriateness of the tool and media for the target audience (e.g. suitable language, pictures, diagrammes, or other graphical support) should be user tested in advance, in order to optimise the success of the implementation phase.

The content of any educational material should be fully aligned with the currently approved product information for a medicinal product, such as the SmPC and package leaflet, and should add rather than duplicate SmPC and package leaflet information. Promotional elements, either direct or veiled (e.g. logos, product brand colours, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimisation.

Any educational programme should be completely separated from promotional activities and contact information of physicians or patients gathered through educational programmes should not be used for promotional activities.

The educational tools described below can be considered individually or in combinations while developing an educational programme for the purpose of additional risk minimisation.

XVI.B.2.1.1. Educational tools

An educational tool should have a clearly defined scope and should include unambiguous statement(s) regarding the important risk(s) of concern to be addressed with the proposed tool, the nature of such risk(s) and the specific steps to be taken by healthcare professionals and/or patients in order to minimise those risks. This information should focus on clearly defined actions related to specific safety concerns described in the RMP and should not be unnecessarily diluted by including information that is not immediately relevant to the safety concern and that is adequately presented in the SmPC or package leaflet. Educational tools should refer the reader to the SmPC and the package leaflet. In addition to an introductory statement that the educational material is essential to ensure the safe and effective use and appropriately manage important selected risks, elements for inclusion in an educational tool could provide:

- guidance on prescribing, including patient selection, testing and monitoring;
- guidance on the management of such risks (to healthcare professionals and patients or carers);
- guidance on how and where to report adverse reaction of special interest.

Further guidance on the responsibilities of the applicant or marketing authorisation holder and the competent authorities are provided in **XVI.C.1.** of this Module.

XVI.B.2.1.1.1 Educational tools targeting healthcare professionals

The aim of any educational tool targeting a healthcare professional should be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (how to manage adverse reactions) associated with the medicine and the specific important risks needing additional risk minimisation measures, including:

- selection of patients;
- treatment management such as dosage, testing and monitoring;
- special administration procedures, or the dispensing of a medicinal product;
- details of information which needs to be given to patients.

The format of a particular tool will depend upon the message to be delivered. For example, where a number of actions are needed before writing a prescription for an individual patient, a checklist may be the most suitable format. A brochure may be more appropriate to enhance awareness of specific important risks with a focus on the early recognition and management of adverse reactions, while posters for display in certain clinical environments can include helpful treatment or dosage reference guides. Other formats may be preferable, depending on the scope of the tool.

XVI.B.2.1.1.2. Educational tools targeting patients and/or carers

The aim of tools targeting patients should be to enhance the awareness of patients or their carers on the early signs and symptoms of specific adverse reactions causing the need for additional risk minimisation measures and on the best course of action to be taken should any of those symptoms occur. If appropriate, a patient's educational tool could be used to provide information on the correct administration of the product and to remind the patient about an important activity, for example a diary for posology or diagnostic procedures that need to be carried out and recorded by the patient and eventually discussed with healthcare professionals, to ensure that any steps required for the effective use of the product are adhered to.

Patient alert card

The aim of this tool should be to ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate. The information should be kept to the minimum necessary to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including emergency. Ability to carry with ease (e.g. can be fitted in a wallet) should be a key feature of this tool.

XVI.B.2.2 Controlled access programme

A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures i.e. legal status. Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is life-threatening), and whether this risk is expected to be managed by the interventions. Therefore,

controlled access should only be considered as a tool for minimising an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination):

- Specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria;
- Prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product;
- Explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry;
- Medicines made available for dispensing only to Pharmacies which are registered and approved to dispense the product.

On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example, monitoring of the patient's health status, laboratory values or other characteristic (e.g. an ECG) prior to and/or during treatment, e.g. liver function tests, regular blood tests, pregnancy test (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

XVI.B.2.3. Other risk minimisation measures

XVI.B.2.3.1 Controlled distribution systems

A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription and/or pharmacy dispensing the product. Orders and shipments of product from a single or multiple identified distribution points in the EU facilitate traceability of the product. For instance, this sort of measures could be considered for those products controlled in each Member State under the respective national legislations about the misuse and abuse of medicines.

XVI.B.2.3.2 Pregnancy prevention programme

A pregnancy prevention programme (PPP) is a set of interventions aiming to minimise pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects. The scope of such a programme is to ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It could also target male patients when use of a medicinal product by the biological father might have a negative effect on pregnancy outcome.

