EUROPEAN MEDICINES AGENCY
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User guide for micro, small and medium-sized enterprises

on the administrative and procedural aspects of the provisions laid down in regulation (EC) No 726/2004, that are of particular relevance to SMEs

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1. Introduction

This guide has been prepared for micro, small and medium-sized enterprises (SMEs) operating in the pharmaceutical sector. Its aim is to facilitate understanding of the main aspects of medicinal product legislation. The guide is structured to follow the chronological stages of developing a medicinal product. An overview of the scientific data requirements for obtaining a marketing authorisation in the European Union (EU) is provided. The regulatory procedures in place to optimise development and obtain an EU marketing authorisation are also summarised.

The guide focuses primarily on the requirements for authorising innovative medicinal products for human or veterinary use. The guide is not intended to be an exhaustive document but rather to raise SMEs' awareness of the various more detailed sources of information available, with links throughout the text to additional information.

In December 2005, Commission regulation (EC) no 2049/2005[1] introduced provisions aimed at promoting innovation and the development of new medicinal products for human and veterinary use by SMEs. This guide is intended to fulfil the obligation laid down in article 12 of that regulation, which calls for a 'User Guide', on the administrative and procedural aspects of medicines legislation that are of particular relevance to smaller companies, to be published by the European Medicines Agency (EMA).

Pursuant to the SME regulation, companies can access financial assistance (in the form of fee reductions and deferrals) and administrative assistance from the Agency, details of which are outlined in section 2 of this guide. To facilitate contact with the Agency, an 'SME Office' was launched in December 2005 and is dedicated to addressing the particular needs of smaller companies.

Any feedback on the content or format of this guide should be forwarded to the SME office: smeoffice@ema.europa.eu.

1.1. Obtaining a marketing authorisation within the European Union

Prior to marketing a medicinal product in the EU, a marketing authorisation (product licence) must be obtained. The company responsible for placing the medicinal product on the market (so-called marketing authorisation holder) must be "established"[2] within the EEA (Iceland, Liechtenstein, Norway and the Member States of the European Union).

In the EU, there are two types of marketing authorisation:

National marketing authorisations:

issued by the competent authorities of individual Member States. The medicinal product may be put on the market in all Member States that have granted an authorisation for it.

or

Community marketing authorisation:

granted by the European Commission, following a positive opinion from the Agency. This is a single authorisation that allows the medicinal product to be put on the market in all Member States.

[1] *Official Journal L 329, 16/12/2005 pp. 4-7* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:329:0004:0007:EN:PDF

[2] Being established, here, means having a permanent legal structure (formed in accordance with the law of an EU Member State or other EEA country) that allows the concerned person to assume the duties and responsibilities as well as to perform the tasks laid down by EU law, see annex II of chapter I, vol. 2A (human medicines) or 6A (veterinary medicines) of the notice to applicants: http://ec.europa.eu/health/documents/eudralex/index_en.htm

Approved conditions of use are laid down in the summary of product characteristics[3] (prescribing information for health professionals), the labelling and the package leaflet for users[4].

This user guide will focus on the use of the centralised procedure for obtaining an EU marketing authorisation. Further information on the regulatory routes for obtaining national marketing authorisations, namely the mutual recognition and decentralised procedure, are highlighted in section 1.1.2 below. Applicants are advised to refer to volume 2A and volume 6A of the notice to applicants[5], for more detailed information.

1.1.1. EU marketing authorisation – the centralised procedure

The European Medicines Agency coordinates the existing scientific resources of the Member States to evaluate and supervise medicinal products for both human and veterinary use throughout the European Union. The EMA is primarily involved in the centralised procedure for obtaining an EU marketing authorisation.

The Agency also gives scientific advice to research-based companies on the development of new medicinal products (see section 3.3) and develops guidelines on quality, safety and efficacy testing requirements (see section 3.4).

For queries relating to: orphan designation, paediatric investigation plans, pan-European scientific advice, filing an application for marketing authorisation through the centralised procedure, and EudraVigilance, the Agency is the primary point of contact.

If an SME has any doubt about the appropriate point of contact for a particular issue, the SME office can provide assistance: smeoffice@EMA.europa.eu

The centralised procedure is mandatory for certain types of medicinal products and optional for others. Medicinal products (both for human and veterinary use) made of recombinant proteins, veterinary medicinal products intended primarily for use as performance enhancers, advanced therapy medicinal products (ATMPs) for human use, human medicinal products containing a new active substance for treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, viral diseases, auto-immune diseases/other immune dysfunctions and designated orphan medicinal products fall within the mandatory scope and must be filed centrally at the EMA.

The centralised procedure is optional for products containing new active substances for indications other than those stated above and for products which constitute a significant therapeutic, scientific or technical innovation, or products for which the granting of an EU authorisation would be in the interest of patients or animal health at EU level. It is also optional for immunological veterinary medicinal products for the treatment of animal diseases that are subject to EU prophylactic measures. Applicant companies should confirm eligibility for evaluation through the centralised procedure with the EMA at least 7 months prior to submitting the centralised marketing application (see section 6.1).

In order to obtain an EU marketing authorisation, an application should be submitted to the EMA. The scientific evaluation of the application is carried out by the committee for medicinal products for human use (CHMP) or committee for medicinal products for veterinary use (CVMP) of the EMA, and a scientific opinion is prepared in co-operation with other EMA committees as applicable. The opinion is sent to the European Commission, which drafts a decision and, having consulted the Member States through the relevant standing committee, adopts the decision and grants a marketing authorisation.

[3] In accordance with article 11 of directive 2001/83/EC for human medicines and article 14 of directive 2001/82/EC for veterinary medicines.
[4] In accordance with articles 54, 55, 59 and 63 of directive 2001/83/EC for human medicines and articles 58-61 of directive 2001/82/EC for veterinary medicines.
[5] http://ec.europa.eu/health/documents/eudralex/index_en.htm

Such a marketing authorisation is valid throughout the European Union and confers the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State.

The centralised procedure is briefly detailed in section 6 of this guide. Chapters 4 and 6 of volume 2A and volume 6A of the notice to applicants[6] should be consulted for further information.

1.1.2. National marketing authorisations – mutual recognition & decentralised procedures

Each Member State of the European Union, Iceland, Liechtenstein and Norway has its own national authority(ies) responsible for regulating medicinal products for human and veterinary use. These authorities have a common website called the heads of agencies website[7] that serves as a useful connection point to the websites of individual authorities.

Sponsors with queries relating to: regulatory approval for the conduct of clinical trials, national scientific advice, manufacturing authorisations, filing an application for marketing authorisation nationally, through the mutual recognition or decentralised procedure, reporting of adverse events, or pricing and reimbursement matters, are advised to contact the relevant national competent authority.

The authorities of the Member States are responsible for granting marketing authorisations for medicinal products placed on their markets, with the exception of medicinal products subject to centralised EU marketing authorisations. If a company seeks a national marketing authorisation, an application must be submitted to the competent authority of the Member State concerned. If a company is seeking a national marketing authorisation in more than one Member State, the mutual recognition or decentralised procedure are available to facilitate the granting of harmonised national authorisations across Member States. Chapter 2 of volume 2A and volume 6A of the notice to applicants[8] should be consulted for further information.

1.2. Overview of (data) requirements for obtaining marketing authorisation in the EU

An application for marketing authorisation for a new medicinal product for human use must generally be accompanied by the particulars and documents set out in article 8(3) and annex I of directive 2001/83/EC[9]. The requirements include data generated from pharmaceutical (physicochemical, biological or microbiological) tests, non-clinical (toxicological and pharmacological) tests and clinical trials, evaluation of the potential environmental risks posed by the medicinal product, as well as a risk management plan and a summary of the pharmacovigilance site master file (see sections 4.1-4.3 and 7.0). For new medicines there is a requirement to agree a paediatric investigation plan and/or deferral and/or waiver with the EMA early in development (see section 4.5).

Article 12(3) and annex I to directive 2001/82/EC[10] list the requirements for the individual sections of the dossier that need to be submitted as part of the application for authorisation of a veterinary medicinal product.

An overview of the key issues to be addressed in the development of medicinal products for human use and veterinary use are outlined in section 4 and 5 of this guide respectively.

[6] http://ec.europa.eu/health/documents/eudralex/index_en.htm
[7] http://www.hma.eu/
[8] http://ec.europa.eu/health/documents/eudralex/index_en.htm
[9] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83/2001_83_ec_en.pdf
[10] http://ec.europa.eu/health/files/eudralex/vol-5/dir_2009_9/dir_2009_9_en.pdf

1.3. EU legislative framework for pharmaceuticals

All EU legislative texts are published in the official journal of the European Union (OJEU) in all official EU languages[11]. For sponsors unfamiliar with the EU legislative process, a useful starting point is the overview of the hierarchy of Community texts given in chapter 1, annex I of volumes 2A (human) and 6A (veterinary) of the notice to applicants.

Commission regulation 2049/2005 of 15 December 2005 introduces **provisions for SMEs**.
Regulation (EC) no 726/2004[12] of the European Parliament and of the council of 31 March 2004, as amended, is the legal base for the **centralised procedure** for the authorisation and supervision of human and veterinary medicinal products and the establishment of the European Medicines Agency (EMA).
Directives 2001/82/EC and 2001/83/EC[13] of the European Parliament and of the Council of 6 November 2001, as amended, lay down the **Community code** relating to medicinal products for veterinary use and human use respectively.
Regulation (EC) no 141/2000 of the European Parliament and of the Council of 16 December 1999 on **orphan medicinal products**, (which entered into force on 22 January 2000), introduces provisions to stimulate the development of medicinal products for patients suffering from rare diseases.
Regulation (EC) no 1901/2006 of the European Parliament and of the Council of 12 December 2006, as amended on **medicinal products for paediatric use**.
Regulation (EC) no 1394/2007 of the European Parliament and of the Council of 13 November 2007 on **advanced therapy medicinal products**.
Regulation (EC) no 470/2009 of the European Parliament and of the Council of 6 May 2009 lays down Community procedures for the **establishment of residue limits** of pharmacologically active substances in foodstuffs of animal origin.

The above-mentioned directives and regulations are available in the EudraLex section[14] of the European Commission's health website. These legislative texts — together with directives 2001/20/EC and 2005/28/EC on good clinical practice (in the conduct of clinical trials on human medicinal products and as regards investigational products for human use respectively), and directives 2003/94/EC and 91/412/EEC on good manufacturing practice (for human medicinal products and veterinary medicinal products respectively) — form the legislative backbone of medicinal product regulation in the EU.

[11] http://eur-lex.europa.eu/JOIndex.do?ihmlang=en
[12] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_cons_en.pdf
[13] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83/2001_83_ec_en.pdf
[14] http://ec.europa.eu/health/documents/eudralex/index_en.htm

The notice to applicants facilitates the interpretation and application of EU pharmaceutical legislation, and should be consulted by any potential applicant. It is not legally binding, and in case of doubt about legislative requirements, companies should always refer to the legal texts themselves.

1.3.1. Upcoming legislative changes

New legislation on falsified medicines

New legislation on falsified medicines, directive 2011/62/EU[15], entered into force on 2nd Jan 2013. The new directive introduces tougher rules to improve the protection of public health with new harmonised, pan-European measures to ensure that medicines are safe and that the trade in medicines is rigorously controlled. To implement some of the new measures, several further legislative acts will be prepared by the European Commission. Further information is available on the European Commission's website[16]. Please also refer to section 4.6 of this guide for information relating to control of active substances and good distribution practice.

Revision of the clinical trials directive

In July 2012, the European Commission adopted a proposal to simplify the rules for conducting clinical trials in the EU. The new legislative proposal aims to speed up and simplify authorisation and reporting procedures, while maintaining the highest standards of patient safety and robustness and reliability of data. It should also better differentiate the obligations according to the risk-profile of the trial, and improve transparency including on trials done in third countries. The proposed regulation, once adopted, will replace the 'clinical trials directive' of 2001. The legislative proposal is under discussion in the European Parliament and the Council and is expected to come into effect in 2016. Further information on the proposal is available on the European Commission's website[17].

Revision of the legal framework for veterinary medicinal products

The European Commission is currently undertaking a review of the legislation on veterinary medicinal products. The purpose of this revision will be to increase the availability of veterinary medicinal products, to reduce the administrative burden on enterprises, to improve the functioning of the internal market for veterinary medicinal products and to assess the possibilities to have an improved response to antimicrobial resistance related to the use of veterinary medicines. Further information, including a roadmap for the review, is available on the European Commission's website[18].

[15] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf
[16] For more information on falsified medicines: http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm
[17] For more information on clinical trials: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm
[18] http://ec.europa.eu/health/veterinary-use/rev_frame_index_en.htm

2. SME initiative

2.1. Objective

The primary aim of the SME initiative is to promote innovation and the development of new medicinal products by smaller companies. To achieve this, incentives are provided to help SMEs overcome the main financial and administrative hurdles associated with pre-marketing procedures, particularly scientific advice, marketing authorisation application and inspection procedures.

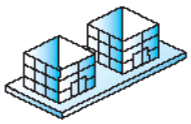
2.2. Definition of an SME

In determining which companies are eligible for SME incentives, the EMA applies the EU definition of micro, small and medium-sized enterprises provided in Commission recommendation 2003/361/EC[19]. This means that companies are classified according to their category (autonomous, partner or linked) and size (micro, small or medium), as defined below:

Autonomous enterprise*

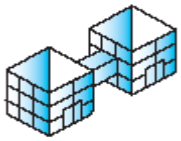
My enterprise holds less than 25% (capital or voting rights) in another and/or another holds less than 25% in mine.

** Note: there are exceptions for certain types of investors. See article 3(2)(D) in the annex of Commission recommendation 2003/361/EC.*



Partner enterprise

My enterprise holds at least 25%, but no more than 50% in another and/or another holds at least 25%, but no more than 50%, in mine.



Linked enterprise

My enterprise holds more than 50% of the shareholders' or members' voting rights in another and/or another holds more than 50% in mine.

Depending on the category in which the enterprise fits, some or all of the headcount and financial data from other partner or linked enterprises may need to be counted when calculating whether the SME criteria are met.

[19] http://eur-lex.europa.eu/LexUriServ/site/en/oj/2003/l_124/l_12420030520en00360041.pdf

SME thresholds (Commission recommendation 2003/361/EC)

Enterprise category	Headcount: Annual work unit (AWU)	Annual turnover	or	Annual balance sheet total
Medium-sized	< 250	≤ € 50 million	or	≤ € 43 million
Small	< 50	≤ € 10 million	or	≤ € 10 million
Micro	< 10	≤ € 2 million	or	≤ € 2 million

The information above has been extracted from 'The new SME definition - user guide and model declaration'[20], published by the European Commission, which provides further information on the definition of an SME. The user guide is available in a number of EU languages[21].

2.3. Incentives for SMEs (EU provisions and national provisions)

2.3.1. Incentives offered by the EMA

The EU incentives offered by the Agency apply to both the human and veterinary sectors, and include:

- Regulatory, administrative and procedural assistance from the Agency's SME office;
- Fee reductions for scientific advice, scientific services, inspections and (for veterinary medicines) establishment of maximum residue limits;
- Fee exemptions for certain administrative services of the EMA;
- Deferral of the fee payable for an application for marketing authorisation or related inspection;
- Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful;
- Certification of quality/non-clinical data for advanced therapy medicinal products (ATMPs) intended for human use;

[20] http://ec.europa.eu/enterprise/enterprise_policy/sme_definition/sme_user_guide.pdf
[21] http://ec.europa.eu/enterprise/policies/sme/facts-figures-analysis/sme-definition/index_en.htm

- Translations of the product information documents submitted in the application for marketing authorisation;
- Waiver of the MedDRA licensing fee when registering with EudraVigilance. This is only available for micro- or small enterprises and not for medium-sized enterprises;
- Inclusion in the public SME register.

Fee reductions / deferrals

SMEs operating in the pharmaceutical sector are often innovative companies that can notably benefit from the pooling of scientific expertise at EU level. The SME initiative has been designed, with a substantial 90% fee reduction for scientific advice, to encourage SMEs to seek advice from the EMA on all issues relating to the development of new medicinal products, with a view to maximising the chances of a successful marketing authorisation (see section 3.3).

Other financial incentives include a 90% fee reduction for any good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), or pharmacovigilance inspections requested by the EMA, and the possibility to request deferred payment of the inspection fee. For veterinary medicines, there is also the possibility to request a 90% fee reduction for establishment of maximum residue limits. Full fee exemptions are also offered for administrative services from the EMA (e.g. EMA certificates of medicinal products).

In the run up to filing an application for marketing authorisation, the fee payable to the EMA for review of the application may place financial constraints on smaller companies. For SMEs, fee payment may now be deferred by up to 45 days after the date of notification of the centralised marketing authorisation, or, in the event of withdrawal of the application, within 45 days of the date of notification of withdrawal. In the event of a negative outcome, where scientific advice has previously been sought from the EMA and taken it into account in the development of the medicinal product, the fee for the application for marketing authorisation will be fully waived by the Agency.

Certification of advanced therapy medicinal products

Advanced therapy medicinal products (ATMPs) are often developed by SMEs. As an incentive to develop such products, an SME can submit to the EMA, the results of studies carried out to demonstrate the quality and non-clinical safety of ATMPs and request evaluation and certification of the data, independently of any MAA. Although not legally binding, the certification procedure should facilitate the evaluation of any future application for clinical trials and marketing authorisation based on same data (see section 3.5 for information on certification).

Translation of product information

Because translating product information into all EU languages represents a considerable financial and administrative burden to SMEs entering the EU market, the EMA will provide translations of product information (summary of product characteristics, label, package leaflet and relevant opinion annexes) required to grant an EU marketing authorisation. Translation into EU official languages will be provided free of charge by the Agency.

Due to the timelines required to translate the product information, the Agency will initiate translations through the centre for translation (CdT) in Luxembourg at the time of CHMP/CVMP opinion. These translations will then be checked through the national competent authorities in the Member States. To be eligible for translation assistance the company's SME status must be valid at the time that the translations are initiated. It will be the responsibility of the applicant SME to provide Norwegian and Icelandic translations.

With regard to the linguistic versions provided by the EMA, upon the company's request there will be an opportunity to comment on some of the translations within a short time-frame (3 days), at the time the translations are circulated to Member States for their quality review in the post-opinion phase. More practical details will be sent to the applicant, together with the translations timetable, prior to the opinion.