A PPP combines the use of educational tools with interventions to control appropriately access to the medicine. Therefore, the following elements should be considered individually and/or in combination in the development of a PPP:

- Educational tools targeting healthcare professionals and patients to inform on the teratogenic risk and required actions to minimise this risk e.g. guidance on the need to use more than one method of contraception and guidance on different types of contraceptives; information included for the patient on how long to avoid pregnancy after treatment is stopped; information for when the male partner is treated;
- Controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescription or dispensing of the medicinal product (and);
- Prescription limited to a maximum of 30 days supply;
- Counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

The design and implementation of a pregnancy registry (as a stand-alone activity or as part of a pregnancy prevention programme) should also be considered for universal enrolment of patients who become pregnant during treatment or within an appropriate time from the end of treatment e.g. 3 months. Use of this systematic tool to collect pregnancy outcome information can be helpful in assessing the effectiveness of the pregnancy prevention programme and/or in facilitating further characterisation of the risk, particularly in the early period post authorisation when human pregnancy data may be very limited and/or when the potential concern may be based on non-clinical data alone.

XVI.B.2.3.3 Direct health care professional communication (DHPC)

A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product (see [Annex I](#)). For example, a DHPC may aim at adapting prescribing behaviour to minimise particular risks and/or to reduce the burden of adverse reactions with a medicinal product. Situations where dissemination of a DHPC should be considered are detailed in [Module XV](#).

XVI.B.3. Implementation of risk minimisation measures

Additional risk minimisation measures can consist of one or more interventions that should be implemented in a sustainable way in a defined target group. Careful consideration should be given to both the timing and frequency of any intervention and the procedures to reach the target population. For example, a one-off distribution of educational tools may be insufficient to ensure that all potential prescribers and/or users, including new prescribers and users, are reached. Additional periodic re-distribution of the tools might be necessary. Conversely, educational materials required at the time of launch of a new medicinal product may no longer be necessary or relevant once it has been available for a number of years. Because risk minimisation measures serve different purposes, some measures such as alert cards, controlled access programmes and pregnancy prevention programmes, will usually apply to all future applications for the same medicinal product, whilst others, such as DHPCs and training materials, may not necessarily be needed for all future applications. The appropriateness of each measure and whether these will be required for the future applications for the same medicinal products should be carefully considered at the time of authorisation of the product (and made clear in the RMP). Careful consideration should be given to the layout and content of the educational tools to ensure a clear distinction from any promotional material distributed. Submission of educational material for review by the national competent authority should be separate from submission of promotional material and a covering letter should clearly state whether the materials are promotional

or educational. Furthermore, educational tools should be distributed separately from promotional materials as a 'stand-alone' communication and it should be clearly stated that the tools are not promotional material, but rather have risk minimisation purposes. Quality assurance mechanisms should ensure that the distribution systems in place are fit for purpose and auditable.

XVI.B.4. Effectiveness of risk minimisation measures

Evaluating the effectiveness of additional risk minimisation measures is necessary to establish whether an intervention has been effective or not, and if not why not and which corrective actions are necessary. The evaluation should be performed for the additional risk minimisation tools individually and for the risk minimisation programme as a whole.

Effectiveness evaluation should be conducted at the most appropriate time, accounting for time required for launch of interventions, estimated use of the product into the healthcare system and other relevant circumstances.

Periodic review of the effectiveness of one or more specific tools or the overall programme, as appropriate should be also planned. Time points of particular relevance are as follows:

- after initial implementation of a risk minimisation programme (e.g. within 12-18 months), in order to allow the possibility of amendments, should they be necessary;
- in time for the evaluation of the renewal of a marketing authorisation; and

whenever effectiveness is evaluated, careful consideration should be given on the need for continuing with the additional risk minimisation measure.

Effectiveness evaluation should address different aspects of the risk minimisation, the process itself (i.e. to what extent the programme has been implemented as planned), its impact on knowledge and behavioral changes in the target audience (i.e. the measure(s) in affecting behavioural change), and the outcome (i.e. to what extent the predefined objectives of risk minimisation were met, in the short and long term). In designing an evaluation strategy, due consideration needs to be made toward what aspects of process and outcomes can be realistically measured in order to avoid the generation of inaccurate or misleading data or placing an undue burden on the healthcare system or other stakeholders. The time of assessing each aspect of the intervention as well as setting of realistic metrics on which the effectiveness of the tool is judged, should also be carefully considered and planned prior to initiation.

To evaluate the effectiveness of additional risk minimisation measures two categories of indicators should be considered:

- Process indicators;
- Outcome indicators.

Process indicators are necessary to gather evidence that the implementing steps of additional risk minimisation measures have been successful. These process indicators should provide insight into what extent the programme has been executed as planned and whether the intended impacts on behaviour have been observed. Implementation metrics should be identified in advance and tracked over time. The knowledge gained may be used to support corrective implementation action as needed. Assessing the implementation process can also improve understanding of the process(es) and causal mechanism(s) whereby the additional risk minimisation measure(s) did or did not lead, to the desired control of specified important risks.

Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimisation measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.

In rare circumstances when it is fully justified that the assessment of outcomes indicators is unfeasible (e.g. inadequate number of exposed patients, very rare adverse events), the effectiveness evaluation may be based exclusively on the careful interpretation of data on process indicators.

The conclusion of the evaluation may be that risk minimisation should remain unchanged or modifications are to be made to existing activities. Alternatively, the assessment could indicate that risk minimisation is insufficient and should be strengthened (e.g. through amendment of warnings or recommendations in the SmPC or package leaflet, improving the clarity of the risk minimisation advice and/or by adding additional tools or improving existing tools). Another decision may be that the risk minimisation is disproportionate or lacking a clear focus and could be reduced or simplified (e.g. by decreasing the number of tools or frequency of intervention, or by eliminating interventions proved to be non-contributory to risk minimisation). In all circumstances, the burden on the patient and the healthcare system should be given careful consideration.

In addition to assessing the effectiveness of risk minimisation measures in managing safety concerns, it is also important to monitor if the risk minimisation intervention may have had unintended (negative) consequences relevant to the public health question under consideration, either in the short and/or long term. Examples of unintended consequences may include undue burden on the healthcare system, or discontinuation of a product even if its risk-benefit balance remains positive.

The legislation defines “Any studymeasuring the effectiveness of risk management measures” as a post-authorisation safety study [DIR Art 1 (15)]. Therefore, if a study is conducted to assess behavioural or safety outcome indicators the detailed guidance for conducting a post-authorisation safety study, which is provided in **Module VIII**, should be followed. Such guidance does not apply to the measurement of simple process markers (e.g. distribution of the tools reaching the target population). The **ENCePP Guide on Methodological Standards in Pharmacoepidemiology**¹ should be considered as appropriate.

XVI.B.4.1. Process indicators

Process indicators are measures of the extent of implementation of the original plan, and/or variations in its delivery. Process indicators should complement but not replace the assessment of the attainment of the objectives of the risk minimisation measures (i.e. outcome indicators). Depending on the nature of the interventions various process indicators can be identified for the assessment of their performance.

XVI.B.4.1.1 Reaching the target population

When risk minimisation measures involve the provision of information and guidance to healthcare professionals and/or patients by mean of educational tools, measures of distribution should be used to acquire basic information on implementation. These metrics should focus on assessing whether the materials were delivered to the target audience and whether they were actually received by the target population.

¹ <http://www.encepp.eu>

XVI.B.4.1.2 Assessing clinical knowledge

In order to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision (for example via an educational programme with a goal of preventing drug exposure during pregnancy), scientifically rigorous survey methods should be applied. [Appendix I](#) summarises key methodological aspects to be considered for the design and implementation of a survey.

A survey generally includes a core of standard questions administered through telephone contact, in person interview, or self-administered through postal/electronic communication, which are repeated over time. Such an approach may be tailored to the monitoring of attitude and knowledge in a diverse sample, that includes representatives from each segment of interest in the target populations of healthcare professionals and/or patients. Psychometric measures should be used as appropriate. Whenever feasible a randomised sample and an adequate sample size should be selected. In contrast, use of advocacy groups or patient support groups to survey knowledge can be considered to be inherently biased through self-selection, and should be avoided.

Appropriate attention should be given to the research objectives, study design, sample size and representativeness, operational definition of dependent and independent variables, and statistical analysis. Thorough consideration should also be given to the choice of the most appropriate data collection instruments (e.g. questionnaires).

XVI.B.4.1.3 Assessing clinical actions

In order to evaluate the effectiveness of educational interventions and/or information provisions, not only clinical knowledge but also the resulting clinical actions (i.e. prescribing behaviour) should be measured. Drug utilisation studies by means of secondary use of electronic records or through medical chart abstraction are valuable options to quantify clinical actions, if representative of the target population and where adequate databases are accessible. The analysis of prescription records, especially when linked to other records of patients (e.g. clinical and demographic data), may allow the evaluation of prescribing behaviour, including co-prescribing of two interacting medicinal products, compliance with laboratory monitoring recommendations, as well as patient selection and monitoring. By applying appropriate statistical methods (e.g. time series analyses, survival analyses, logistic regression) to a cohort of medicines users, different aspects of prescribing or use may be assessed, which can provide insights beyond purely descriptive evidence. Careful consideration should be given to the conduct and interpretation of drug utilisation studies across Member States, including the legal status of the medicine and how it is prescribed and dispensed, since prescription patterns may reflect not only the product information and any risk minimisation intervention, but also national guidelines, aspects related to healthcare services, local medical practice, and reimbursement constraints. Such a diversity of national healthcare delivery systems across the EU may justify the conduct of a study with the same objectives in multiple countries.