Access to incentives

Access to the fee reductions and deferrals outlined above will be subject to the applicant company's SME status being assigned by the EMA and remaining valid on the date that the fee falls due for the relevant application or procedure (see section 2.5). The financial incentives will not be applied retrospectively.

If a product is out-licensed to another company during a procedure, the SME office at the EMA should be informed immediately. If the company licensing in the product does not meet the SME criteria, there will be no further access to the provisions of the SME regulation with effect from the date of the licensing agreement. Any fees shall no longer be subject to fee deferral pursuant to article 5 of the SME Regulation.

Further information on fee reductions/deferrals is available in the document 'Fee reductions/deferrals for micro, small and medium-sized enterprises (SMEs)' (EMA/366526/2005)[22].

2.3.2. Other EU incentives for SMEs

Further information on the whole spectrum of EU policies, legislation, programmes and initiatives relevant to Europe's SMEs is available from the European Commission through its European portal for SMEs[23].

An overview of initiatives to support financing of SMEs (EMA/986534/2011) and research funding opportunities (EMA/986519/2011) from the European Commission have been published on the EMA website[24].

Detailed information on the EU financial support available to SMEs can also now be accessed via a single access point on EU finance[25].

2.3.3. National provisions for SMEs

Article 12 of Commission regulation (EC) no 2049/2005 requires the SME user guide to reference existing national provisions for SMEs, applicable to the pharmaceutical sector. These are provided in annex 1.

If companies have a query relating to any existing national provision and would like to contact the national competent authority in question, contact points are also provided in annex 1.

[22] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004165.pdf
[23] http://ec.europa.eu/small-business/index_en.htm
[24] www.ema.europa.eu Regulatory / Human Medicines / SME office / Related Information
[25] http://access2eufinance.ec.europa.eu

2.4. Role of the SME office

The SME office was established at the EMA to offer assistance to SMEs who, due to lack of experience with the centralised authorisation procedure or lack of familiarity with the Agency and its procedures, may otherwise experience difficulties with the development and marketing of their new medicinal products. The SME office will facilitate contacts with the relevant scientific and regulatory staff within the Agency to address any questions that may arise during development of a medical product, particularly in the run up to submitting a marketing authorisation application.

2.5. How to request SME status

2.5.1. Assignment of SME status

Companies wishing to benefit from SME incentives should visit the SME office section of the EMA website[26] first. Before requesting financial or administrative assistance from the Agency, companies should complete the form 'Declaration on the qualification of an enterprise as a micro, small or medium-sized enterprise (SME)'[27]. This should be submitted to the SME office, together with the most recent annual accounts (audited, if possible) for the applicant enterprise and any linked or partner enterprise, the proof of establishment of the organisation in the EEA (i.e. an EU Member State, Iceland, Liechtenstein or Norway), and details of upstream (i.e. owners of your enterprise's shares or voting rights) and downstream ownership structure (i.e. your enterprise's participation in other companies in terms of shares or voting rights) in the form of e.g. an overview chart of the company structure. Companies are strongly recommended to read 'The new SME definition – user guide and model declaration'[28], published by the European Commission, before completing the form. It is particularly useful in helping to determine whether the applicant company is an autonomous, partner or linked enterprise, and whether it is necessary to complete the annexes to the declaration form. There is also a frequently asked questions[29] document on the SME assignment process published by the SME office.

If the documentation appears to be in order and no clarification is required, the EMA will issue the enterprise with an EMA-SME number. At that point the company may request access to the incentives offered by the SME regulation. The Agency reserves the right to request further information from the company to establish that the SME criteria are met and may, at any time, perform audits as part of its SME programme. The applicant enterprise will be liable to consequences in case of a false declaration.

2.5.2. Newly established or non-EEA enterprises

If your enterprise is newly established and does not have finalised financial reports, estimates should be provided for the reference period declared together with an indication of when the first annual accounts will be available.

[26] http://www.ema.europa.eu Regulatory / Human Medicines / SME Office
[27] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2012/12/WC500135919.pdf
[28] http://ec.europa.eu/enterprise/enterprise_policy/sme_definition/sme_user_guide.pdf
[29] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099978.pdf

For non-EEA companies, there are essentially 2 options to access SME incentives:

- to apply once the company has established a subsidiary in the EEA. For proof of establishment the SME office requires a copy of the certificate of incorporation in the company register. In such cases, the SME declaration can be submitted in the name of the newly established subsidiary with details of the parent company as a 'linked' enterprise, or
- to indirectly benefit from the SME incentives through an EU established SME regulatory consultancy.

SME regulatory consultancies may seek to benefit from the provisions of the SME regulation on behalf of non-EEA based clients only if both they and the client meet the SME criteria (i.e. fall below headcount and financial thresholds). In this case, both the regulatory consultant and the non-EEA based company should submit SME declarations. If successful the regulatory consultant would receive an SME notification and the non-EEA based company would be listed in annex to that notification as an SME client company. An SME regulatory consultant would not be considered eligible if they were acting on behalf of non-SME clients as this would be in contradiction to the objectives of the SME regulation.

2.5.3. Maintenance of SME status

A company's SME status will expire two years after the date of closure of the accounts on which the declaration has been based. In order to extend SME status, companies are advised submit via e-mail an updated SME declaration form (duly signed and scanned) for the company based on the latest approved accounts. It is only necessary to submit supporting accounts and ownership data where one of the following applies:

- changes in ownership structure of the applicant enterprise, its parent company and any linked or partner enterprise where applicable (including acquisition, takeover and merger activity);
- headcount greater than 225;
- annual turnover greater than €42.5 million and balance-sheet total greater than €36.5 million.

The EMA will send out individual reminders for renewal prior to SME status expiry.

In the event that a registered SME is acquired by or merges with another company, the SME office at the EMA should be informed immediately. If the SME criteria are no longer met by the newly formed company, then with effect from the date of the change in ownership, the company will have no further access to the provisions of the SME regulation.

3. Support to medicinal product development

3.1. Classification as a medicinal product

3.1.1. CHMP scientific recommendation as medicinal product to Agency procedures

A medicinal product for human use is defined in EU legislation[30] as:

a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

[30] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001.

b) any substance or combination of substances which may be used 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.

Sponsors developing novel therapies or borderline products may require confirmation that they are eligible to Agency procedures. Regulatory advice on classification is given by the committee for medicinal products for human use (CHMP) and, where appropriate, the European Commission. This advice is provided, free of charge, within 60 days of receipt of a valid request from an applicant.

Further information on this procedure which is handled by the innovation task force (ITF) (see section 3.2) is available on the EMA website[31]. General queries can be sent to ITFsecretariat@ema.europa.eu.

3.1.2. Classification procedure as ATMP

Advanced therapy medicinal products (ATMPs) are defined in legislation[32] as gene therapy, somatic cell therapy and human tissue engineering.

Sponsors requiring clarification as to whether their product is classified as an ATMP can receive confirmation from the committee for advanced therapies (CAT) prior to submitting any application to the Agency. This advice is provided, free of charge, within 60 days of receipt of a valid request from an applicant. The Agency publishes summaries of these recommendations, after deletion of all information of a commercially confidential nature.

For more information SMEs are advised to refer to the procedural advice on classification as an ATMP (EMA/CAT/99623/2009)[33].

3.1.3. Classification as a veterinary medicinal product

A veterinary medicinal product is defined in EU legislation[34] as:

a) any substance or combination of substances presented as having properties for treating or preventing disease in animals; or

b) any substance or combination of substances which may be used in or administered to animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Sponsors developing novel therapies or borderline products may require confirmation that they are eligible to Agency procedures. Queries relating to classification of veterinary medicinal products can be sent to vet.applications@ema.europa.eu.

3.2. Innovation task force

For sponsors developing innovative medicines (e.g. advanced therapies), new technologies (e.g. nanotechnologies), and new scientific approaches (e.g. non-clinical methods and models, biomarkers, -omics, synthetic biology, assay [co-] development, modelling & simulation or novel clinical trial methodology), the innovation task force (ITF) provides a platform to open up an informal dialogue with the Agency for both human and veterinary products. SMEs can approach the ITF and proactively identify scientific, legal and regulatory issues arising from their developments for discussion. The

[31] http://www.ema.europa.eu Regulatory / Human Medicines / Innovation Task Force
[32] Council regulation (EC) no 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.
[33] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500074745.pdf
[34] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001.

scientific discussions are led by experts from the Agency network, working parties and committees, where the best available scientific expertise is represented.

Borderline medicinal products are also included in the scope of the ITF.

The scope of the briefing meetings covers regulatory, scientific and other issues arising from the development of new therapies and technologies, -omics, nanotechnologies and combination borderline products. The meetings are free of charge and aim to facilitate the informal exchange of information and guidance in the development process, complementing and reinforcing existing formal procedures (e.g. scientific advice, ATMP certification).

Further information on how to contact the ITF, including forms for requesting briefing meetings, is available on the EMA website[35].

General queries can be sent to ITFsecretariat@ema.europa.eu.

For innovative veterinary medicinal products, queries can be sent to: vet.applications@ema.europa.eu.

3.3. Scientific advice / protocol assistance

At any stage of development, and irrespective of eligibility to use the centralised procedure for marketing authorisation, sponsors can request scientific advice from the EMA for both human and veterinary medicinal products. SMEs are particularly encouraged to initiate an early dialogue with the Agency, in the form of scientific advice. This helps the sponsor to ensure that the appropriate tests and studies are performed, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing authorisation application. Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the marketing authorisation. Following the Agency's advice, therefore, increases the probability of a positive outcome.

For human medicinal products, scientific advice is given by the EMA's committee for medicinal products for human use (CHMP) on the recommendation of the scientific advice working party (SAWP-H). For veterinary products, it is given by the committee for medicinal products for veterinary use (CVMP) on the recommendation of the veterinary equivalent, the SAWP-V. Both scientific advice working parties have monthly meetings.

Guidance on how to put together a request for scientific advice for human medicinal products[36] and veterinary medicinal products[37] is available on the Agency's website. Detailed information on how to apply, including a template for notifying intent of submission, submission deadlines and details of the programme for EMA-FDA parallel scientific advice are available on the EMA website.

The Agency offers assistance to applicants in putting their scientific advice requests together through free pre-submission meetings. SMEs are strongly recommended to request a pre-submission meeting or teleconference at the time they notify their intent to file the request.

Scientific advice is restricted to purely scientific issues. Regulatory requests should be the subject of separate advice from the EMA and can be sent to the SME office.

[35] http://www.ema.europa.eu Regulatory / Human Medicines / Innovation Task Force
[36] http://www.ema.europa.eu/pdfs/human/sciadvice/426001en.pdf
[37] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004147.pdf

3.3.1. Scope of scientific advice

Scientific advice may be sought on the tests required to support an application for marketing authorisation for a medicinal product (see sections 4.1-4.3 and sections 5.1-5.5) in the areas of:

- quality (chemical, pharmaceutical and biological testing);
- non-clinical/safety (toxicological and pharmacological tests);
- clinical aspects (clinical safety and efficacy);
- data requirements for minor use minor species (MUMS) products in line with the published MUMS guidelines;
- the establishment of new MRLs or extrapolation of existing MRLs for veterinary medicinal products.

Scientific advice for designated orphan medicinal products (applies to medicinal products for human use only. See section 4.4) is called 'protocol assistance' and, in addition to the above, may include questions relating to:

- demonstration of significant benefit within the scope of the designated orphan indication;
- issues addressing similarity/clinical superiority in case other potentially similar orphan medicinal products have market exclusivity in the concerned therapeutic indication.

Guidance on how to seek protocol assistance for designated orphan medicinal products is available on the EMA website.

It is also now possible for sponsors to approach the EMA and National Health Technology Assessment bodies in parallel to discuss scientific advice/protocol assistance. HTAs provide information to decision makers about the clinical effectiveness, cost effectiveness and broader impact of medicines, medical technologies and health systems. Many EU Member States have established HTA systems to support decision makers in their pricing and reimbursement decisions. Sponsors considering such parallel requests are advised to contact the scientific advice secretariat (scientificadvice@ema.europa.eu).

For veterinary medicinal products, scientific advice requests may include questions relating to limited markets (including MUMS applications). Sponsors may request scientific advice on the data requirements for MUMS products in line with the MUMS guidelines on a case by case basis (see section 5.7).

Sponsors can also request advice from the EMA on innovative methods or drug development tools for medicinal products for human use through a voluntary qualification process[38]:

- qualification advice on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted;
- qualification opinion on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.

Sponsors that are intending to seek scientific advice for either human or veterinary products in the EU and the US may consider asking for parallel EMA-FDA scientific advice[39]. In this case, the application is evaluated by both agencies at the same time and the EU and US experts discuss together with a view to reaching the same conclusions.

[38] http://www.ema.europa.eu Regulatory / Human Medicines / Scientific advice and protocol assistance / Novel methodologies / Biomarkers
[39] http://www.ema.europa.eu/htms/human/sciadvice/parallel.htm

3.3.2. Fee reductions for scientific advice

The scientific advice procedure attracts a fee, which varies depending on the scope of the advice. This may deter some companies from seeking advice early on in development, or from making several successive requests. Therefore, access for SMEs to the Agency's scientific advice has been facilitated with a substantial 90% fee reduction. Furthermore, as the scientific evaluation of a marketing authorisation application is more likely to be favourable where scientific advice has been sought from the Agency, in the event of a negative outcome, a conditional exemption of the fee for the application for marketing authorisation will be given to applicants who have requested such advice and who have actually taken it into account in the development of their medicinal product. Further information on the level of fee reductions/deferrals available to SME applicants is available in the document 'Fee reductions/deferrals for micro, small and medium-sized enterprises (SMEs)' (EMA/366526/2005)[40].

For designated orphan medicinal products, scientific advice (or so-called protocol assistance) is free of charge. The Agency also provides free advice on the paediatric development of medicinal products.

In order to support the research and development of veterinary medicinal products for minor species and for rare indications in animals, a programme of free scientific advice for such products has been initiated by the CVMP. Requests for free scientific advice under this initiative, and in accordance with the published criteria[41], should be sent to the CVMP for a decision on the granting of the fee waiver. Scientific advice may also be requested on reduced data requirements for veterinary medicinal products considered to be MUMS/limited market products in accordance with the adopted CVMP guidelines (quality, safety, efficacy and immunologicals).

3.4. Scientific guidelines and position papers

The EMA has streamlined the presentation of scientific guidelines for human and veterinary medicinal products on its website[42]. This compilation supersedes the publication of guidelines for medicinal products by the European Commission in the Eudralex volumes 3 and 7 that had been previously supplemented with further publications or revisions on the EMA website.

Documents which do not fall under the heading of scientific guidelines, such as historical position papers, question-and-answer documents, or general regulatory guidelines can be found on the:

EMA website:

on the 'regulatory and procedural guidance' folder on the 'human medicines' page or for 'veterinary medicines' under 'general guidance'.

and

European Commission website:

in the notice to applicants, vol. 2C and 6C – regulatory guidelines.

[40] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004165.pdf
[41] http://www.ema.europa.eu/pdfs/vet/iwp/37066309en.pdf
[42] Human: http://www.ema.europa.eu Regulatory / Human Medicines / Scientific Guidelines
Vet: http://www.ema.europa.eu Regulatory / Veterinary Medicines / Scientific Guidelines

3.5. Certification for advanced therapy medicinal products (ATMPs)

The certification procedure for ATMPs[43], which is open exclusively to SMEs, provides a mechanism for companies to receive scientific feedback on quality and non-clinical data generated during the course of development. As such, it provides support for companies seeking to attract investors for the continued development of their product or to license out their technology.

The aim of certification is to facilitate dialogue between SMEs and the regulators ideally at an early-stage in development and is complementary to the scientific advice process (see section 3.3). Whereas, scientific advice provides feedback on future development proposals and protocols, certification provides a scientific evaluation of experimental data already generated with the product. Through certification, companies can receive a "snapshot" of their data evaluated to the current review standards for marketing authorisation. Companies can then seek scientific advice on how to resolve any deficiencies that may have been highlighted during the certification assessment (see section 3.3).

An SME can submit an application for certification containing either quality data alone or both quality and non-clinical data at any time during the development of an ATMP. The process can be repeated as development proceeds. The procedure for certification consists of a 90 day review by the CAT with the possibility to request clarifications on the data submitted during the review.

For more information SMEs are advised to refer to the procedural advice[44] and guidance[45] on the EMA website. Any queries can be sent to: AdvancedTherapies@ema.europa.eu.

4. Medicinal product development (human)

The data requirements for an application for marketing authorisation for a human medicinal product are laid down in EU legislation, in particular annex I of directive 2001/83/EC (see sections 1.2 and 1.3). Guidance is available in the scientific guidelines adopted at ICH and EU levels, and in the notice to applicants (NTA)[46] which includes guidance on the common technical document (CTD) (see section 6.6).

An overview of the pharmaceutical, non-clinical and clinical development of a medicinal product for human use is provided in sections 4.1-4.3 below. For detailed information, SME companies should consult the EMA website where all current scientific guidelines are published (see section 3.4).

The SME office monitors applications for marketing authorisation (MAA) submitted to the Agency by SMEs and reports annually on the outcomes[47]. To date, the success rate of SMEs has been below the average for all applicant companies. The need for additional clinical data (module 5) to support the applications is one of the main reasons for refusal or withdrawal of the MAAs. The quality documentation (module 3) has also been found to be a particular problem area for many SMEs. Experience has shown elements of premature filing, evidenced by the number of SMEs, which are seeking scientific advice subsequent to a negative outcome and then re-submitting the MAA once further data has been generated. Moreover, many companies are seeking advice late in development.