The study of behaviour based on data collected through surveys should only be considered when no pre-existing data are available to evaluate clinical actions (i.e. conduct a drug utilisation study based on self-reported data collected in healthcare professionals and/or patients survey).

XVI.B.4.2. Outcome indicators

The ultimate measures of success of a risk minimisation programme are the safety outcomes, i.e. the frequency and/or severity of adverse reactions in relation to patients' exposure to the medicine outside of an interventional study setting (i.e. non-interventional setting) and those safety outcomes should be the outcome indicator(s). Such an evaluation should involve the comparison of epidemiologic

measures of outcome frequency such as incidence rate or cumulative incidence of an adverse reaction, obtained for example in the context of post-authorisation safety studies. The use of appropriate safety-related outcomes of interest should be considered (e.g. a surrogate endpoint such as an adequate biomarker as a substitute for a clinical endpoint) if such an approach facilitates the effectiveness evaluation. Under any approach, scientific rigour and recognised principles of epidemiologic research should always guide the assessment of the final outcome indicator of interest. Comparisons of frequency before and after the implementation of the risk minimisation measures (i.e. pre-post design) should be considered. When a pre-post design is unfeasible (e.g. risk minimisation measures are put in place at the time of initial marketing authorisation), the comparison of an outcome frequency indicator obtained post-intervention against a predefined reference value obtained from literature review, historical data, expected frequency in general population, would be acceptable (i.e. observed versus expected analysis) and should take into account any stimulated reporting, changes in patient care and/or risk minimisation measures over time. The selection of any particular reference group should be appropriately justified.

Methods to measure the effectiveness of risk minimisation measure should be proportionate to the risks being minimised. As such use of spontaneous reporting rates (i.e. number of suspected adverse reaction reports over a fixed time period) may be acceptable in the context of routine risk minimisation. Spontaneous reporting should be considered with caution when estimating the frequency of adverse events in the treated population, but it may be used in very specific circumstances, for instance when the adverse reaction with the product is rare and there is a negligible background incidence of the adverse event in the general population and a strong association between treatment and the adverse event. In those circumstances when a direct measure on the risk in the treated population is not feasible, spontaneous reporting could offer an approximation of the frequency of the adverse reaction in the treated population, provided that reasonably valid data can be obtained to evaluate the reporting rate in the context of product use. However, the well known biases that affects reporting of suspected adverse reactions may provide misleading results. For instance, the introduction of a risk minimisation measure in response to a safety concern detected in the post-authorisation phase of a medicinal product may raise awareness regarding selected adverse reactions which ultimately may result in an increased reporting rate. In these circumstances an analysis of spontaneous reporting may lead to the erroneous conclusion that the intervention was ineffective. Decreasing reporting rates over time may also lead to the erroneous conclusion that the intervention was effective.

XVI.B.5. Coordination

If several products, including medicinal products authorised according to art. 10(1) or 10(3) (herein referred to as “generics” or “hybrids”, as appropriate), of the same active substance are available in a market there should be a consistent approach in the use of additional risk minimisation measures coordinated and overseen by the national competent authorities. When a coordinated action for a class of products is needed a harmonised approach should be agreed if appropriate. Under these circumstances advanced planning should ensure that the effectiveness of risk minimisation measures (see [XVI.B.4.](#)) can be considered for each individual product as well as for the products collectively.

XVI.B.6. Quality systems of risk minimisation measures

Although many experts may be involved in developing and implementing risk minimisation measures, the final responsibility for the quality, accuracy and scientific integrity of those measures and the plan describing them lies with the marketing authorisation holder and its qualified person responsible for pharmacovigilance in the EU (QPPV).

The marketing authorisation holder is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in [Module I](#). Tracked versions of the RMP should be submitted to facilitate regulatory assessment. These records, the RMP and the associated risk management systems, as well as any documents on risk minimisation measures may be subject to audit or inspection.

The marketing authorisation holder should ensure appropriate version control of the risk minimisation tools in order to ensure that all healthcare professionals and patients receive up-to-date risk minimisation tools in a timely manner and that the tools in circulation are consistent with the approved product information. To this purpose the market authorisation holders are encouraged to keep track of the receipt of any risk minimisation tools. These records may be subject to audit and inspection.