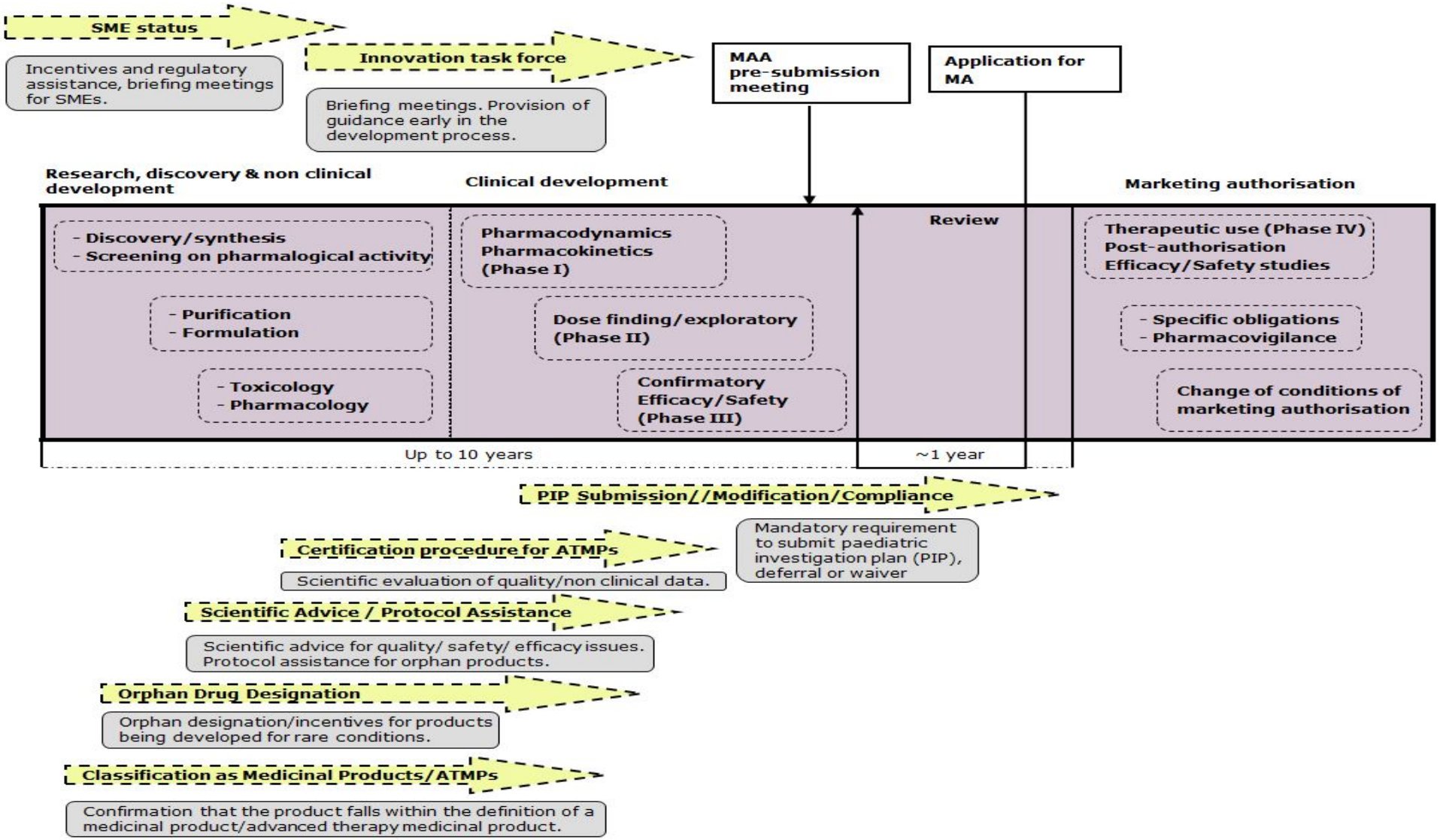
Companies unfamiliar with the EU regulatory approval process are encouraged to approach the SME office to request a briefing meeting to discuss their planned regulatory strategy. To ensure that the appropriate studies are performed and that there are no major objections regarding the study design

[43] Advanced therapy medicine products (ATMPs) are defined in legislation as gene therapy, somatic cell therapy and human tissue engineering.
[44] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500070030.pdf
[45] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070031.pdf
[46] http://ec.europa.eu/health/documents/eudralex/index_en.htm
[47] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000116.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024b9c

at the time of the evaluation of the marketing authorisation application, SMEs are particularly encouraged to seek scientific advice from the EMA (see section 3.3). The importance of opening up an early dialogue with the Agency on all aspects of development, including quality, is underlined.

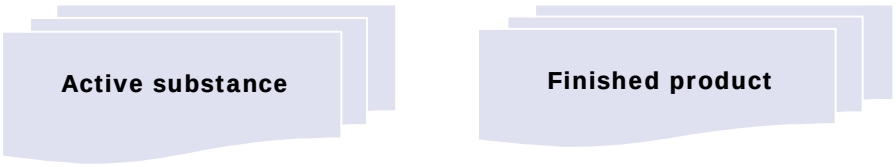
The following chart provides an overview of the various opportunities for dialogue offered to SMEs throughout the development of a medicinal product:

Figure 1: Overview of medicinal product development and opportunities for dialogue with EMA



4.1. Quality

The pharmaceutical quality of a medicinal product (human or veterinary) consists of two main pillars:



The purpose of the pharmaceutical development is to develop a formulation that will be fit for its intended use, that is, to consistently deliver the active substance at the site of action at the required dose and that will be stable throughout its shelf-life.

4.1.1. Active substance (drug substance)

Active substance means a substance with physiological or pharmacological activity, which is responsible for the claimed clinical effect of the product, be it therapeutic, prophylactic or diagnostic. Depending on their source, active substances can be classified as inorganic substances, herbal drugs and herbal preparations, 'chemical' (synthetic or semi-synthetic, or isolated from herbal sources or microorganisms) and biological active substances.

The amount of information to be generated during development depends on whether the active substance is a new substance, being used for the first time in a medicinal product, or an existing active substance (either described in a pharmacopoeia, or not). However in all cases the active substance should be well characterised and manufactured by well-described and adequately controlled manufacturing methods (see section 4.6.1).

For new active substances, applicants are encouraged to apply for an international non-proprietary name (INN) as early as possible in the clinical development. INNs are assigned by the WHO[48], to whom requests should be submitted.

When developing a medicinal product, the following key issues should be addressed with regard to active substances:

General information: Structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. The solid-state properties that might affect the *in vivo* performance are of particular importance. Additionally for proteinaceous biological active substances the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and biological activity should be available.

Manufacture: The manufacturing process should be well described and understood. All critical parameters should be identified and appropriately controlled. It should also be demonstrated that the process can reproducibly produce a substance with the desired quality characteristics. In addition the starting materials, that is all the materials from which the active substance is manufactured, should be evaluated and documented.

[48] http://www.who.int/medicines/services/inn/en/

Biological active substances are often generated by cell substrates (microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the active substance). For cell substrates having a cell banking system, all procedures to generate the master cell bank and the working cell bank(s) should be documented. Characterisation and testing of banked cell substrates should be carried out to confirm their identity, purity, stability and suitability for manufacturing use. Particular attention should be given to potential contamination from adventitious agents (see section 4.1.3).

When there is a change in the manufacturing process of a chemical or biological active substance, it should be ensured that it will not affect the product. For biological active substances in particular, consideration should be given to performing a comparability exercise. If the analytical data are not sufficiently reassuring, additional evidence from bridging non-clinical and clinical studies will be required.

Characterisation: Extensive characterisation is performed in the development phase and, where necessary, following significant process changes. Characterisation is necessary to allow relevant specifications to be established.

The potential for isomerism, identification of stereochemistry, and polymorphism should be evaluated. The purity of a substance is often judged by examining the impurities it contains. Therefore special emphasis should be given to characterising the impurities which arise from the method of manufacture and also those produced on storage, by degradation. Similarly, how impurities are generated should be described. If the level of impurities exceeds certain thresholds specified in the (V)ICH guidelines on impurities[49], their toxicological significance becomes important from a safety point of view. Therefore these impurities have to be 'qualified' (usually with reference to formal toxicology studies) to demonstrate they are safe.

Control of active substance: Specifications are critical quality standards that are based on thorough characterisation and on the mechanistic understanding of how formulation and process factors can impact product performance. Specifications should reflect the characteristics an active substance should have to meet its intended purpose. Conformity with specifications should provide assurance that quality is maintained from the time of release to the end of the shelf-life/re-test period. The acceptance criteria should be established and justified based on data obtained during development, including manufacturing consistency studies, stability studies and lots used in non-clinical and/or clinical studies. The analytical procedures that will be used to test the critical-to-quality attributes should be adequately validated in accordance with (V)ICH guidelines.

Stability: The applicant should study how the quality of the active substance varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. This will allow the definition of practical storage conditions and a 'window of use' called the shelf life/re-test period (during which the substance may be used without further testing).

Submission of information for active substances: There are three ways to present the information relating to the active substance in a marketing authorisation application:

- Full data are presented in the dossier.
- Active Substance Master File (ASMF): An ASMF contains all the necessary information on the active substance and is composed of two separate sections. The "applicant's part" contains the majority of the information (non-confidential) and is available to the applicant. However, in the "restricted

[49] Scientific guidelines for human and veterinary medicinal products:
Human: http://www.ema.europa.eu Regulatory / Human Medicines / Scientific Guidelines
Vet: http://www.ema.europa.eu Regulatory / Veterinary Medicines / Scientific Guidelines

part" the active substance manufacturer can submit detailed information relating to the manufacturing process, controls and validation and this is submitted directly to the competent authorities in order to protect the manufacturer's intellectual property. The concept of the ASMF applies only to "well-defined active substances". It therefore cannot be used for biological active substances, excipients, finished products, container materials, etc.

- Certificate of suitability (CEP): The manufacturer of the active substance may apply to the European pharmacopoeia (Ph. Eur.) secretariat[50] with documentation requesting evaluation of the suitability of the relevant Ph. Eur. monograph for the control of the chemical purity and microbiological quality of their active substance. If a CEP is available from the active substance manufacturer, reference to this is made in the application and no additional information needs to be submitted for those parts of the dossier covered by the CEP. However, additional information might be necessary depending on how the attributes of the active substance affect the finished product performance, for example, particle size, sterility, etc. Manufacturers or suppliers of excipients, herbal products used in the production or preparation of pharmaceutical products or any product with transmissible spongiform encephalopathy (TSE) risk, may also choose to apply for a CEP.

4.1.2. Finished product (drug product)

The key issues that applicants should address during the development of the finished product are summarised below:

Formulation development: When developing a formulation it is important to identify attributes that are critical to the quality of the finished product, taking into consideration its intended usage, route of administration and the specific needs of the intended patient population e.g. paediatrics, geriatrics.

The choice of all the excipients should be justified. Although excipients are usually inactive substances, their safety for the target population (for example, paediatric population, or which species of animal) should be considered.

The potential effect of the physicochemical properties of the active substance (for example, water content, solubility, particle size distribution, polymorphic or solid state form) on the performance of the finished product should be evaluated. Other key issues to be investigated are the compatibility of the active substance with excipients, containers and closures. For combination products, the compatibility of active substances with each other should also be evaluated.

It is highly likely that during the product's development there will be changes in the formulation and manufacturing process. In all cases the differences between the clinical formulations used and the formulation intended to be marketed should be discussed and their equivalence demonstrated (using either *in vitro* or comparative *in vivo* studies, as appropriate).

If the formulation contains a novel excipient, that is, an excipient used for the first time in a medicinal product, or by a new route of administration, then full details of its manufacture, characterisation and control, with cross references to supporting safety data (non-clinical/safety and/or clinical) should be provided. As there can be no confidential master file for excipients, applicants should provide all such information in the application for marketing authorisation.

Microbiological attributes: All parameters relevant to the microbiological attributes of the dosage form should be evaluated. Examples include the selection and effectiveness of preservative systems in products containing antimicrobial preservatives, and, for sterile products, the sterilisation process and

[50] http://www.pheur.org/site/page_628.php

the integrity of the container/closure system for prevention of microbial contamination. The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should also be demonstrated.

Process development: It is important to consider the critical formulation attributes, together with the manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of its components. The manufacturer must have adequate knowledge of the manufacturing process in order to ensure that material and process variability is adequately understood and managed. In general, process development studies should provide the basis for process improvement, process validation and continuous process verification. In some cases, e.g., for complex products, the applicant may decide to perform enhanced development studies over a wider range of material attributes, manufacturing process options and process parameters. These studies coupled with the use of statistical experimental design techniques, risk management principles and on- or at-line analytical methods may lead to a better understanding of the process and the product. Such studies may be used to support real time release testing and more flexible regulatory approaches in setting the operational limits of the process as well potential process changes during the lifecycle of the product. For manufacturing process changes for biological/biotechnological products, the same recommendations as mentioned above (for active substances) apply.

Manufacture - control of excipients and finished product and stability: As with active substances, the manufacturing process used for the finished product should be carefully designed so that it consistently produces product of the intended quality. All critical steps should be identified and controlled with appropriate in-process controls. Batch to batch consistency must be demonstrated using appropriate process validation studies. The usual process validation approach is to manufacture a number of production scale batches to confirm that the process is under control. For non-standard processes (e.g. manufacture of specialised dosage forms, or use of new/highly specialised technologies, as well as non-standard sterilisation methods) the validation data usually need to be provided with the submission. For all other processes these data may be generated in accordance with approved protocols once production starts. It is also possible to follow other validation approaches, e.g., a continuous process verification scheme, provided that this is appropriately justified and supported by adequate development studies.

Appropriate specifications should be set for the excipients and the finished product and validated methods should be used for their testing. The stability of the finished product should be demonstrated throughout its proposed shelf life under the proposed storage conditions. The stability studies should be performed in accordance with the (V)ICH recommendations (storage conditions, duration, etc.) unless otherwise justified. For multiple dose containers, the proposed in-use shelf life should be similarly demonstrated. In all cases the analytical methods that are used to test the product should be stability indicating.

4.1.3. Other specific issues

Adventitious agents: All materials of human or animal origin used in the manufacturing processes of either the active substance or the finished product, or coming into contact with the active substance or finished product during the manufacturing process, should be identified. The risk with respect to potential contamination with adventitious agents of human or animal origin should be assessed.

TSE agents: The current "note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01)[51] should be applied. Suppliers of any substances with a TSE risk used in production or preparation of medicinal

[51] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf

products can apply to the Ph. Eur. for a TSE certificate. Such certificates can then be used by marketing authorisation applicants. (For more information see the EDQM website[52].)

Viral safety: The risk of introducing viruses into the product and the capacity of the manufacturing process to remove or inactivate viruses should also be evaluated.

Other adventitious agents: Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi should be provided.

4.2. Non-clinical development

The non-clinical development consists of three main parts:

Pharmacology | **Pharmacokinetics & Metabolism** | **Toxicology**

The purpose of non-clinical development is to evaluate the pharmacodynamic and toxicity profile prior to initiating clinical studies, to predict potential safety problems at a given exposure and to investigate particular safety aspects as detailed below.

Some of the non-clinical studies need to be performed before administration of first dose to man while others can run in parallel to clinical trials (see figure 1). The summary below outlines the important tests generally required, for comprehensive details please refer to the relevant scientific guidelines (section 3.4). ICH M3[53] and CHMP guidance on first-in-human clinical trials (EMA/CHMP/SWP/28367/07)[54] provide guidance on the non-clinical safety studies required for the conduct of clinical trials.

4.2.1. Pharmacology

This part of the development addresses the pharmacodynamics of a new product in the non-clinical setting.

The pharmacodynamics includes investigation of “primary” pharmacodynamics, which comprises *in vitro* and *in vivo* effects related to the proposed therapeutic indication. There are many established animal models for various conditions. If there are no models available, sponsors should investigate the added value of developing a relevant model. Moreover several novel products react only with human epitopes which may be different in experimental animals. In this case sponsors may consider developing a homologous product which would react with the animal epitope or develop transgene animal models. In addition, investigation of the “secondary” pharmacodynamics (effects other than those related to the proposed therapeutic indications) is required. Safety pharmacology addresses undesired pharmacodynamic effects on specific physiological systems, mainly central nervous, cardiovascular and respiratory

[52] http://www.edqm.eu/site/News_amp_General_Information-164.html
[53] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002720.pdf
[54] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf

systems in relation to exposure in the therapeutic range and above. ICH S7A & S7B provide guidance[55].

Finally it is necessary to investigate pharmacodynamic drug interactions with medicinal products that are likely to be administered for the same condition.

4.2.2. Pharmacokinetics & metabolism

This part of the development comprises studies investigating absorption, excretion, tissue distribution, metabolism and pharmacokinetic drug interactions. The area under the matrix level concentration-time curve (AUC), C_{max} at the expected peak concentration, and C (time) at certain time points after administration are the most commonly used parameters in assessing exposure in pharmacokinetics studies. Other parameters include urinary & faecal excretion, bioavailability, half-life, fraction of unbound drug and volume of distribution.

4.2.3. Toxicology

The following studies should generally be performed during the development.

Single and repeated dose toxicity: The primary goal is to characterise the toxicological profile of the medicinal product following repeated administration. This includes identification of target organs of toxicity, exposure response relationship and potential reversibility of toxic effects. Unless justified, experiments in two species are required one of which should be non-rodent and the duration depends upon the planned human use. Single dose toxicity studies are not required unless this is the planned clinical utility. For products for chronic use in humans, repeated dose toxicity studies of at least six months duration are requested (ICH M3). In addition to investigating toxicity, the kinetics should be investigated in the pivotal repeated-dose toxicity studies (toxicokinetics). The toxicokinetics provide a means of obtaining multiple dose pharmacokinetic data in the test species; the parameters assessed are the exposures (AUC). ICH S3A & S3B provide guidance[56].

Reproductive toxicity: The primary goal is to investigate the effects of the medicinal product on the following steps of reproduction:

- male and female fertility and early embryonic development (to implantation) in one species, usually rats;
- embryo foetal development (development of organs during pregnancy) in two species, one of which should be a non-rodent (usually rabbit);
- prenatal and postnatal development in one species, usually rats.

Juvenile toxicity: For medicinal products intended for paediatric use, possible effects of the product on the ongoing developmental processes in the age group(s) to be treated are taken into consideration. In some instances, studies in juvenile animals are required to allow benefit/risk assessment in these patient populations. Juvenile animal studies should be considered to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials. Serious adverse reactions that may be irreversible are of particular concern. The design of non-clinical studies in juvenile animals will vary depending on the findings observed in adult human studies and previous animal studies. Even if adverse reactions on developing organ(s) can be predicted from adult human or

[55] S7A: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002831.pdf
S7B: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002841.pdf
[56] S3A: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002770.pdf
S3B: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002771.pdf

animal data, studies in juvenile animals might be warranted if there is a need to further address a specific concern for the paediatric population or to establish safety factors. The CHMP guideline on non-clinical testing in juvenile animals (EMA/CHMP/SWP/169215/2005)[57] provides recommendations on such studies (see section 4.5).

Genotoxicity: Genotoxicity tests are *in vitro* and *in vivo* tests designed to detect compounds which induce genetic damage in the DNA directly or indirectly by various mechanisms. The standard battery comprises tests for genotoxicity in bacteria (Ames test), as well as *in vitro* tests for genotoxicity in mammalian cells and *in vivo* test for chromosomal damage (micronucleus test usually in the mouse). Compounds which are genotoxic have the potential to induce cancer and/or heritable defects. Genotoxicity test are required for any product, with the exception of most biological products. ICH S2A and S2B provide guidance[58]

Carcinogenicity: The objectives of carcinogenicity studies are to identify tumorigenic potential in animals and to assess the relevant risk in humans. They are required for pharmaceuticals expected to be administered regularly over a period of at least 6 months and for pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. For pharmaceuticals administered infrequently or for a short duration of exposure (e.g. anaesthetics and radiolabelled imaging agents) carcinogenicity studies are not needed unless there is cause for concern. For anticancer medicinal products carcinogenicity studies are normally also not required.

The carcinogenicity battery consists of two long-term (2-year) studies in the rat and mouse or one long-term study in the rat and one short-term study (6-months) in a transgenic model.

Immunotoxicity: In the context of medicinal product development, it is defined as unintended immunosuppression or enhancement. All new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity. Methods include evaluating parameters of the immune system in the standard repeated dose toxicity studies mentioned above and additional immunotoxicity studies conducted, as appropriate, if there is cause for concern. In case additional specific immunotoxicity studies are required, a generally accepted study design in rodents is a 28-day study with consecutive daily dosing. Endpoints can include functional tests, such as T-cell dependent antibody response, as well as immunophenotyping of leucocyte populations.

Local tolerance: The purpose of these studies is to investigate whether pharmaceuticals are tolerated at sites of the body that may come into contact with the product as a result of its administration in clinical use. Usually one species is required for each type of test (e.g. ocular tolerance and skin toxicity in the rabbit) and the route of administration is guided by the envisaged clinical use. The local tolerance can be specifically evaluated as part of the repeated dose toxicity study or as a specific study (usually single or repeated administration over a number of days).

Environmental risk assessment (ERA): The purpose of ERA, which is required for all medicinal products, is to investigate the potential environmental risk of the medicinal product under development. The first part of the investigation assesses the estimated exposure of the environment to the active substance. Based on an action limit the assessment of environmental risk may be terminated at this stage. Above this limit, the fate of the substance in and the effects on the environment should be investigated in a second phase of investigation. The required tests for fate and effects in the environment include a long-term toxicity study in fish, and tests in daphnia and algae may be required to determine the predicted no-effect concentration. If there are concerns further tests may be required.

[57] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003305.pdf
[58] S2A: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003146.pdf
S2B: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003147.pdf

4.3. Clinical development

The purpose of clinical development is to establish a dose-response relationship, demonstrate the efficacy and establish the safety profile of a medicinal product in a therapeutic indication in order to provide an adequate basis for assessing the benefit/risk relationship to support licensing.

Traditionally clinical development has been often described as consisting of four temporal phases: I – IV. Although these terms are not officially used anymore, they are useful to separate the goals of the different stages of the clinical development. The phase concept is a description of the objectives which are summarised below, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies since for some medicinal products in a development plan the typical sequence will not be appropriate or necessary. Detailed information is available in the ICH E8 'note for guidance on general considerations for clinical trials' (CPMP/ICH/291/95)[59]. For comprehensive details please refer to the relevant scientific guidelines (section 3.4).

4.3.1. Human pharmacology studies (phase I)

This is the initial administration of a new product into humans. Studies in this phase of development do not aim to assess efficacy and may be conducted in healthy volunteer subjects or certain types of patients, e.g. patients with mild hypertension. Due to ethical reasons medicinal products with significant potential toxicity, e.g. cytotoxic compounds used in cancer treatment, are usually studied in patients already in this phase.

The objectives of these studies typically involve one or a combination of the following:

Using both single and multiple administration of increasing doses, initial safety and tolerability is assessed, which helps guide the dose for future therapeutic trials. Preliminary characterisation of absorption, distribution, metabolism, and excretion (pharmacokinetics) is another goal of these initial studies. For many orally administered medicinal products, especially modified release products, the study of food effects on bioavailability is important. Moreover, depending on the product and the endpoint studied, pharmacodynamic studies and studies relating blood levels of the product to response (PK/PD studies) may be conducted in healthy volunteer subjects or in patients. Pharmacodynamic endpoints may include biochemical or physiological parameters, receptor occupancy etc. Although clinical activity is normally not the goal of this first phase, in some cases data may be collected as a secondary objective; for example, when assessing the pharmacokinetics of a sleeping pill it is possible to obtain some results on potential activity (sleep-inducing effect).

4.3.2. Therapeutic exploratory studies (phase II)

The goal of this phase is to explore therapeutic activity in patients. These studies are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population. An important goal for this phase is to determine the dose(s) and regimen for the clinical efficacy and safety trials. Early studies in this phase often utilise dose escalation designs

[59] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf

(see note for guidance ICH E4)[60] to give an early estimate of dose response, whereby an initial low dose is increased until optimal response or until occurrence of adverse events. The dose response relationship for the indication in question can be confirmed in later parallel dose-response design studies. In this phase, therapeutic activity can be explored using endpoints, which can be evaluated in a shorter time period than the actual therapeutic goal. For example, shrinking of the tumour mass in a particular cancer could be a suitable endpoint to assess activity in phase II, but would normally not be sufficient to demonstrate efficacy in phase III, where "hard" clinical endpoints like survival of the patient would be more relevant. When the results of this phase become available, it is decided if it is justified to proceed to the extensive phase III development.

4.3.3. Clinical efficacy and safety (phase III)

The goal is to confirm the preliminary evidence accumulated in the exploratory stage and to establish efficacy and safety. These studies are intended to provide an adequate basis for establishing benefit/risk ratio and marketing approval. Therefore a sufficiently high number of patients must be enrolled (usually several hundred to several thousand) and exposed to the investigational medicinal product for a duration which will provide adequate efficacy and safety data for the envisaged clinical use. Generally for medicines being developed for chronic use studies of at least 6 months duration are required. The studies must generally be controlled, i.e. compare the product under development to placebo (a pharmaceutical preparation containing no active agent, made to look just like the test compound) and/or to active treatment depending on the condition and the product under investigation. In addition the studies must generally be double-blind, i.e. neither the treating physician nor the patient know the treatment administered (test drug, placebo, active comparator). Usually two phase III trials would be required for approval but under specific circumstances one well-conducted large trial may be sufficient. In addition to clinical efficacy, demonstration of safety is the second important goal of this phase. The requirements for investigating the adverse events profile are described in the ICH E 1: 'note for guidance on population exposure: the extent of population exposure to assess clinical safety' (CPMP/ICH/375/95)[61]. Generally, 300-600 patients treated for six months and 100 patients exposed for a minimum of one-year are considered to constitute an acceptable safety database. However, clinical trials before marketing authorisation have limitations to detect rare adverse events. An event occurring in less than 1:1,000 patients will normally not be detected in the pre-marketing phase.

4.3.4. Therapeutic use/clinical utility (traditionally phase IV)

These are studies related to the approved therapeutic indication which are conducted post marketing. Their goal is to gather additional information about the medicinal products benefits, risks and optimal use in the broad population. Commonly conducted studies include additional drug-drug interaction, safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies. Please refer to section 7.2 for further information on Post-Authorisation Efficacy and Safety (PASS/PAES) studies.

4.3.5. Adaptive designs

Traditionally the protocol of a clinical trial is finalised prior to study start and no changes are allowed during the conduct of the study. In some instances, however, studies can be planned with a so-called adaptive design involving design modifications based on the results of an interim analysis during the study. Such a design has the potential to speed up the process of drug development or can be used to

[60] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002834.pdf
[61] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002747.pdf

allocate resources more efficiently without lowering scientific and regulatory standards. For further information, there is a reflection paper[62] on the EMA website.

4.3.6. Clinical trials – notice to applicants

General information

A compilation of legislative and guidance documents in the field of clinical trials, referred to as the 'EudraLex volume 10– clinical trials'[63] has been published by the European Commission and includes guidance on:

- application for starting a clinical trial, to be submitted to the competent authorities of the Member States and the ethics committees;
- guidance on the European clinical trials database (EudraCT database);
- safety monitoring and reporting of adverse reactions arising during clinical trials;
- requirements for manufacturing and import authorisation of investigational medicinal products (IMP);
- qualification of inspectors and inspection procedures;
- the modalities for non-commercial trials;
- recommendation for the trial master file and archiving;
- detailed guidelines on good clinical practice specific to advanced therapy medicinal products[64];
- clinical trial legislation.

EudraCT

EudraCT is a database of all clinical trials initiated in the Community from 1 May 2004 onwards which was established pursuant to article 11 of the clinical trial directive 2001/20/EC.

Sponsors should visit the EudraCT website[65] to access the EudraCT application in order to:

- get a EudraCT number;
- submit a clinical trial application form to the competent authorities and ethics committees.

A clinical trial application consists of administrative information and the scientific data necessary for demonstration of the quality, safety and efficacy of the investigational medicinal product (IMP). With regards to the quality of the IMP, it is anticipated that in the early development stages information on the analytical methods, their validation, the setting of specifications and the stability might be incomplete. For this reason, for human medicinal products, different requirements are set for IMPs to be used in phase I, II and III trials. For further information the 'CHMP Guideline on the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials' (CHMP/QWP/185401/04)[66] should be consulted.

SME companies should be aware that if the final formulation differs from that of the IMP used in earlier clinical trials, the relevance of the earlier material compared to the product tested in later phases

[62] http://www.ema.europa.eu/pdfs/human/ewp/245902enadopted.pdf
[63] http://ec.europa.eu/health/documents/eudralex/index_en.htm
[64] http://ec.europa.eu/health/files/eudralex/vol-10/2009_11_03_guideline.pdf
[65] https://eudract.ema.europa.eu/
[66] http://ec.europa.eu/health/files/eudralex/vol-10/18540104en_en.pdf

should be described. Special consideration should be given to changes in quality parameters with potential clinical relevance, e.g., *in vitro* dissolution rate.

European clinical trials register

The EudraCT database was established as a confidential database serving the EEA regulatory authorities. Subsequent changes to the EU pharmaceutical legislation (article 57 of the regulation (EC) no 726/2004 and article 41 of the paediatric regulation (EC) no 1901/2006) enabled some of the information held in the EudraCT database to be made public. This information is now publicly available through the EU clinical trials register website (EU CTR)[67].

The EU CTR was launched in March 2011 and the information contained therein is extracted from EudraCT. The register allows the public to search for protocol related information on interventional clinical trials for medicines which are authorised in the 27 EU Member States and EEA and also on clinical trials authorised to be carried out outside of the EU where these trials are part of a paediatric investigation plan. Work is ongoing to upgrade the EudraCT database to also satisfy legislative requirements on the entering of results related information on clinical trials.

The guideline and list of fields that are made publicly available are published in chapter V of 'EudraLex volume 10– clinical trials'. Updates on the current status and the development process are available on the EudraCT website.

The EU CTR has also been recognised as a primary registry of the WHO international clinical trials registry platform (WHO ICTRP)[68] in September 2011.

CTFG and voluntary harmonisation procedure (VHP)

The clinical trial facilitation group (CTFG)[69] was established in 2004 to coordinate implementation of the EU clinical trials directive 201/20/EC and provide a forum to discuss and agree on common principles and processes to be applied throughout the European medicines regulatory network. It also promotes harmonisation of clinical trial assessment decisions and administrative processes across the national competent authorities (NCAs).

The CTFG has launched a voluntary harmonisation procedure (VHP) for the assessment of multinational clinical trial applications. The procedure has been set up to ensure the protection of participants as well as the scientific value of clinical trials by harmonising NCAs' processes and practices relating to multinational clinical trials.

The VHP is a tool that may permit applicant companies to achieve through one procedure harmonised and quick approvals of multi-centre clinical trials with trial sites in several EU Member States. VHP accepts electronic submissions only and essentially offers sponsors of multinational clinical trials a one-stop-shop for CTAs. Substantial amendments are also included in the VHP.

Further information on how to apply for clinical trial authorisation through the VHP is available in the CTFG "guidance document for a voluntary harmonisation procedure (VHP) for the assessment of multinational clinical trial applications" (CTFG/VHP/2010).[70] .

A list of official contact points of competent authorities[71] and an overview of the fees[72] charged by different NCAs for submission of different trial types or amendments has been published by the CTFG.

[67] http://www.clinicaltrialsregister.eu
[68] http://apps.who.int/trialsearch/
[69] http://www.hma.eu/78.html
[70] http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-
[71] http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2012_01_CTFG_List_official_contacts.pdf
[72] http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2012_01_CTFG__fees.pdf

Review of EU clinical trials legislation

In July 2012, the European Commission adopted a proposal to simplify the rules for conducting clinical trials in the EU. The new legislative proposal aims to speed up and simplify authorisation and reporting procedures, while maintaining the highest standards of patient safety and robustness and reliability of data. It should also better differentiate the obligations according to the risk-profile of the trial, and improve transparency including on trials done in third countries. The legislative proposal is under discussion in the European Parliament and the Council and is expected to come into effect in 2016. Further information on the proposal is available on the European Commission's website[73].

4.4. Measures for orphan medicines

Orphan designation

'Orphan' medicinal products are those intended to diagnose, prevent or treat life-threatening or very serious conditions that are rare and affect not more than 5 in 10,000 persons in the European Union.

Incentives

- EU incentives available from the EMA for sponsors[74]/pharmaceutical industry developing orphan medicinal products include: a 10 year period of market exclusivity after the grant of a marketing authorisation;
- protocol assistance (scientific advice, see section 3.3);
- fee reductions for certain centralised activities;
- direct access to the EMA centralised procedure for the application for marketing authorisation.

To be eligible for orphan incentives medicinal products should be designated through the Community procedure for orphan designation. Orphan designation may be obtained at any stage of development provided proper scientific justification of the intended use is submitted. The EMA, through its committee for orphan medicinal products (COMP) is responsible for reviewing designation applications and issuing an opinion, which is transformed into a decision by the European Commission.

Guidance on the format and content of applications for designation as orphan medicinal products (ENTR/6283/00)[75] and an application form in annex to guideline[76] are available from the EMA. The designation procedure attracts no fees. Full details on how to apply (including guidance on calculation and reporting of the prevalence and the elements to support medical plausibility and the assumption of significant benefit) are available on the EMA website[77].

To facilitate the application process, for those sponsors which also plan to request orphan designation from the United States Food and Drug Administration (FDA), a common application form[78] for use is both regions is now available on the EMA web-site.

The EMA offers assistance to sponsors on preparation of orphan designation applications through free pre-submission meetings, for more information contact: orphandrugs@ema.europa.eu.

Contrary to the US legislation on paediatric obligations (PREA), orphan-designated medicinal products are not exempted from the obligations of the paediatric regulation in the EU (see below). Sponsors are

[73] For more information on clinical trials: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm
[74] 'Sponsor' means any legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.
[75] http://ec.europa.eu/health/files/orphanmp/doc/2007_07/format_content_orphan_applications_rev3_200707_en.pdf
[76] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/09/WC500003813.doc
[77] www.ema.europa.eu
[78] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/09/WC500003830.doc

therefore encouraged to consider these requirements and discuss them during the pre-submission meeting.

The Agency also provides free advice on the development of orphan medicinal products following designation (see section 3.3).

Orphan marketing authorisation

Prior to the grant of a marketing authorisation the COMP will review the criteria on which the orphan designation has been based. Accordingly, at the time of submission of the application for marketing authorisation, the applicant is asked to submit a report to the orphan section at the EMA demonstrating that the orphan criteria are still met.

In accordance with article 8 of regulation (EC) no 141/2000[79], once a designated orphan medicinal product is authorised in all EU Member States, it is granted a ten year period of market exclusivity. This market exclusivity protects the originator's medicinal product in the authorised 'orphan' therapeutic indication. As such, 'similar' medicinal products will not be granted a marketing authorisation for the same therapeutic indication unless the originator gives consent, is unable to supply sufficient quantities of the medicinal product, or the second applicant demonstrates that although similar, the medicinal product is clinically superior to the originator.

The definitions of 'similar' medicinal product and 'clinically superior', in this context, are laid down in article 3 of Commission regulation (EC) no 847/2000[80].

It is important for SMEs to note when preparing an application for marketing authorisation, that where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the possible 'similarity' with the authorised orphan medicinal product must be addressed in the application for marketing authorisation. If applicable, the applicant must then argue clinical superiority or justify that one of the derogations noted above applies.

The overall judgment of similarity includes an evaluation of the indication, the mechanism of action and the molecular structure.

4.5. Paediatric development

Legislation[81] governing the development and authorisation of medicines for use in children was introduced in the European Union in January 2007.

The overall aim is to improve the health of the children in the EU by increasing the research, development, and authorisation of medicines for use in children. To this end, a system of obligations, incentives and rewards has been put in place. It is imperative that SMEs familiarise themselves with these requirements early on in development, to avoid delays in the regulatory approval process.

System of obligations, incentives and rewards

The obligations and rewards listed below apply irrespective of the route of authorisation of the medicinal product (centralised vs. non-centralised).

[79] *Official Journal L 18, 22/1/2000 p. 1–5*
[80] *Official Journal L 103, 27/4/2000 p. 5-8*
[81] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

For unauthorised medicinal products: Since 26 July 2008, there is an obligation to submit the results of studies conducted in compliance with an agreed paediatric investigation plan (PIP)[82] in order to have a valid application for a new marketing authorisation. Decision on a waiver may be issued by the EMA when such paediatric development is not needed or not appropriate. Deferrals may also be granted: this means that the initiation or completion of some or all the studies in the agreed PIP can occur after the company has applied for marketing authorisation in adults, in the same condition(s). However, even for deferred measures a binding date of initiation (where indicated) and completion needs to be identified.

For non-orphan medicinal products, the reward for conducting the paediatric development in compliance with a paediatric investigation plan is a six-month extension of the supplementary protection certificate[83], provided that the results are included in the product information and that authorisation is obtained in all EU Member States.

Applications under certain types of legal bases (for example generic, biosimilar, homoeopathic and traditional herbal products, or those applied for as "well-established use") are exempt from these requirements.

For orphan medicinal products: The obligations for unauthorised medicinal products outlined above also apply. The reward for orphan medicinal products is two years of market exclusivity in addition to the existing 10-year exclusivity awarded under the EU orphan regulation, if the results are included in the product information.

For authorised patented medicinal products: As of 26 January 2009, the requirements described above also apply when seeking a variation or extension of an existing marketing authorisation for a new indication (including paediatric), new route of administration or new pharmaceutical form, when the product is covered by a supplementary protection certificate or a qualifying patent. As with new medicines, waivers or deferrals may also be granted, and the reward is a six-month extension of the supplementary protection certificate (or two years for orphan products). The PIP and/or waiver must cover all existing and new indications, pharmaceutical forms and routes of administration.