The marketing authorisation holder should ensure that mechanisms for reporting the results of studies or analyses for evaluation of the effectiveness of risk minimisation measures are documented. These may be subject to audit or inspection.

XVI.C. Operation of the EU regulatory network

For centrally authorised products additional risk minimisation measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) and agreed by the Committee for Medicinal Products for Human Use (CHMP) will become, once agreed by the European Commission, conditions for the safe and effective use of a medicinal product.

Annex II of the CHMP opinion will outline the key elements of any additional risk minimisation measures imposed on the applicant or marketing authorisation holder as a condition for the safe and effective use of a medicinal product. An annex related to Article 127a of DIR may describe the responsibilities of national competent authorities in ensuring that the additional risk minimisation measures are implemented in the Member States in accordance with defined key elements. Further details or key elements on any additional risk minimisation measures may be included in annex 10 of the RMP (see [Module V](#)).

For products authorised under the mutual recognition and decentralised procedure, additional risk minimisation measures may be included in the RMP or laid down as conditions of the marketing authorisation.

In all cases, implementation of additional risk minimisation measures takes place at national level and allows Member States to tailor the required conditions and restrictions to any national legal requirements and local healthcare systems.

XVI.C.1. Roles and responsibilities in the EU for implementing additional risk minimisation measures

This section outlines the responsibilities of different bodies as having clear obligations. This includes the Agency and its PRAC, national competent authorities, and the applicant or marketing authorisation holder in the process of developing, implementing and evaluating additional risk minimisation measures introduced for the safe and effective use of a medicinal product in the EU.

In order to respect the diversity of EU health care systems, key elements will be agreed at EU level, which need to be implemented in a coordinated manner across the Member States while providing for agreement of the detail of local implementation at national level. In circumstances where some key elements are specific for only some Member States (e.g. an activity is specifically linked to the healthcare system of one Member State) or where additional risk minimisation measures are not imposed as a condition for marketing authorisation these shall be included in the RMP.

XVI.C.1.1. Roles and responsibilities within the EU regulatory network

XVI.C.1.1.1 The European Medicines Agency

The Agency shall, in collaboration with the Member States and facilitated through the PRAC, monitor the outcome of risk minimisation measures contained in RMPs and of conditions referred to in points (c), (ca), (cb) and (cc) of Article 9(4) or in points (a) and (b) of Article 10a(1), and in Article 14(7) and (8) of Regulation (EC) No 726/2004 [REG Art 28a(1)(a)].

In monitoring the outcome of risk minimisation measures, the Agency should support the PRAC scientific assessment of the outcome of risk minimisation measures which comprise additional risk minimisation measures, through the integration of data provided by Member State resources and research activities. The PRAC will make recommendations to the CHMP or the Coordination Group – Human (CMDh), as appropriate, regarding any necessary regulatory action.

XVI.C.1.1.2. The Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC should evaluate the outcome of risk minimisation measures, including additional risk minimisation measures and make recommendations as appropriate regarding any necessary regulatory action.

In addition to advising on the studies and measures described in the RMP, the PRAC will assess both protocol and results of imposed post-authorisation safety studies which aim to evaluate the effectiveness of risk minimisation measures (see [Module VIII](#)).

XVI.C.1.1.3. Competent authorities in Member States

The national competent authorities are responsible for the oversight at national level of the implementation of additional risk minimisation measures imposed as a condition of the marketing authorisation for the safe and effective use of a medicinal product in the EU, irrespective of the route of marketing authorisation.

For those risk minimisation measures introduced after the initial marketing authorisation, the national competent authorities should ensure prompt consideration and agreement of the interventions with the marketing authorisation holder.

The national competent authorities assisted by the PRAC and CHMP or CMDh, as appropriate, may facilitate harmonization of the implementation of risk minimisation tools for generic products of the same active substance. When additional risk minimisation measures are considered necessary for generic medicinal product(s) based on safety concerns related to the active substance, the risk minimisation measures applicable to the generic product(s) should be aligned with those for the reference medicinal product. Additional risk minimisation measures for hybrid products may be required in some circumstances beyond those of the reference medicinal product (e.g. different formulation or route of administration or incompatibility issues). To facilitate this, the PRAC may give advice on the key elements that should be implemented for all concerned nationally authorised products (as conditions of their marketing authorisation) and on agreement, may make these general requirements publicly available to facilitate harmonised implementation at national level.