For "off-patent" medicinal products: Medicines not covered by a supplementary protection certificate or a qualifying patent, and developed solely for paediatric use and with an appropriate formulation can benefit from a specific type of marketing authorisation — the paediatric-use marketing authorisation (PUMA) — which benefits from 10 years of data protection. The obligations referred to above concerning the PIP also apply.

It is important for SMEs to be aware that there is a requirement to agree the paediatric investigation plan (PIP) early on in development of the medicinal product, by the time human pharmacokinetic studies are completed in adults. The Agency, through its paediatric committee (PDCO) is responsible for assessing the content of paediatric investigation plans, waivers and deferrals and formulating an opinion, which is subsequently transformed into a decision.

The PIP covers the timing and measures required to obtain a paediatric indication, with an age appropriate formulation if relevant, in all paediatric subsets affected by the condition.

The EU Commission has issued guidance on the format and content of applications for agreement or modification of a paediatric investigation plan, requests for waivers or deferrals, the operation of the compliance check and the criteria for assessing significant studies (2008/C 243/09)[84]. Further details

[82] The PIP is a research and development programme, aimed at ensuring that the necessary data are generated to determine the conditions in which a medicinal product may be authorised for the paediatric population.
[83] With reference to Council regulation (EEC) no 17687/92 of 18 June 1992.
[84] http://ec.europa.eu/health/files/eudralex/vol-1/com_2008_jo243/com_2008_243_en.pdf

on how to apply, including a questions & answers document, are available on the Agency's website[85]. There is no fee associated with these applications.

The Agency offers the possibility of a pre-submission meeting (via teleconference) for SMEs in advance of the submission of their application for a PIP and/or deferral and/or waiver. This is particularly recommended for (potential) orphan medicinal products.

The Agency also provides free advice on the development of medicinal products for paediatric indications (see section 3.3).

Once the PDCO has agreed the PIP, the applicant company will need to comply with the plan, as the agreed PIP is binding to the company. As the development of the medicinal product progresses, there may be a need for companies to apply for a modification of the agreed PIP when it is no longer appropriate or unworkable. If the medicinal product is approved in the EU, annual reports on the deferred measures in the PIP must be submitted to the Agency.

A compliance check may be necessary before any application for marketing authorisation (even for an adult indication) can be considered valid, if there was no deferral for at least one of the studies agreed in the PIP, or after the due date of initiation or completion of a study/measure. The same applies to some regulatory applications for authorised products, as described above. To avoid delays in the validation process, applicants are invited to submit a compliance check request to the PDCO at least 3 months in advance of submission of the regulatory application.

Other key measures in the paediatric regulation

These include:

- An increased transparency of paediatric information. In particular, the results of paediatric studies should be submitted to the competent authorities on an ongoing basis within 6 months of their completion. Protocols and results of paediatric clinical trials performed both inside the EU and anywhere else in the world, if the trial is part of a paediatric investigation plan, will be publicly available in the EU clinical trials register (EU CTR, see section 4.3.6).
- Community funding for research on off-patent medicines delivered through the EU framework programme; this funding, should cover the development of off-patent medicinal products with a view to submit an application for a paediatric-use marketing authorisation. In order to ensure that funds are directed into research of medicinal products with the highest need in the paediatric population, the PDCO adopts a priority list of off-patent products for which studies are required.
- Measures to increase the robustness of pharmacovigilance (safety monitoring) for medicines;
- an EU inventory of the therapeutic needs of children to focus research, development and authorisation of paediatric medicines;
- an Agency-based EU network of investigators and trial centres to conduct research and development on medicines for children (EnprEMA).

SMEs are advised to familiarise themselves with the requirements by visiting the Agency and Commission[86] websites. Questions relating specifically paediatric requirements or more generally to the paediatric regulation may be submitted to: paediatrics@ema.europa.eu.

[85] http://www.ema.europa.eu Regulatory / Human Medicines / Paediatric Medicine / Application Guidance
[86] http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm

4.6. GMP/GDP/GCP/GLP

4.6.1. Good manufacturing practice (GMP)

Good manufacturing practice (GMP) is defined as that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. The principles and guidelines for GMP are stated in two directives: directive 2003/94/EC[87] for medicinal products and investigational medicinal products for human use and directive 91/412/EEC[88] concerning veterinary medicinal products. Compliance with these principles and guidelines is mandatory within the European economic area. Interpretation of these requirements is provided in 'EU guidelines to good manufacturing practice - medicinal products for human and veterinary use'[89] published by the European Commission. This guide to GMP consists of detailed guidelines (part I and part II) which are supplemented by a series of annexes specific for certain types of product or topics.

A public site of EudraGMDP[90] is also available to get restricted information on manufacturing authorisation and GMP certificates.

The manufacture of medicinal products in the EU is undertaken subject to the holding of a manufacturing and importation authorisation. Such authorisation is also required for imports from third countries into a Member State. The national competent authorities of Member States enter the manufacturing and importation authorisations that they issue into EudraGMDP.

Following a site inspection, a certificate of good manufacturing practice is issued to the manufacturer if the outcome of the inspection demonstrates that the manufacturer complies with the principles of GMP, as provided by Community legislation. The national competent authority of Member States who performs the inspection shall enter the GMP certificates information into EudraGMDP. If the outcome of the inspection is that the manufacturer does not comply with the principles of GMP, the information is also entered into EudraGMDP.

Manufacturing authorisation holders are obliged to comply with GMP requirements for medicinal products and to use as starting materials only active substances manufactured in accordance with the guidelines on GMP for starting materials. The falsified medicines directive 2011/62/EU[91] introduced strengthened provisions for the supervision of active substance manufacture, which includes an obligation for national competent authorities to register active substance manufacturers, importers and distributors established on their territories. These registrations will be publicly accessible through an extension of the EudraGMDP database which is expected in 1st quarter of 2013. Finished product manufacturers will be required to verify that the active substances used in their products are manufactured according to GMP through audits of the manufacturer. The detail of how the assessment of non-EEA countries will be carried will be established by the European Commission through implementing measures. Further information is available on the European Commission's website[92].

The occurrence of shortages of medicines due to manufacturing and quality problems has increased over the past few years. To report potential shortages of medicines caused by GMP-compliance or quality problems, SMEs should e-mail qdefect@ema.europa.eu and clearly indicate if the problem

[87] *Official Journal L 262, 14/10/2003 p. 22 - 26*
[88] *Official Journal L 228, 17/8/1991 p. 70 - 73*
[89] http://ec.europa.eu/health/documents/eudralex/index_en.htm
[90] http://eudragmp.EMA.europa.eu/inspections/displayWelcome.do
[91] *Official Journal L 174, 1/7/2011, p. 74-87*
[92] For more information on falsified medicines: http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm

identified is likely to lead to a shortage. For further information, a reflection paper (EMA/590745/2012)[93] has been published on the EMA website.

4.6.2. Good distribution practice (GDP)

The wholesale distribution of medicinal products is an important activity in the integrated supply chain management. Good distribution practice (GDP) should be implemented through a quality system operated by the distributor or wholesaler. The aim of GDP is to ensure that that the level of quality of authorised medicines, determined by GMP, is maintained throughout the distribution network to retail pharmacists and others selling medicines to the general public. The quality system should also ensure the right products are delivered to the right addressee within a satisfactory time period. A tracing system should enable any faulty products to be found and there should be an effective recall procedure. The principles of GDP are stated in directive 92/25/EEC and guidance on good distribution practice of medicinal products for human use has been published in a Commission guideline 94/C 63/03. This guideline has been recently revised and published for public consultation. The finalised revised guideline is due for publication in January 2013.

In order to strengthen the supervision by regulatory agencies of the supply chain for medicinal products for human use, the falsified medicines directive 2011/62/EU[94] introduced stricter obligations for wholesale distributors and brokers. An extension of the publicly accessible EudraGMDP database to include wholesale distribution authorisations issued by Member States, GDP certificates and registration of active pharmaceutical ingredient (API) manufacturers, importers and distributors is expected in the 1st quarter of 2013.

4.6.3. Good clinical practice (GCP)

Good clinical practice (GCP) concerning human medicinal products is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected; consistent with the principles that have their origin in the declaration of Helsinki, and that the clinical trial data are credible. Requirements for the conduct of clinical trials in Europe including GCP and GMP and inspections of these, have been implemented in the clinical trial directive (directive 2001/20/EC)[95] and GCP directive (2005/28/EC)[96]. This regulatory framework is published in the 'Eudralex – volume 10 clinical trials guidelines'[97]. Clinical trials included in any marketing authorisation application in the EU are legally required to be conducted in accordance with GCP.

For clinical trials of veterinary products, Europe has adopted the Veterinary ICH GL9 'guideline on good clinical practices' CVMP/VICH/595/98[98], which provides guidance on the design and conduct of all clinical studies of veterinary products in the target species. It is directed at all individuals and organisations involved in the design, conduct, monitoring, recording, auditing, analysis and reporting of clinical studies in target species and is intended to ensure that such studies are conducted and documented in accordance with the principles of GCP. The annex to directive 2001/82/EC[99] as amended sets out conditions for the conduct of clinical trials included in applications for marketing authorisation.

[93] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf
[94] *Official Journal L 174, 1/7/2011, p. 74-87*
[95] *Official Journal L 121, 1/5/2001, p. 34–44*
[96] *Official Journal L 91, 9/4/2005, p.13-19*
[97] http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm
[98] http://www.EMA.europa.eu/pdfs/vet/vich/059598en.pdf
[99] *Official Journal L 311, 28/11/2001, p. 1-66*

4.6.4. Good laboratory practice (GLP)

Good laboratory practice (GLP) defines a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which non-clinical studies are planned, performed, monitored, recorded, reported and archived. Detailed information about GLP can be found on the linked websites of the organisation for economic co-operation and development (OECD)[100] and the European Commission[101] (see directive 2004/9/EC[102] and 2004/10/EC[103]). For human products, annex I to directive 2001/83/EC[104] as amended indicates that safety tests reported in marketing authorisation applications should be performed in compliance with the principles of GLP. For veterinary products, in accordance with annex I to directive 2001/82/EC[105] as amended the same principles apply, as well as for tests carried out for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

4.6.5. Inspections

GMP, GCP and GLP Inspections may be requested in connection with an application for a marketing authorisation at national or a Community level. The sites to be inspected (manufacturing and quality control sites and/or non-clinical study sites and/or clinical trials sites) should be "inspection ready" at the time of submission of the application and throughout the assessment.

The EMA is responsible for the co-ordination of pre-authorisation GMP, GCP, GLP and pharmacovigilance inspections in connection with the granting of a marketing authorisation by the Community. All information concerning centralised inspections activities can be found on the inspection section[106] of the external EMA web page. Additional information is available in the EMA pre-submission guidance (see section 6.1).

5. Medicinal product development (veterinary)

The data requirements for an application for marketing authorisation for a veterinary medicinal product are laid down in EU legislation, directive 2001/82/EC, as amended by Commission directive 2009/9/EC on the Community code relating to medicinal products for veterinary use. Further guidance is available in the scientific guidelines adopted at VICH and EU level as well as in the notice to applicants[107]. In addition, many veterinary products are subject to the requirements of individual European pharmacopoeia monographs. Foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues which might constitute a health hazard to the consumer. Therefore, no marketing authorisation for any veterinary medicinal product intended for food-producing animals can be granted in the European Union unless maximum residue limits (MRLs) have been established for any pharmacologically active substance contained in the product. The

[100] http://www.oecd.org/env/glp
[101] http://ec.europa.eu/enterprise/sectors/chemicals/documents/specific-chemicals/laboratory-practice/index_en.h
[102] *Official Journal L 50, 11/2/2004, p. 28–43*
[103] *Official Journal L 50, 20/2/2004, p. 44–59*
[104] *Official Journal L 311, 28/11/2001, p. 67–12*
[105] *Official Journal L 311, 28/11/2001, p. 1-66*
[106] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000161.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024592
[107] http://ec.europa.eu/health/documents/eudralex/vol-6/index_en.htm

establishment of MRLs is a Community procedure regulated by regulation (EC) no 470/2009[108]. The requirement for MRLs applies to the active principle(s) but also excipients or adjuvant, if they are pharmacologically active.

An overview of the studies required to establish the safety and efficacy of a medicinal product for veterinary use as well as MRLs is provided in sections 5. For detailed information, SME companies should consult volume 8 of the rules governing medicinal products in the European Union[109] the EMA website where all current scientific guidelines are published (see section 3.4).

To ensure that the appropriate studies are performed and that there are no major objections regarding the study design at the time of the evaluation of the marketing authorisation application, SMEs are particularly encouraged to seek scientific advice from the EMA (see section 3.3).

5.1. Maximum residue limits (MRL)

In order to establish or modify MRLs for residues of veterinary medicinal products in foodstuffs of animal origin, an application should be submitted to the Agency for evaluation by the CVMP. Procedural and administrative information e.g. dossier contents are explained in volume 8 of the rules governing medicinal products in the EU and EMA procedural guidance (SOP/V/4051)[110].

Safety and residue studies have to be conducted and submitted with an MRL application. These studies are intended to demonstrate that no harmful residues result in foodstuffs of animal origin from the normal conditions of use of the substance under consideration. Details on the studies to be conducted can be found on the EMA website[111].

Safety studies should include pharmacological, toxicological and other relevant studies such as studies on potential microbiological activity. The toxicological studies include repeat-dose toxicity, reproduction and developmental toxicity, genotoxicity and carcinogenicity testing, and testing of other effects, e.g. delayed neurotoxicity, where appropriate due to the type of substance.

The safety studies are required to establish the acceptable daily intake (ADI). The ADI is an estimate of the substance and/or its residues, expressed in terms of µg or mg per kg body weight that can be ingested daily over a lifetime without any appreciable health risk to exposed individuals.

Residue studies, including pharmacokinetics tests, are required to determine the nature and actual level of residues and their elimination in the target animal and in particular edible tissues (muscle, fat or fat and skin, liver and kidney) and other food products of animal origin (milk, eggs or honey). Therefore, investigations of the elimination of residues from edible tissues and other food products of animal origin should be conducted. In order to allow the validation of the residue depletion studies and for the purpose of residue control validated analytical methods for identifying and measuring the residues in the tissues and food products should be developed.

On the basis of the safety and residue studies MRLs are established for the animal species for which the veterinary medicinal product is intended to be used (e.g. cattle). Where extension of existing MRLs to other animal species (e.g. extension to pigs) or specific food commodities (e.g. milk, eggs) is considered, only residue studies with regard to the relevant target species should be performed, because the ADI is the same regardless of the indications.

Modifications of the MRLs can be requested, if new safety studies allow the modification of the ADI, or if new residue studies allow amendment of the MRLs.

[108] *Official Journal L 152, 16/6/2009, p. 11–22*
[109] http://ec.europa.eu/health/documents/eudralex/vol-8/index_en.htm
[110] http://www.ema.europa.eu/pdfs/vet/sop/4051SOP.pdf
[111] www.ema.europa.eu Regulatory / Veterinary Medicines / Scientific Guidelines

At the end of the evaluation process the CVMP adopts an opinion, which is then submitted to the European Commission for adoption by the standing committee. Depending on the conclusions a pharmacologically-active substance may be included in table 1 (allowed substances) or table 2 (forbidden substances) of Commission regulation (EU) no 37/2010[112]. Table 1 (allowed substances) of the regulation includes substances for which MRLs, including provisional MRLs, have been established, and substances for which it was concluded that consumer safety could be ensured without the need to establish MRLs. Table 2 (forbidden substances) includes substances for which no safe limit could be established or for which there were insufficient data to allow a recommendation for inclusion of the substance in table 1. Specific questions on MRLs can be addressed to: MRL@ema.europa.eu.

5.2. Quality

A common quality section, covering both medicinal products for human use and veterinary use, has been provided in this guide for ease of reference (see section 4.1).

5.3. Safety

The safety of a product has to be demonstrated through “safety” studies, and for products intended for food-producing species also with “residue” studies. This part of development should address safety for the target animal (companion animals or food producing species), consumer safety, user safety and the environmental impact of the product.

Safety studies investigate the active substance(s) and excipients, if relevant. The research should focus both on the pharmacology (pharmacodynamics and pharmacokinetics) and toxicology.

The pharmacodynamic studies should take into account tests in experimental and target animals. The pharmacokinetic studies should investigate the absorption of active substance, its distribution, metabolism and excretion in animals.

Toxicology studies should assess single and repeated dose toxicity, tolerance in the target species, reproduction and developmental toxicity, genotoxicity and carcinogenicity. Tests on other effects such as immunotoxicity, dermal or eye irritation, neurotoxicity and antimicrobial properties might also be needed depending on the veterinary medicinal product. For products for food-producing animals many of the safety studies required for marketing authorisation will have been provided in the preceding MRL application.

An assessment of the user safety should be conducted, evaluating the risks for the persons that may be exposed to the product (pet owners, veterinarians, farmers, etc.) based on the safety studies conducted and considering the potential exposure.

An environmental risk assessment is required for all applications. The environmental risk assessment is conducted in two phases. In phase I an exposure driven screening is conducted to determine if the product leads to an extensive exposure of the environment. In most cases only data already available in the dossier are required. If, based on the conclusions of the phase I assessment, an in depth environmental risk assessment become necessary, specific investigations on the effects and fate in environment e.g. studies on effects on aquatic organisms and biodegradation, will be required (phase II assessment).

Residue studies to establish a withdrawal periods should be carried out if the product is intended for use in food producing animals. These studies should include research on pharmacokinetics in the target

[112] *Official Journal L 15, 20/1/2010, p. 1–2*

species following administration by the intended route and take into account the edible tissues muscle, fat or fat and skin, liver and kidney, as well as milk, eggs or honey, as appropriate.

5.4. Efficacy

The efficacy of a product can be demonstrated with “pre-clinical” and “clinical” studies.

Preclinical studies should investigate the pharmacology, dose selection, tolerance in the target animal species and resistance development, if relevant. Usually these studies are undertaken in healthy animals, although some studies may also involve diseased animals.

Pharmacology studies should investigate the pharmacodynamics and pharmacokinetics (absorption, distribution, metabolism, excretion) relevant for the application i.e. for the proposed indication, dosage, route of administration and target species.

The pre-clinical studies should address the dose selection; this is usually done with dose determination (titration) studies. In the absence of such studies, e.g. for certain product classes or indications where such studies cannot be performed or would not provide adequate data, a justification for the proposed dose should be provided including references to other appropriate studies (e.g. dose confirmation/field studies).