In addition to the above, for centrally authorised products the responsibility of the national competent authorities in ensuring implementation of the risk minimisation measures as addressed to them by the European Commission decision may be outlined in the annex related to Article 127a of DIR. In the absence of such an annex, the general responsibilities of supervisory authorities will apply. Additionally, the national competent authorities should agree the final content, format and media of

the risk minimisation tools, including printed material, web-based platforms and other audio-video media, as well as the schedule planning of interventions with the applicant or marketing authorisation holder before a product is introduced to their market or at any time thereafter as needed.

The national competent authority is autonomous in deciding appropriate national educational materials and/or other risk minimisation tools as long as these are aligned with the key elements agreed at EU level and as outlined in the RMP. Similarly, measurement of effectiveness of additional risk minimisation measures may be required in one Member State in reason of its specific health care delivery setting or when, due to national specificities, results of the effectiveness studies cannot be extrapolated from studies conducted in other Member States.

National competent authorities in collaboration with the Agency facilitated through the PRAC shall monitor at national level the outcome of risk minimisation measures contained in RMPs and of the conditions referred to in Articles 21a, 22 or 22a of DIR [DIR Art 107h(1)(a)].

XVI.C.1.2. Marketing authorisation applicant or holder

The applicant or marketing authorisation holder should clearly define the objectives of any proposed additional risk minimisation measure and the indicators to assess their effectiveness. Any additional risk minimisation intervention should be developed in accordance with the general principles outlined in XVI.B.1. and XVI.B.2. and should be fully documented in the RMP (see Module V).

The measures adopted in the RMP should be implemented at national level after agreement with the national competent authorities.

The applicant or marketing authorisation holder should provide information regarding the status of implementation of additional risk minimisation measures as agreed with the national competent authorities and keep them informed of any changes, challenges or issues encountered in the implementation of the additional risk minimisation measures. Any relevant changes to the implementation of the tools should be agreed with the national competent authorities before implementation.

In the implementation of web-based tools the applicant or marketing authorisation holder should apply requirements specific for each Member State, with particular consideration of potential issues linked to accessibility, recognisability, responsibility, and privacy and data protection.

For generic products the applicant or marketing authorisation holder should develop risk minimisation in line with the scope, content, and format of the tools used for the reference medicinal product. Scheduling and planning of interventions should be carefully coordinated in order to minimise the burden on the healthcare systems.

For generic products, the effectiveness of risk minimisation measures should be assessed by the marketing authorisation holders in close cooperation with the competent authorities. Where formal studies are justified, joint studies for all medicinal products involved are strongly encouraged in order to minimise the burden on the healthcare systems. For instance, if a prospective cohort study is instituted, study entry should be independent from the prescription of a product with a specific invented name or marketing authorisation holder. Recording of specific product details would still be important to enable rapid identification of any new safety hazard with a particular product.

The marketing authorisation holder shall monitor the outcome of risk minimisation measures which are contained in the RMP or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a of DIR [DIR Art 104(3)(d)]. General principles for effectiveness evaluation are provided in XVI.B.3..

The applicant or marketing authorisation holder should report the evaluation of the impact of additional risk minimisation activities when updating the RMP (see V.B.11.4.).

The applicant or marketing authorisation holder should report in the Periodic Safety Update Report (PSUR) the results of the assessment of the effectiveness of risk minimisation measures which might have an impact on the safety or risk-benefit assessment (see VII.B.5.16.5. and VII.C.5.5).

The applicant or marketing authorisation holder should ensure timely communication with the competent authorities for relevant regulatory evaluation and actions, as appropriate (see also XVI.C.2. and Modules V and VII).

XVI.C.1.3. Healthcare professionals and patients

Healthcare professionals and patients hold no legal obligations with respect to the implementation of the pharmacovigilance legislation. Nonetheless the cooperation of healthcare professionals and patients is paramount to the success of educational programmes and/or controlled access programmes in order to optimise the risk-benefit balance. It is desirable that they give careful consideration to any additional risk minimisation measure which may be introduced for the safe and effective use of medicines.

XVI.C.2. Impact of risk minimisation measures effectiveness on RMP/PSUR

PSUR and RMP updates should include a summary evaluation of the outcome of specific risk minimisation measures implemented to mitigate important risks in the EU. In the RMP, the focus should be on how this informs risk minimisation and/or pharmacovigilance planning. In the PSUR, there should also be evaluation of how the implemented measures impact on the safety profile and/or risk-benefit balance of the product. In general, the focus should be on information which has emerged during the reporting period or since implementation of the most recent risk minimisation measure(s) in the EU. Where there is parallel submission of a PSUR and a RMP update, the use of a common content Module should be considered (see GVP Modules V and VII).

Results of the assessment(s) of the effectiveness of risk minimisation measures should always be included in the RMP. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation measures. This critical analysis may include reference to experience outside the EU, when relevant.

The evaluation of the effectiveness of risk minimisation measures should focus on whether these have succeeded in minimising risk. This should be analysed using a combination of process and outcome indicators, as described in XVI.B.3. It may be appropriate to distinguish between risk minimisation measures implemented at the time of initial marketing authorisation and those introduced later in the post-authorisation phase.

When presenting the evaluation of the effectiveness of a risk minimisation measure, the following aspects should be considered:

1. The evaluation should provide context by a) briefly describing the implemented risk minimisation measure(s), b) defining their objective(s), and c) outlining the selected process and outcome indicators.
2. The evaluation should incorporate relevant analyses of the nature of the adverse reaction(s) including its severity and preventability. Where appropriate logistical factors which may impact on clinical delivery of the risk minimisation measure should also be included.

3. The evaluation should include an examination of the delivery of the risk minimisation measures in routine clinical practice, including any deviation from the original plan. Such an evaluation may include the results of drug utilisation studies.
4. Outcome indicators (i.e. adverse reaction frequency and/or severity; other safety-related outcomes) should normally be the key endpoint when assessing the attainment of risk minimisation measures objectives.

Proposals for changes to enhance risk management should be presented in the regional appendix of the PSUR (see VII.C.5.). The RMP should be updated to take account of emerging information on the effectiveness of risk minimisation measures.

In general, generic products are exempt from routine PSUR reporting in the EU. The frequency of RMP updates should be proportionate to the risks of the product. In general, the focus of RMP updates should be on the risk minimisation measures and in providing updates on the implementation of those measures where applicable. If there is a consequential change to the summary RMP, this should also be highlighted in the cover letter. Changes to the product information should not be proposed via a standalone RMP update but rather a variation application should be submitted. A PSUR can also result directly in an update to product information (if PSURs are being submitted by the marketing authorisation holder for a given generic product).

XVI.C.3. Transparency

Procedures should be in place to ensure full transparency of relevant information pertaining to the risk minimisation measures in place for the concerned medicinal products.

In accordance with Article 106 of Directive 2001/83/EC and Article 26 of Regulation (EC) No 726/2004, the Agency and national competent authorities shall make publicly available public assessment reports for medicinal products, as well as summaries of RMPs (Commission Implementing Regulation (EU) No 520/2012, [IR Art 31], including risk minimisation measures therein described.

For centrally authorised products the Agency shall make public:

- a summary of the risk management plan [REG Art 26(1)(c)], with specific focus on risk minimisation activities described therein [IR Art 31.1];
- the European Public Assessment Report (EPAR) that includes any conditions of the marketing authorisation, such as additional risk minimisation measures [REG Art 26(1)(j)].

By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

- public assessment report; this shall include a summary written in a manner that is understandable to the public [DIR Art 21(4), Art 106(a)];
- summary of product characteristics and package leaflets [DIR Art 21(3), Art 106(b)];
- conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions [DIR Art 21(3)];
- summaries of risk management plans [DIR Art 106(c)]; with specific focus on risk minimisation activities described therein [IR Art 31.1].

To promote public health, it is recommended that the Agency and the national competent authorities make the following information available via their websites:

- details of additional risk minimisation measures required as a condition of the marketing authorisation (e.g. when risk communication tools consist of printed material, a copy is provided or whenever possible, provision of electronic access to the educational material, patient card, check lists or other risk minimisation tools is advised);
- details of disease or substance registries requested as part of a restricted distribution system.

XVI. Appendix 1. Key elements of survey methodology

Surveys are systematic methods of collecting primary data directly from a sample of participants from a larger population. These are conducted in order to characterise the larger population and may be cross-sectional (one-time only) or longitudinal (repeated over time).

In the context of the evaluation of the effectiveness of risk minimisation measures a survey can be conducted to evaluate understanding, knowledge and behaviour resulting from educational interventions in a specified target population with respect to the safety and risk management of a medicinal product.

The survey methodology might not be the most appropriate approach for the evaluation of behaviour, since surveys collect and analyse self-reported data from healthcare professionals and patients. Furthermore, participation in a survey in itself may introduce behaviour changes or may not be representative of the target users given that participation is more likely amongst engaged healthcare professionals and/or more motivated or educated individuals.

As a minimum, the following elements should be considered in the design and implementation of a survey in order to minimise potential biases and to optimise the generalisability of the results to the intended population:

1. Sampling procedures and recruitment strategy;
2. Design and administration of the data collection instrument (s);
3. Analytical approaches;
4. Ethics, privacy, and overall feasibility of a study.