Tolerance in the target species should usually be demonstrated by target animal tolerance studies using multiples of the recommended daily dose over an extended time period. In addition and/or in cases where such classical studies cannot be conducted (e.g. for ethical reasons), this should be justified and other appropriate studies such as field or dose determination studies should be provided.

For antibiotic or anthelmintic products, the possibility of resistance development should be investigated in view of the potential impact on the efficacy of the product.

Clinical studies are performed in diseased animals, under laboratory and, ideally, under field conditions. These studies should provide a clear picture of the therapeutic efficacy and safety of the product, in comparison with other product(s) authorised for the same indication (positive control) or untreated animals (negative control). Field trials should include sufficient animal numbers and should usually be conducted in Europe with the final product formulation using the proposed dose, route and duration of administration. They should take into account different climatic/animal husbandry systems, especially for products such as anti-infectives and anthelmintics.

5.5. Immunologicals

Due to the widespread use of bovine serum in many immunological veterinary medicinal products (IVMPs), specific measures concerning the prevention of the transmission of animal spongiform encephalopathies may be required (see section 4.1.3).

The testing for extraneous agents is particularly relevant for IVMPs and due note should be taken of the relevant guidelines concerning this issue. Annex I to directive 2001/82/EC, as amended and the Ph. Eur. monographs on vaccines and immunosera for veterinary use (0062 0030) requires the testing of immunological veterinary medicinal products for potential contaminants. Further guidance is available on the EMA website[113].

If the IVMP contains or consists of genetically modified organisms (GMOs), as defined by directive 2001/18/EC, the requirements of article 31 (2) of regulation EC no 726/2004 on the authorisation of veterinary medicinal products which contain or consist of GMOs should be fulfilled.

[113] www.ema.europa.eu Regulatory / Veterinary Medicines / Scientific Guidelines / Immunologicals / General

Various tests and/or field studies should be conducted to show the potential risks from the product under the proposed conditions of use including target animal safety. For live vaccines, the assessment should focus on the potential shedding by vaccinated animals, the risk to unvaccinated animals or any other species and the potential of the strain used to revert to virulence.

Various tests and/or field trials should be conducted to confirm efficacy of the product in relation to all claims made for the product with regard to the properties, effects and use.

5.6. GMP/GDP/GLP/GCP

A common GMP/GDP/GLP/GCP section, covering both medicinal products for human use and veterinary use, is provided in this guide for ease of reference (see section 4.6).

5.7. MUMS products

The data requirements for products classified as intended for MUMS/limited markets by CVMP may be more flexible and are decided on a case by case basis in accordance with the published MUMS guidelines[114] on quality, safety, efficacy, and immunologicals. Products are authorised in accordance with directive 2001/82/EC as amended, but data requirements can be discussed with the regulatory authorities in advance of any submission or by requesting scientific advice on the dossier requirements. The MUMS/limited market policy is published on the Agency website along with the template for requesting classification by CVMP. Specific questions may be sent to VetMUMSapplications@ema.europa.eu.

6. Application for centralised marketing authorisation

6.1. Access to the centralised procedure

The centralised procedure is mandatory for certain types of human medicinal products such as those developed by certain biotechnological processes, advanced therapy medicinal products, designated orphans, and those containing new active substances for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, auto-immune diseases, other immune dysfunctions and viral diseases.

The centralised procedure may also be used on a voluntary basis for other medicinal products containing a new active substance, or medicinal products which constitute a significant therapeutic, scientific or technical innovation or that the granting of a Community marketing authorisation would be in the interests of patients at EU level. It is also an option for certain medicinal products intended for paediatric use, or for generics of reference medicinal products authorised through the centralised procedure or nationally via mutual recognition or the decentralised procedure. Further guidance on the mandatory (EMA/CHMP/121944/2007)[115], and optional scope of the centralised procedure is given in the pre-submission questions & answers[116] on the EMA website.

The centralised procedure is mandatory for veterinary products developed by certain biotechnological processes and for medicinal products intended primarily for use as performance enhancers. The centralised procedure may be used on a voluntary basis for products containing a new active substance, other innovative products, veterinary products for which the granting of a Community

[114] www.ema.europa.eu Regulatory / Veterinary Medicines / Availability (Minor Uses/Minor Species)
[115] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004085.pdf
[116] www.ema.europa.eu Regulatory / Human Medicines / Pre-authorisation /Q&A: Innovative Products

marketing authorisation would be in the interests of animal health at EU level, and immunological products for the treatment of animal diseases subject to EU prophylactic measures.

Regardless of whether the product falls into the mandatory or optional scope, an 'eligibility request' should always be submitted using the 'pre-submission request form' template together with relevant additional justification in annex (e.g. draft SmPC, and for optional scope the justification for eligibility). The applicant should address the documents by email to CPeligibility@ema.europa.eu or vet.applications@ema.europa.eu respectively.

EMA recommends providing the eligibility request preferably, at the earliest, 18 months before submission of the marketing authorisation application (MAA) and, at the latest, 7 months before the MAA is filed with the EMA, at which point it may be submitted together with the "letter of intent to submit".

For veterinary applications eligibility for the centralised procedure may be checked at any time however a letter of intent (i.e. official notification that an applicant will submit an eligible application) should be made at least 6 months in advance of any submission date. Following discussion at CHMP or CVMP, the EMA will inform the applicant of the outcome of the eligibility procedure. Further guidance on how to request access to the centralised procedure, is given in the EMA pre-submission guidance (EMA/339324/2007)[117] on the EMA website.

6.2. Selection of rapporteur/co-rapporteur

For any scientific evaluation in the centralised procedure a 'rapporteur', and if relevant a 'co-rapporteur' will be appointed from the members of the CHMP/CVMP or the alternates. A (co-) rapporteur from the pharmacovigilance risk assessment committee (PRAC) will also be appointed for all new medicinal products for human use and for advanced therapy medicinal products a (co)rapporteur will also be appointed by the committee for advanced therapies (CAT). The role of the (co-)rapporteur is to perform the scientific evaluation and to prepare an assessment report for the relevant committee according to an agreed timetable.

The appointment of the rapporteur/co-rapporteur is made on the basis of objective criteria, which will ensure the provision of objective scientific opinions and will allow the use of the best and available expertise in the EEA in the relevant scientific area.

The appointment process for rapporteur/co-rapporteur is usually initiated at the CHMP/CVMP meeting following the receipt of the 'pre-submission request form' (intent to submit MA) and their request to assign rapporteurs, which should optimally be provided **seven months** before the intended MAA submission date. Such appointment can be but is not always connected to a possible earlier request for eligibility for assessment via the centralised procedure (see section 6.1). Further guidance on the appointment of rapporteur and co-rapporteur for human medicinal products (EMA/151751/2010)[118] and veterinary medicinal products (EMA/CVMP/468877/2009)[119], is given on the EMA website.

If the intended application is deemed to be admissible, the EMA will inform the applicant of the names of the (co-)rapporteur(s) appointed and will provide information on the dossier requirements of the committee members.

The rapporteur and co-rapporteur will select the experts of their assessment teams from the list of European experts[120] accessible through the EMA website.

[117] www.ema.europa.eu Regulatory / Human Medicines / Pre-authorisation / Q&A: Innovative Products or Regulatory / Veterinary Medicines / Pre-authorisation / Q&A: Innovative Products
[118] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004163.pdf
[119] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005241.pdf
[120] www.ema.europa.eu About Us / Who We Are / European Experts

6.3. (Invented) Name of products evaluated via the centralised procedure

Medicinal products authorised via the centralised procedure will have the same name across the European economic area (EEA). The name of the medicinal product may be either an invented name, or a common name or scientific name accompanied by a trademark or the name of the marketing authorisation holder

To ensure that the proposed name of the product is acceptable for all Member States and does not create a public-health concern or potential safety risks, the EMA/CHMP has set up a group, the name review group (NRG), to perform reviews of proposed (invented) names for medicinal products for human use.

In particular, the invented name of a medicinal product:

- should not be liable to cause confusion in print, handwriting or speech with the invented name of an existing medicinal product;
- should not convey misleading therapeutic or pharmaceutical connotations;
- should not be misleading with respect to the composition of the product;
- should not be similar to an existing INN;
- should not contain an existing INN stem (as per WHO INN stem location recommendations).

For veterinary medicinal products, the CVMP is responsible for checking the proposed invented name according to the above criteria.

Provided that the medicinal product is eligible for evaluation under the centralised procedure, the applicant should inform the EMA of the proposed (invented) name(s) for their medicinal product at the earliest 18 months prior to the planned submission date of the marketing authorisation application.

When proposing an (invented) name, it is crucial that the applicant follows the EMA guidelines (CPMP/328/98[121]and CVMP/328/98)[122] bearing in mind the paramount criteria of 'potential safety risk'.

For medicinal products for human use, the proposed (invented) names are sent to every NRG contact point nominated by each EU-Member State (Norway and Iceland included) and the European Commission (EC) for review. They are discussed at the NRG meeting considering the objections, concerns and comments received on grounds of safety. The conclusions are presented to the subsequent plenary CHMP meeting, after which the applicant is informed of the outcome.

For veterinary medicines, the names are sent to the contact points nominated by each EU-Member State (Norway and Iceland included) for review. Objections are then discussed at the CVMP meeting, after which the applicant is informed of the outcome.

Invented names accepted by the NRG will remain valid for an initial period of 3 years. If the MAA is not filed during this period, the applicant should seek reconfirmation from the NRG for the re-use of the name at least 3 months before the expiry date even if it is to be used for the same product profile.

Further information on how to submit (invented) name(s) for review, including the request form for completion, can be found in the pre-submission guidance on the EMA website[123].

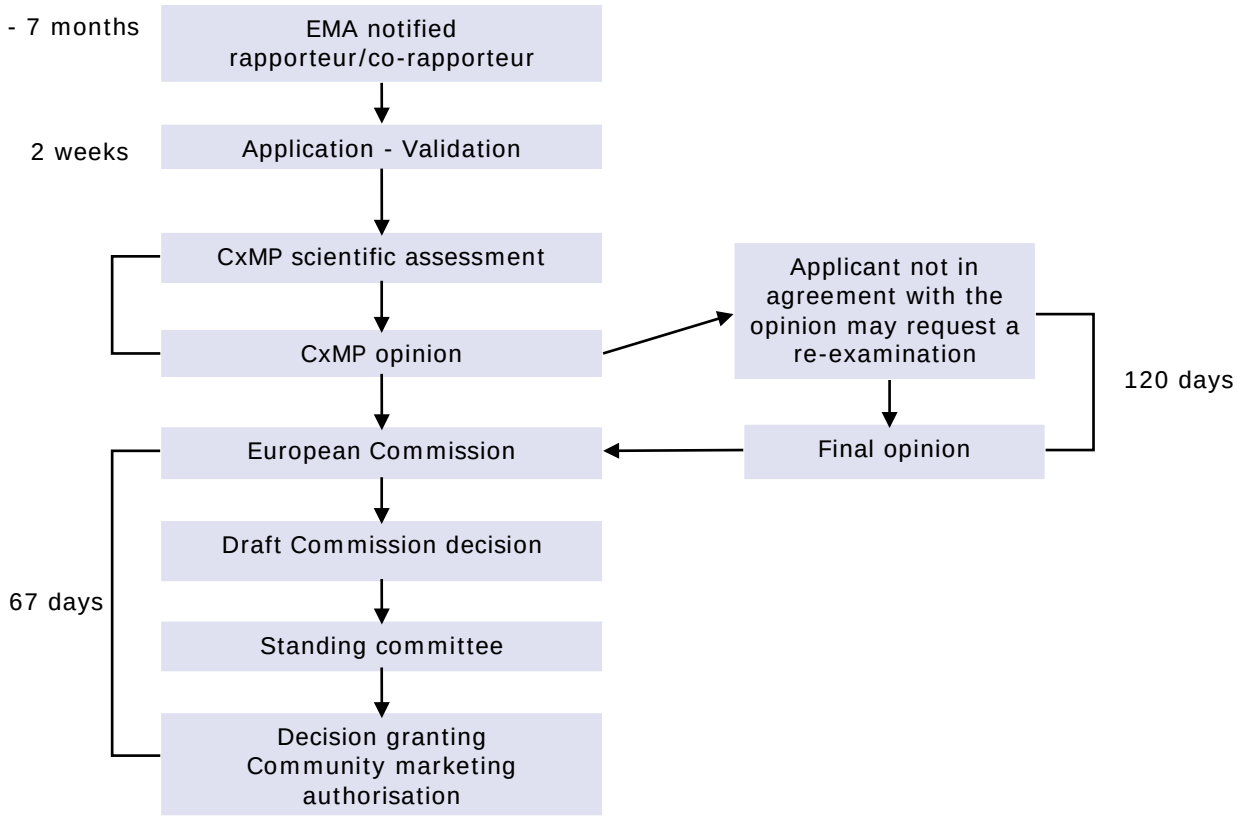
[121] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004142.pdf
[122] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500005231.pdf
[123] www.ema.europa.eu Regulatory / Human Medicines / Pre-authorisation / Q&A: Innovative Products or Regulatory / Veterinary Medicines / Pre-authorisation / Q&A: Innovative Products

6.4. EMA contact point in the centralised procedure

An **EMA 'product team'** is set up for each human medicinal product intended to be submitted through the centralised procedure. The Product Team consists of a **product team leader (PTL)** and product team members (PTM) nominated by the EMA. For veterinary products there is a single **project manager (PM)** for each product. The applicant is notified of the appointed PTL or PM.

The PTL or PM, in co-operation with the rapporteur and co-rapporteur, will ensure that the applicant is kept informed of all issues relating to the application. The PTL or PM will serve as the main liaison person between the EMA, the rapporteur, the co-rapporteur and the applicant.

Figure 2 - Overview of the centralised procedure



6.5. EMA pre-submission meeting

When preparing the submission of a marketing authorisation application, applicants have the opportunity to meet the EMA to discuss procedural or regulatory issues in relation to the upcoming submission, and to establish contacts with the EMA staff that will be involved with the application. Experience has shown the usefulness of these “pre-submission meetings”, even where the applicant has experience with the centralised procedure. Applicants are therefore strongly advised to request such a meeting. Guidance on pre-submission meetings with the EMA can be found in the EMA pre-submission guidance for human[124] and veterinary[125] products on the EMA website.

Pre-submission meetings are free of charge and should take place approximately 6-7 months prior to the anticipated date of submission of the application. A completed pre-submission meeting request

[124] www.ema.europa.eu Regulatory / Human Medicines / Pre-authorisation / Q&A: Innovative Products
[125] www.ema.europa.eu Regulatory / Veterinary Medicines / Pre-authorisation / Q&A: Innovative Products

form for human or veterinary medicines detailing the topics for discussion should be sent to the EMA: to pa-bus@ema.europa.eu for human products and to vet.applications@ema.europa.eu for veterinary applications.

6.6. Compilation of the application dossier

As explained in section 1.2, data generated from pharmaceutical tests, non-clinical and clinical tests and trials with the medicinal product concerned, as well as other information required by the EU legislation, need to be provided to the EMA and all CHMP/CVMP members for evaluation.

The application dossier for medicinal products for human use must be presented in accordance with the **EU-CTD (common technical document)** presentation outlined in volume 2B of the notice to applicants[126] published on the Commission website. The CTD is an internationally agreed format for the preparation of a well-structured application to be submitted to regulatory authorities in the three ICH (International Conference on Harmonisation) regions of Europe, USA and Japan. The CTD gives no information on the content of a dossier, but provides for a harmonised format of presentation of the necessary data to support the application in accordance with the legal/scientific requirements of each region.

The EU-CTD is organised in five modules: module 1 contains the specific EU administrative and prescribing information. The structure of modules 2, 3, 4, and 5 is common for all regions and will contain the high level summaries and quality, non-clinical and clinical documentation respectively.

For veterinary medicinal products the application dossier should be presented in accordance with volume 6B of the notice to applicants[127] published on the Commission website.

For the product information (SmPC, labelling and package leaflet texts), the EMA provides the applicant with a template of what must be included in these documents. The latest version of these templates for human and veterinary medicines are available on the EMA website[128].

All applications need to be submitted in **English**. Detailed information on the submission requirements for the EMA, (co-)rapporteur, and CHMP/CVMP members are given in the EMA pre-submission guidance[129] on the EMA website.

For medicinal products for human use, the EMA has implemented electronic-only submission of applications for marketing authorisation with electronic Common Technical Document (e-CTD) as the required format. Since the 1st January 2010, eCTD has been the only acceptable electronic format for all applications and all submission types. Non-eCTD electronic applications are no longer a valid format for submission. The latest version of the ICH M2 eCTD specification can be found on the ICH website[130], and the current version of the eCTD EU module 1 specification can be found in volume 2B of the notice to applicants[131]. Further detailed practical guidance on eCTD submissions is also available in the TIGes harmonised guidance[132] for eCTD submissions in the EU.

Applicants should submit only 1 full electronic copy of the MAA, including the applicant's part of the active substance master file, if any, to the Agency on CD-ROM or DVD, together with 1 original, signed paper copy of the cover letter providing information as to the origin and nature of the application (& incorporating the summary table template).

[126] http://ec.europa.eu/health/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf
[127] http://ec.europa.eu/health/files/eudralex/vol-6/b/vol6b_04_2004_final_en.pdf
[128] www.ema.europa.eu Regulatory / Human Medicines / Product Information / Product Information Templates or Regulatory / Veterinary Medicines / Product Information / Product Information Templates
[129] www.ema.europa.eu Regulatory / Human Medicines / Pre-authorisation / Q&A: Innovative Products or Regulatory / Veterinary Medicines / Pre-authorisation / Q&A: Innovative Products
[130] http://www.ich.org
[131] http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm
[132] http://esubmission.ema.europa.eu/

In January 2013, the EMA launched an eSubmission gateway to submit centralised eCTD applications for marketing authorisation for human medicines to the Agency instead of sending CDs/DVDs via mail. The web client is a free web based tool which is mainly designed for applicants with low transmission volumes, such as SMEs. Applicants can register for the eSubmission web client on the EMA eSubmission website[133].

For medicinal products for veterinary use electronic only submissions are now accepted. A guideline[134] prepared by the expert sub group (made up of representatives from national competent authorities, the EMA and industry) exists on the specifications for provision of an electronic submission for a veterinary medicinal product vet version 1.0 – October 2009-Rev.1. The guideline provides a specification for the folder structure ("the granularity") to be used in a basic electronic submission to be known as "VNees". Additional guidance is available in a questions and answers document on electronic submissions of veterinary dossiers[135].