XVI.App1.1. Sampling procedures and recruitment strategy

In any survey, the sampling frame and recruitment of participants may be subject to selection bias leading to a study population that is not similar to, or representative of, the intended population in one or more aspects. Furthermore, it should be considered that a bias cannot be eliminated only by increasing the sample frame, sample size and response rate. Bias can be minimised by selecting the optimal sampling frame, taking into account age, sex, geographical distribution and additional characteristics of the study population. Bias can also be minimised by assuring the sample contains appropriate diversity to allow stratification of results by key population characteristics (e.g., by oversampling a small but important subgroup). Key elements to be considered in the sampling frame include age, gender, geographical distribution, and additional characteristics of the study population. For example, in a physician survey, the strategy for randomly selecting the study sample should consider whether a general random sample would be sufficient or if the sample should be stratified by key characteristics such as specialty, type of practice (e.g., primary care, specialist ward, academic institution). In a patient survey, income and education, medical condition(s), chronic vs acute use, should be considered.

In addition to the overall representativeness of the target population the recruitment strategy of a survey should give careful consideration of the potential recruitment sources. For the recruitment of healthcare professionals, sponsor lists, web panels, professional and learned societies may represent feasible approaches. However, their representativeness for the intended target population of physicians needs to be carefully reviewed for each study. For patient recruitment the relevant clinical setting, existing web-panels, and patient advocacy groups should be considered. A recruitment strategy should be designed while accounting for the chances of achieving accurate and complete data collection.

Efforts should be made to document the proportion of non-responders and their characteristics to evaluate potential influences on the representativeness of the sample.

XVI.App1.2. Design and administration of the data collection instrument(s)

Data collection approaches in a survey may vary from in-person interview, testing, and measurement or collection of biological samples as for routine clinical practice, to telephone interview, web-based or paper-based questionnaires. Audio computer-assisted self-interviewing (A-CASI), interactive voice response systems (IVRS), or mixed mode approaches may also be appropriate. The choice of the most suitable data collection approach will depend on the target population characteristics, the disease and the treatment characteristics and the data to be collected.

Each data collection approach will require the ad hoc design of one or more specific instruments. Nonetheless general design considerations that may apply to all instruments include the following:

- Burden to participant: e.g. length or duration, cognitive burden, sensitivity to participant;
- Clarity and sequence of questions: e.g. use of unambiguous language, minimising assumptions, starting with the most important questions and leaving sensitive questions until later;
- Completeness of responses: e.g. structure questions in order to lead to a single unambiguous answer, allow for choices such as “unknown” or “don’t know”;
- Layout of data collection instrument: e.g. clear flow, technology-assisted guides (avoid patterns, reminders for non-response and visual images);
- Testing and revision of instrument: e.g. formal testing using cognitive pre-testing such as one-to-one interviews, probing questions, interview guide or trained interviewer, and “think aloud” process;
- Incentives to improve response rate: e.g. fed back aggregated data to the survey participants.

XVI.App1.3. Analytical approaches

The key analytical elements of a survey should include:

- Descriptive statistics, such as:
 - The percentage of participants responding correctly to knowledge questions;
 - Stratification by selected variable;
 - Data on no-response or incomplete response;
- Comparison of responders and non-responders characteristics (if data available);
- Comparison of responders and overall target population characteristics.

When survey results are weighted, the following key points should be considered:

- Differences in selection probabilities (e.g. if certain subgroups were over-sampled);
- Differences in response rates;
- Post-stratification weighting to the external population;
- Clustering.

Examples of stratified analyses of physician’s survey include the following:

- Specialty of physician;
- Geographic location;
- Receipt of any educational material;
- Volume of prescribing.

XVI.App1.4. Ethics, privacy and overall study feasibility

Ethical and data privacy requirements are not harmonised across Member States, with notable differences in national (or regional) processes. National (or regional) differences may exist regarding the appropriateness of providing incentives to survey participants. There may also be privacy considerations in allowing contact with physicians based on a prescriber list that is held by a pharmaceutical company.

The overall feasibility assessment of a study is a key step in the successful implementation of a survey. For clinical-based data collection, key elements of such an assessment include:

- Gathering information on site and characteristics of study population (patients or healthcare professionals);
- Estimating reasonable study sample size, the number of sites required to achieve the sample size, and approximate length of the data collection period (e.g. based on estimated patient volume, frequency of patient visits, and expected patient response rate);
- Evaluating site resources and interest in the study.

Key elements of a feasibility assessment may be different for other study designs (e.g. web-based recruitment and data collection) and for physician assessments.