6.7. Submission and validation of the application dossier

Target dates for submission for human[136] and veterinary medicinal products[137] are published on the EMA website. If the original indicated submission date cannot be met, the applicant should immediately inform the EMA, rapporteur and co-rapporteur. A delayed submission can have consequences for already planned activities of the assessment teams of the rapporteurs and co-rapporteurs.

The EMA will check if the application meets all relevant legal and procedural EU requirements ('validation'), before the start of the scientific evaluation. Applicants should be aware that for medicinal products for human use a compliance check for paediatric requirements may be necessary, (see section 4.5). The EMA will issue an invoice on the date of the notification of the administrative validation to the applicant, and fees will normally be payable within 45 days of the date of the said notification. For SME applicants, the fee payment may be deferred (see section 2.3).

6.8. Evaluation of the application

Once the application is validated, the EMA starts the evaluation procedure at the monthly starting date published on the EMA website. The EMA will ensure that the **evaluation is finalised within 210 days** (less any clock-stops for the applicant to provide a response to questions from the CHMP/CVMP).

The procedure can be **summarised** as follows:

In the first evaluation phase, the rapporteur and co-rapporteur prepare assessment reports on the application within 80 days (85 days for veterinary products). The assessment reports are sent to all other CHMP/CVMP members for comment and to the applicant for information. Following discussion of the assessment reports, the CHMP/CVMP adopts a "list of questions", identifying 'major objections' and/or 'other concerns', which will be sent to the applicant by day 120. The CHMP/CVMP may consult scientific advisory groups (SAGs) in connection with the evaluation of specific types of medicinal products or treatments, to which the committee may ask for expert's views on a number of points. Scientific advisory groups are established by the relevant committee. They consist of European experts selected according to the particular expertise required on the basis of nominations from the CHMP/CVMP or the EMA.

[133] http://esubmission.ema.europa.eu/index.htm
[134] http://esubmission.ema.europa.eu/doc/Guideline%20-%20minor%20amendment%20February%202010.DOC
[135] http://esubmission.ema.europa.eu/tiges/vetesub.htm
[136] www.ema.europa.eu Regulatory / Human Medicines / Pre-authorisation / Submission Dates
[137] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004957.pdf

The rapporteur and co-rapporteur then assess the applicant's responses (second evaluation phase), submit their joint assessment for discussion to the CHMP/CVMP and, taking into account the conclusions of this debate, prepare a final assessment report which also includes the draft SmPC, labelling and package leaflet. The CHMP/CVMP will adopt such report together with a list of outstanding issues if necessary. Based on the content of the list of outstanding issues, an oral explanation with the applicant might be planned. Once the evaluation is completed within the 210 days, the CHMP/CVMP adopts a favourable or unfavourable opinion on whether to grant the authorisation.

A more detailed **standard timetable** for the evaluation of an application in the centralised procedure is provided below:

DAY	ACTION
1	Start of the procedure
80 (85 Vet)	Receipt of the assessment report(s) from rapporteur and co-rapporteur(s) by CHMP/CVMP members and EMA. Sent to applicant for information only.
100	Rapporteur, co-rapporteur, other CHMP/CVMP members and EMA receive comments from members of the CHMP/CVMP.
115	Receipt of draft list of questions (including the CHMP/CVMP recommendation and scientific discussion) from rapporteur and co-rapporteur.
120	CHMP/CVMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA. Clock stop.

The applicant is expected to respond within the timeframe agreed by the CHMP/CVMP from the date of receipt of the questions, which is usually 3 months for human medicinal products. Applicants may request an additional 3-month period by writing to the CHMP chairman outlining their reasons. For veterinary procedures the standard timeframe for response is 6 months, which may be extended upon justified request. If the applicant is unable to respond within the timeframe, then careful consideration should be given to withdrawing the application and resubmitting, if necessary after obtaining scientific advice, when the full information is available.

Further guidance on the response time for procedures relating to human medicinal products is provided in the EMA guidance (EMA/75401/06)[138] on the EMA website.

DAY	ACTION
121	Submission of the applicant's responses, including revised SmPC, labelling and package leaflet texts in English. Restart of the clock.

After receipt of the responses, the following standard timetable applies:

DAY	ACTION
150 (160 Vet)	Joint response assessment report from rapporteur and co-rapporteur received by CHMP/CVMP members and the EMA. Sent to applicant for information only.
170	Deadline for comments from CHMP/CVMP members to be sent to rapporteur and co-rapporteur, EMA and other CHMP/CVMP members.

[138] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005056.pdf

DAY	ACTION
180	CHMP/CVMP discussion and decision on the need to adopt a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation. Clock stop.

Applicants should normally respond (or prepare for an oral explanation) within one month. In exceptional circumstances an extension may be granted if scientifically justified.

DAY	ACTION
181	Restart of the clock and oral explanation (if needed).

Information on how oral explanations are conducted (CPMP/2390/01)[139], is available on the EMA website.

At the conclusion of the oral explanation, representatives of the applicant will be invited to leave and the CHMP/CVMP will discuss and provide a preliminary recommendation on the acceptability of the application. The applicant will be informed of the trend at CHMP/CVMP level at the end of the scientific discussion ahead of any formal vote to conclude the evaluation process.

DAY	ACTION
By 210	Adoption of CHMP/CVMP opinion + CHMP/CVMP assessment report (and timetable for the provision of product information translations)

The EMA will prepare a "summary of opinion" (for favourable as well as unfavourable opinions) in liaison with the applicant. Such summaries will be published on the EMA website[140] after the adoption of the CHMP/CVMP opinion.

If an applicant decides to **withdraw** its application before an opinion is adopted, the EMA will make this public on its website together with the relevant assessment report.

Evaluation of the risk management plan by the PRAC for human medicines

Applicants are required to submit a risk management plan at the time of marketing application and keep it updated during the lifecycle of the product. The RMP will be subject to review by the pharmacovigilance risk assessment committee (PRAC) in parallel to the CHMP review.

For more information on the RMP, please refer to GVP module V and the EMA website (see also section 7.2).

Evaluation of advanced therapy medicinal products by the CAT

For advanced therapy medicinal products (ATMPs) the scientific evaluation is carried out primarily by the committee for advanced therapies (CAT), which prepares the draft opinion on the quality, safety and efficacy for final approval by the CHMP. For this reason, a slightly different timetable applies to ATMP applications.

For more information on the ATMPs evaluation procedure, please refer to the following guidance: EMA/630043/2008[141].

[139] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004673.pdf
[140] www.ema.europa.eu Find Medicine / Human Medicines / Pending EC decisions or Find Medicine / Veterinary Medicines / Pending EC decisions
[141] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500070340.pdf

6.9. Re-examination of the CHMP/CVMP opinion

The applicant may notify the EMA/CHMP/CVMP in writing of their intent to request a re-examination of the CHMP/CVMP opinion within 15 days of its receipt (after which if such a request is not made, the opinion becomes final). Upon receipt of the notification of intent, the CHMP/CVMP will appoint a new set of (co)rapporteur to re-examine its opinion. The detailed grounds for the re-examination request must be forwarded to the EMA **within 60 days** after receipt of the opinion. The applicant may also request review by the relevant scientific advisory group (SAG).

At the end of the re-examination procedure the CHMP/CVMP will adopt a final opinion either confirming its previous opinion or changing that opinion on the application. If considered necessary, an oral explanation can be held within this 60 days' timeframe, as well as the consulting of the SAG. No clock-stops apply to this procedure.

For further guidance on the re-examination procedure for human medicinal products and CHMP timetable for assessment (EMA/CHMP/50745/2005)[142], refer to the EMA website. For veterinary medicinal products please refer to the veterinary procedural advice (EMA/CVMP/2128/2007-Rev1)[143].

For ATMPs, please refer to the following guidance: EMA/CHMP/50745/2005[144].

6.10. Decision-making process

After adoption of the CHMP/CVMP opinion, the EMA has 15 days to forward its (final) opinion to the Commission. This is the start of the "decision-making process", whereby the CHMP/CVMP Opinion will be turned into a legally binding Commission decision for all Member States and the applicant.

The Commission decision granting a marketing authorisation to the medicinal product concerned includes the agreed SmPC, conditions for use, labelling and package leaflet texts (product information). The Commission decision is legally binding on all Member States, the product information must, therefore, be provided in all Community languages. The translations of the product information are normally provided by the applicant five days after adoption of the CHMP/CVMP opinion.

Further details on the handling of translations (EMA/5542/02)[145] are available on the EMA website. For SME applicants, the EMA will provide translations of product information (summary of product characteristics, label and package leaflet and relevant annexes) into EU official languages. The translations will be reviewed by the Member States before transmission to the Commission (see section 2.3.1).

During the decision-making process, the Commission services check that the marketing authorisation complies with Community law, consulting various Commission directorates-general. In addition, the Commission consults the standing committee, which consists of representatives of all EU Member States. The opinion of the standing committee will normally be given by written procedure.

The Commission prepares a draft Commission decision within 15 days. Member States have 22 days to forward their written observations on the draft decision to the Commission. Within this time-limit, Member States must inform the Commission whether they approve the draft, reject it, or abstain. Any Member State failing to respond within the time-limit to express its opposition or intention to abstain from voting is deemed to have approved the draft.

[142] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004024.pdf
[143] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005252.pdf
[144] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004024.pdf
[145] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004182.pdf

The Commission will take a final decision within 15 calendar days after the end of the standing committee phase. The decision will be sent to the applicant and published in the EU official journal.

The Community marketing authorisation for the medicinal product will be granted in **67 days after adoption** of the final CHMP/CVMP opinion.

Once the Community marketing authorisation is granted, the EMA will publish the CHMP/CVMP assessment report on the medicinal product which includes the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature. This document is called the **European public assessment report (EPAR**). The EPAR includes a summary, in all EU languages, written in a manner that is understandable to the public. EPARs[146] and their summaries are published on the EMA website.

A marketing authorisation for a medicinal product is generally valid for five years. There is an exception when a conditional marketing authorisation for human medicinal products has been granted (see section 6.11.2). The marketing authorisation may be renewed after five years on the basis of a re-evaluation by the EMA/CHMP/CVMP of the benefit-risk balance of the product, upon application by the holder at least six months before expiry. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Commission decides on the basis of the CHMP/CVMP recommendation that due to justified grounds relating usually to pharmacovigilance that there is a need to proceed with one additional five-year renewal.

6.11. Early access to the EU market

6.11.1. Accelerated assessment

In order to meet the expectations of patients as well as animal owners and to take account of the increasingly rapid progress of science and therapies, it is possible to obtain a marketing authorisation via an 'accelerated assessment procedure' (that is, within up to **150 days instead of 210 days**) for products which are of major public or animal health interest, in particular from the viewpoint of therapeutic innovation.

The applicant should notify their intent to request an accelerated assessment procedure as part of the "letter of intent" (see section 6.1). The request itself for accelerated assessment can be submitted any time prior to the submission of the marketing authorisation application. The applicant's request needs to be duly substantiated. It should be sent to the PTL, (co-)rapporteur, all CHMP members for human products and to the PM, (co-)rapporteur and all CVMP members for veterinary medicinal products.

For further details on the documentation required to substantiate a request for accelerated assessment, and on the reduced timetable, refer to the EMA guidance on the procedure for accelerated assessment for human medicinal products (EMA/419127/05)[147] and veterinary medicinal products (EMA/32995/06)[148] published on the EMA website.

6.11.2. Conditional marketing authorisation (human medicines only)

In addition to 'accelerated assessment', in order to meet unmet medical needs of patients and in the interests of public health, the CHMP can recommend the grant of marketing authorisations on the basis of less complete data than is normally required. In such cases, the granting of a marketing authorisation is **subject to certain specific obligations** to be reviewed annually ('conditional marketing authorisation').

[146] www.ema.europa.eu Find medicine / Human Medicines (Veterinary Medicines) / European Public Assessment Reports
[147] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004136.pdf
[148] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005266.pdf

This may apply to medicinal products used in seriously debilitating or life-threatening diseases, emergency situations in response to public health threats, or products designated as orphan medicinal products.

A conditional marketing authorisation can be granted where the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all of the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide comprehensive clinical data;
- unmet medical needs will be fulfilled;
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Conditional marketing authorisations are **valid for one year**, on a renewable basis. The holder will be required to complete ongoing studies or to conduct new studies to confirm that the risk-benefit balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

The granting of a conditional marketing authorisation allows medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and ensures that additional data on a product are generated, submitted, and assessed.

For further guidance on the criteria for conditional marketing authorisation, justifications to be provided and the procedure to be followed, refer to the implementing regulation (EC) no 507/2006[149] on the Commission website and to guidance (EMA/509951/2006)[150] published on the EMA website.

6.11.3. Marketing authorisation under exceptional circumstances

In exceptional circumstances, a marketing authorisation can be granted subject to a requirement for the applicant to introduce **specific procedures, in particular concerning the safety** of the product ('marketing authorisation under exceptional circumstances'). Continuation of the authorisation will be linked to the annual reassessment of these procedures.

This can apply in cases where the applicant can show that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information.

For further guidance on the conditions and procedures for the granting of a marketing authorisation under exceptional circumstances, refer to the EMA guidance for human medicinal products (EMA/357981/2005)[151] published on the EMA website.

[149] *Official Journal L 92, 30/3/2006 p. 6- 9*
[150] http://www.EMA.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004908.pdf
[151] http://www.EMA.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf

6.12. Marketing of the medicinal product in the Community

The marketing authorisation holder is legally obliged to inform the EMA of the dates of the actual marketing of the product in the respective Member States, taking into account the various presentations authorised. Marketing authorisation holders must also notify the EMA if the product, or any of its presentations, ceases to be marketed in any of the Member States, either temporarily or permanently. Such notification should normally be notified to the EMA no less than two months before the marketing interruption.

Any authorisation, which is not followed by the **actual marketing in at least one Member State in the Community within three years** after authorisation, will cease to be valid (so-called sunset clause). Similarly, when a product previously marketed in the Community is no longer actually present on the market of any of the Member States of the Community for three consecutive years, the authorisation will cease to be valid. However, the Commission in exceptional circumstances may grant exemptions from these provisions on duly justified public health grounds.

For more details on this provision, refer to the 'list of questions and answers' on this topic included in the EMA post-authorisation guidance[152] on the EMA website.

7. Risk management and pharmacovigilance

Pharmacovigilance, or the surveillance of the safety of a medicinal product during its life on the market, is extensively regulated by EU directives and regulations. The EMA is co-ordinating pharmacovigilance at EU level. EU legislation requires Member States to establish national pharmacovigilance systems to collect and evaluate information on adverse reactions to medicinal products or their side effects and to take appropriate action where necessary. It also requires marketing authorisation holders to report suspected adverse reactions to the authorities in certain formats and within specified timeframes. Applicants and marketing authorisation holders are also required to provide competent authorities with a description of their pharmacovigilance system and, where appropriate, of product-related risk management systems.

When a medicinal product is first authorised, the information available comes from experience in non-clinical testing and clinical trials. During the evaluation its potential risks are weighed against its potential benefits based on what is known about the medicinal product at that time. Once it is placed on the market and used in a wider population, more information on its benefits and risks becomes available. Pharmacovigilance systems are designed to collect and continuously evaluate this information. If a medicinal product's overall risk/benefit balance changes significantly for any reason, it may become necessary to vary, withdraw or suspend its use.

New pharmacovigilance legislation (Regulation (EU) no 1235/2010 and Directive 2010/84/EU), adopted by the European Parliament and European Council in December 2010, has been effective since July 2012. It has significant implications for applicants and holders of European Union marketing authorisations. Further information is detailed in the questions & answers document (EMA/228816/2012) on the EMA website.

[152] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500003981.pdf

Pursuant to the revised pharmacovigilance legislation, the EMA together with the Member States has drawn up good pharmacovigilance practices (GVP), which are a new set of guidelines for the conduct of pharmacovigilance in the EU. The GVP modules replace volume 9A of the rules governing medicinal products in the EU for medicinal products for human use (see section 7.1).

Volume 9B of the rules governing medicinal products in the European Union should be consulted in relation to medicinal products for veterinary use (see section 7.6).

7.1. Good pharmacovigilance practices (GVP)

Good pharmacovigilance practices (GVP) apply to marketing-authorisation holders (MAHs), the Agency and medicines regulatory authorities in EU Member States. They cover medicines authorised centrally via the Agency as well as medicines authorised at national level.

The guidance on GVP contains 16 modules, each of which covers one major process in pharmacovigilance:

Module I: pharmacovigilance systems and their quality systems

- Establishment and maintenance of quality assured pharmacovigilance systems for MAHs, competent authorities and EMA, according to ISO general principles.

Module II: pharmacovigilance system master file (PSMF)

- Requirements for the PSMF, including its maintenance, content and associated submissions to competent authorities, from July 2012, during the transition period[153] and after 2015.

Module III: pharmacovigilance inspections

- Planning, conduct, reporting and follow-up of pharmacovigilance inspections in the EU and the role of the different parties involved.

Module IV: pharmacovigilance audits

- Planning and conduct of legally required audits, and the role, context and management of pharmacovigilance audit activity.

Module V: risk management systems

- Modular approach to risk management, aimed at characterising the safety profile of a medicinal product, and planning and implementing risk minimisation and mitigation activities.

Module VI: management and reporting of adverse reactions to medicinal products

- Obligations of competent authorities, MAHs and EMA regarding the collection, data management and reporting of suspected adverse reactions associated with medicinal products in the EU.
- The reporting of emerging safety issues or suspected adverse reactions occurring in special situations.

Module VII: periodic safety update report (PSUR)

- Preparation, submission and assessment of PSURs and publication of PSUR-related documents.

Module VIII: post-authorisation safety studies (PASS)

- Transparency, scientific and quality standards of non-interventional PASSs conducted by MAHs.

[153] Q&A on Transitional Arrangements: http://ec.europa.eu/health/files/pharmacovigilance/2012-07_qa_transitional_en.pdf

- Procedures whereby a competent authority may impose an obligation to conduct a clinical or non-interventional study and the impact on the risk management system.

Module IX: signal management

- Structures and processes for signal management and their application in the setting of EU pharmacovigilance.

Module X: additional monitoring (draft/released for consultation)

Module XI: public participation in pharmacovigilance (under development)

Module XII: continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication (under development)

Module XIII: for incident management refer to module XII

Module XIV: international collaboration (under development)

Module XV: safety communication

- Communication and coordination of safety information in the EU.

Module XVI: tools, educational materials and effectiveness measurement for risk minimisation (under development)

Each GVP module should be consulted for further information on general pharmacovigilance requirements for medicinal products for human use.

In addition to the module chapters, GVP will, in future, contain chapters covering product- or population-specific considerations (e.g. on vaccines) will be released for public consultation. The GVP webpage is updated regularly.

7.2. Some of the recent changes in pharmacovigilance

This section highlights some of the important changes stemming from the 2010 pharmacovigilance legislation. A comprehensive overview of all the changes brought about by the new legislation can be found on the EMA website[154].

Establishment of the PRAC

The pharmacovigilance risk assessment committee (PRAC) has been established within the EMA to provide scientific expertise in all matters relating to pharmacovigilance and to finalise pharmacovigilance assessments and recommendations on the safety of medicines at European level.

Pharmacovigilance system master file (PSMF)

MAHs are now required to maintain a PSMF related to one or more products. The PSMF should be permanently available for submission or inspection by the national competent authority within seven days of a request. It should 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 (QPPV) operates. This file may be also stored in electronic form. The PSMF replaces the detailed description of the pharmacovigilance system (DDPS).

The applicant should submit electronically in the extended EudraVigilance medicinal product dictionary (XEVMPD) information on the PSMF location using the agreed format for an extended EudraVigilance

[154] www.ema.europa.eu Regulatory / Human Medicines / Pharmacovigilance / 2010 Pharmacovigilance Legislation

product report message (XEVPRM). The XEVMPD will then assign a unique code (EVCODE) to the master file location, which can be noted in the application. The PSMF is not part of the MA dossier and is maintained independently from the MA. The MAA contains only a reference to the location and a summary of the applicant's pharmacovigilance system. A list of the locations where PSMFs are kept and contact information for pharmacovigilance enquiries will be published by the EMA.

GVP module II provides guidance on the requirements for the PSMF, including its maintenance, content and associated submissions to the competent authorities.

Risk management plan (RMP)

Requirements for the EU-RMP have been reinforced in the new legislation. The RMP is a stand-alone document which summarises what is known about the safety of the product and discusses how the applicant/MAH will monitor and investigate further the safety profile of the product, and manage the risks associated with it. Updated guidance on the RMP is provided in GVP module V. Additional guidance on the format (i.e. integrated format template[155] as well as modular templates to facilitate reuse across regulatory submissions) is available on the EMA website.

All applicants submitting an initial MAA are required to submit an RMP in the application dossier. An RMP (or an update, if one already exists) is also required where there is an application involving a significant change to an existing marketing authorisation or at the request of the Agency or national competent authority. Once a product has an RMP it needs to be updated throughout the life-cycle of the product. Summaries of the RMPs will be made public by the Agency.

SMEs are advised to contact the competent authorities to discuss the RMP in advance of its submission.

Post-authorisation safety and efficacy studies (PASS/PAES)

The ability to require and enforce PASS/PAES studies has become part of the Agency's toolkit for improving the benefit-risk monitoring of medicines. A PASS is a study of an authorised medicine which identifies, characterises or quantifies a safety hazard, confirms the safety profile of the medicine, or gauges the effectiveness of risk management measures during its lifetime. A PAES aims to clarify the efficacy for a medicine on the market including efficacy in everyday medical practice. Such studies will provide information to support regulators in decision-making on the safety and benefit-risk profile of a medicine.

Guidance is on PASS is provided in GVP module VIII. A delegated act is under preparation by the European Commission which will outline the situations where PAES may be required.

Electronic submission of information on medicinal products under article 57(2)

MAHs are required to submit electronically to the Agency information on all medicines authorised or registered in the EU pursuant to article 57(2) of regulation (EC) 726/2004. The XEVMPD data-entry tool, also known as EVWEB (see section 7.5), should be used to submit the information.

The data required are:

- (Invented) name of the medicinal product;
- details of the marketing authorisation holder – name and address;
- details of the marketing authorisation and the status

[155] www.ema.europa.eu Regulatory / Human Medicines / Pharmacovigilance / Guidance

- pharmacodynamic properties - ATC code(s) for the medicinal product ;
- a description of the therapeutic indications – medical concepts coded in MedDRA;
- the qualitative and quantitative composition;
- the pharmaceutical form(s);
- a description of the excipients;
- a description of the medical device(s) for combined advanced therapy medicinal product in accordance with regulation (EC) no 1394/2007 as applicable
- the posology and method of administration - route(s) of administration;
- whether the medicinal product is authorised for the treatment of children;
- an electronic copy of the latest approved summary of product characteristics;
- name, address and contact details of the Qualified Person Responsible for Pharmacovigilance (QPPV);
- contact e-mail and phone number for pharmacovigilance enquiries.

Only the contact information for pharmacovigilance enquires (e-mail and phone) will be made public by the Agency.

Periodic safety update reports

Guidance on the revised content and format of a PSUR has been published in GVP module VII. PSURs should present a critical analysis of the risk-benefit balance of the product taking into account new or emerging safety information in the context of cumulative information on risk and benefits. Detailed listings of individual cases observed are no longer included, as these will have already been reported in EudraVigilance.

Once a medicinal product is authorised and marketed, PSURs have to be submitted immediately upon request and at the following time-points, unless other requirements have been laid down as a condition for the granting of the marketing authorisation: at least every six months during the first two years following the initial placing on the EU market and once a year for the following two years. Thereafter, the reports should be submitted at three-yearly intervals.

Prior to marketing, PSURs have to be submitted at 6 months intervals once the product is authorised and immediately upon request.

A single PSUR assessment procedure, with a recommendation from the PRAC, has been introduced for medicinal products authorised in more than one member state (i.e. products authorised through centralised, mutual recognition or decentralised procedures) and for products subject to different national marketing authorisations containing the same active substance or the same combination of active substances for which PSUR submission dates and frequency have been harmonised in the EU. The approach is more proportionate to the risks posed by medicinal products. Thus, routine PSUR reporting is no longer necessary for products with low risk or established products[156] unless there is condition in the marketing authorisation or a request from a competent authority.

[156] 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).

The list of EU reference dates and frequency of submission of PSURs (EURDS list[157]) provides information to facilitate the harmonisation of data lock points and timelines for submission of PSURs. The EURDS list is the relevant tool for SMEs to plan PSUR-related activities, whilst noting that the competent authorities may still request PSURs at any time if deemed necessary.

In the future a new PSUR repository will be made available at the EMA for sponsors to upload reports into. In the interim period, MAHs should continue to submit the PSUR to all competent authorities of the Member States in which the medicinal product is authorised.

Medicinal products subject to additional monitoring

The Agency will publish a list of medicinal products subject to additional monitoring, including amongst others all medicinal products for human use containing a new active substance and new biological medicinal products.

These products are to be distinguished from others by a black symbol (i.e. the inverted black triangle ▼) and an explanatory sentence in the summary of product characteristics and the package leaflet. Further information will be published on the EMA website.

Literature monitoring

The Agency will be required to monitor the scientific and medical literature to collect further reports of suspected side effects, which will be entered into the EudraVigilance system. A defined list of publications for a defined list of active substances used in medicines will be monitored and this will be made public by the Agency. In the interim period until the Agency initiates literature monitoring activities, MAHs should continue to report cases they have identified from the literature.

7.3. Reporting obligations

The reporting obligations of the various stakeholders are defined in the legislation, in particular regulation (EU) no726/2004, directive 2001/83/EU, and directive 2001/20/EC.

The safety reporting falls 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 studies. Suspected adverse reactions should not be reported under regimes that are directive 2001/20/EC as well as regulation (EC) no 726/2004 and directive 2001/83/EC as this creates duplicate reports. A detailed explanation of the different reporting rules is provided in chapter V1.C.1 of GVP module VI.

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), named "EudraVigilance"[158], was launched in December 2001 (see Section 7.4).

7.3.1. Sponsors of clinical trials – reporting obligations

Sponsors of clinical trials are subject to the following reporting obligations, as laid down in legislation and described in GVP module VI and "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')":

[157] www.ema.europa.eu Regulatory / Human Medicines / Pharmacovigilance / Guidance
[158] EudraVigilance website: http://eudravigilance.ema.europa.eu/highres.htm

All suspected unexpected serious adverse reactions[159] (SUSARs) occurring in interventional clinical trials authorised in the Community have to be reported electronically to the competent authority(ies) and to Eudravigilance Clinical Trial Module (EVCTM) by the sponsor of the clinical trial.

This applies to all investigational medicinal products which are studied in interventional clinical trials conducted in the EEA and includes all SUSARs related to these medicinal products which occur either within or outside the EEA.

- ***for fatal and life-threatening SUSARs***

The EMA, the competent authority(ies) and the relevant ethics committee of the concerned Member State(s) where the SUSARs occurred should be notified as soon as possible, but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting[160]. If the initial report is incomplete a complete report, containing relevant follow-up information, should be submitted within an additional 8 calendar days. If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days.

- ***for non-fatal and non-life-threatening SUSARs***

They must be reported to the EMA, the competent authority(ies) and the relevant ethics committee of the concerned Member State(s) where the SUSARs occurred as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be within 15 calendar days.

The sponsor must inform all investigators concerned of all relevant information about SUSARs. Whenever practicable the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational medicinal product (IMP).

7.3.2. MAHs of medicinal products authorised in EEA - reporting obligations

The Agency receives all relevant information concerning suspected adverse reactions to medicinal products for human use which have been authorised in the EU. Electronic reporting through Eudravigilance Post-authorisation Module (EVPM) has been mandatory since 20 November 2005.

The holder of the marketing authorisation for a medicinal product for human use should ensure that:

- ***All suspected serious adverse reactions[161] to an authorised medicinal product occurring within the Community*****,** regardless of the authorisation procedure[162], which a health-care professional or patient brings to the MAH's attention are recorded and reported promptly to

[159] '**Adverse reaction'**: a response to a medicinal product which is noxious and unintended. 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; and occupational exposure.
'**Serious adverse event or serious adverse reaction**': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
'**Unexpected adverse reaction**': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

[160] The minimum criteria for expedited reporting are a patient, a reporter, a suspect drug and an adverse reaction. For SUSARs, a causality assessment is also required to determine whether the event is suspected to have been caused by the drug. In the absence of a causality assessment from the investigator, the sponsor will have to make the assessment while awaiting causality from the investigator.

[161] For definition, refer to GVP module VI.

[162] National, centralised, decentralised or mutual recognition procedures.

Member States within the territory of which the incident occurred, no later than 15 calendar days following the receipt of the minimum criteria for expedited reporting.

- ***Any other suspected serious adverse reactions to an authorised medicinal occurring outside the Community*** of which the MAH may reasonably be expected to be aware is recorded and promptly notified to the competent authority of Member States where the medicinal product is authorised and the Agency, and no later than 15 days following receipt of the minimum criteria for expedited reporting. This includes, but is not limited to; reactions reported in the medical literature (see also Section 7.2 above).

  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 calendar days.

- ***All suspected non-serious adverse reactions to an authorised medicinal product within the Community*** have to be reported within 90 calendar days.

  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.

The Agency may request specific pharmacovigilance data to be collected by the MAH. Any such data collected should be collated, assessed and submitted to the Agency for evaluation.

7.4. EudraVigilance

EudraVigilance is a data processing network and management system, launched by the EMA in 2001, for reporting and evaluating suspected adverse reactions during development and following the marketing authorisation of medicinal products in the European Economic Area (EEA).

This network enables data to be exchanged efficiently between the EMA, competent authorities, the marketing authorization holders, and the sponsors of clinical trials in the EEA. EudraVigilance is a powerful tool for the EMA and NCAs to monitor the safety of medicinal products and minimise potential risks related to suspected adverse reactions.

Taking into account the pharmacovigilance activities in the pre- and post- authorisation phase, EudraVigilance provides two reporting modules:

- **EudraVigilance clinical trial module (EVCTM)** to facilitate the electronic reporting of suspected unexpected serious adverse reactions (SUSARs) occurring in interventional clinical trials as required by directive 2001/20/EC.
- **EudraVigilance post-authorisation module (EVPM)** designed for reporting post-authorisation individual case safety reports (ICSRs), pursuant to regulation (EU) no 726/2004 and directive 2001/83/EU.

7.5. EVWEB

In addition to automated message generation and processing, the EudraVigilance system also provides a web based tool to allow for a manual safety and acknowledgement message creation as well as generation of medicinal product reports via a web interface, called EVWEB.

It is specifically designed for SMEs and non-commercial sponsors, which do not have a fully ICH E2B(R2)-compliant pharmacovigilance system and/or ESTRI[163] gateway in place. As such it provides the necessary tools to allow SMEs to perform secure electronic reporting to the EMA and all competent authorities in the EEA in accordance with the aforementioned legislation. It allows safety and acknowledgement messages to be sent and received in compliance with the latest ICH M2 standards. EVWEB also enables all messages to be saved locally and permits standardisation of message senders and receivers registered with the Agency as part of the EudraVigilance community. The same principles apply for medicinal product report messages.

Any MAH, applicant or sponsor of a clinical trial in the EEA can use EVWEB. In order to use EVWEB, a computer with Internet Explorer 5.1 or above is required as well as internet access. To access the tool, a staff member of the company (or a nominated and registered representative organisation) is required to undertake and pass EudraVigilance training[164], which is held at the EMA every month and at various venues around the EEA. There is a fee reduction available to SMEs participating in these training sessions. Further information on how to register with EudraVigilance and the list of documents to be provided are detailed on the EudraVigilance website.

Alternatively, SMEs may employ a contract research organisation (CRO) to perform the electronic transmission of ICSRs on their behalf. Some industry associations also offer an electronic reporting service to their member companies, and bilateral agreements with partner organisations are also permitted as long as they are captured within the EudraVigilance registration system.

All medical information in EudraVigilance & EVWEB is coded using MedDRA. MedDRA is a clinically validated international medical dictionary used by regulatory authorities and the regulated biopharmaceutical industry within the USA, the EU and Japan. MedDRA should be used for all regulatory activities especially reporting of ADRs, xEVMPD messages in accordance with article 57, PSURs and RMPs. MedDRA is free within EVWEB for small & micro-sized enterprises, but not for SMEs which are medium-sized.

7.6. Pharmacovigilance for veterinary medicinal products

The MAHs of veterinary medicines are also required to follow-up on the safety and efficacy of their product during its life on the market, including possible environmental problems and investigations into the validity of the withdrawal period in case of products for food producing animals. The detailed requirements can be found in volume 9B of the rules governing medicinal products in the EU[165]. These surveillance activities are captured under the term 'pharmacovigilance' and in general relate to 2 specific systems:

Periodic safety update report (PSUR)

The MAH must maintain detailed records of all adverse events within or outside the EU which are reported to it. Unless otherwise required, these reports need to be submitted to the Agency as part of the PSUR every six months until placing on the EU market and subsequently at least every six months during the first two years, once a year for the following two years and thereafter at three-yearly intervals. The PSUR includes an evaluation of the benefit-risk balance of the product.

Further guidance on preparation and handling of PSURs is available in the post-authorisation procedural question and answers section of the EMA website.

[163] Electronic transfer of regulatory information.
[164] For more information on the EudraVigilance training programme, please refer to http://eudravigilance.ema.europa.eu/human/training.asp
[165] http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm

15-day (or 'expedited') reporting

The MAH is obliged to report any serious adverse event in animals and all human adverse events occurring within or outside the EU (third country reports) and any suspected transmission via a medicinal product of any infectious agent outside the EU. These reports must be submitted promptly and no later than 15 days following the receipt of information to the Member State's competent authority in which the event occurred or directly to the Agency in case of third country reports. The reporting occurs electronically using a central database system, called "EudraVigilance veterinary" (EVVeT)[166]. Reports can be entered directly via the web-interface. The Agency, together with the Member States, monitors the information that becomes available in EVVeT and will determine need for regulatory action.

The MAH must nominate a qualified person responsible for pharmacovigilance (QPPV) who will be responsible for all pharmacovigilance activities and who will need to be registered to EVVeT. A QPPV can be outsourced to a third party.

Further guidance on the pharmacovigilance requirements for veterinary medicinal products is available at the EMA website[167].

8. Other useful information

8.1. Information on medicinal products

The Community register of medicinal products[168] is published on the European Commission's website and contains a list of all medicinal products for human and veterinary use authorised via the centralised procedure and all designated orphan medicinal products for human use.

The EMA's website contains a vast array of additional product information that may interest SMEs, including:

- Public summaries of opinions for orphan designation[169]
- Decisions on a Paediatric Investigation Plan[170]
- CHMP & CVMP summaries of opinion[171]

  Note: The summary of opinion is replaced by the European public assessment report (see below) once the European Commission has taken its decision granting or refusing a marketing authorisation.
- European public assessment reports (EPARs)[172]
- European public MRL assessment reports[173]
- Information on marketing authorisation and marketing authorisation application withdrawals[174]
- Product safety announcements[175]
- Product opinions for non-EU use[176]

[166] http://eudravigilance.ema.europa.eu/veterinary/index.html
[167] www.ema.europa.eu Regulatory / Veterinary Medicines / Pharmacovigilance
[168] http://ec.europa.eu/health/documents/Community-register/index_en.htm
[169] http://www.ema.europa.eu/ - Find a medicine / Human medicines / Rare disease designations
[170] http://www.ema.europa.eu/ - Find a medicine / Human medicines / Paediatrics
[171] http://www.ema.europa.eu/ - Find a medicine / Human medicines (Veterinary medicines) / Pending EC decisions
[172] http://www.ema.europa.eu/ - Find a medicine / Human medicines (Veterinary medicines) / European Public Assessment Reports
[173] http://www.ema.europa.eu/ - Find a medicine / Veterinary medicines / Maximum Residue Limits Reports
[174] http://www.ema.europa.eu/ - Find a medicine / Human medicines (Veterinary medicines) / Withdrawn Applications
[175] http://www.ema.europa.eu/ - Patient Safety

- List of referred applications[177]
- Information on herbal medicines for human use[178]

8.2. List of abbreviations

ADI	Acceptable Daily Intake
ADR	Alternative Dispute Resolution
ASMF	Active Substance Master File
ATMPs	Advanced Therapy Medicinal Products
AUC	Area under the curve
AWU	Annual Work Unit
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CAT	Committee for Advanced Therapies
CD-ROM	Compact Disc – Read Only Memory
CdT	Centre for Translation
CEP	Certificate of Suitability
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CRO	Contract Research Organisation
CTA	Clinical Trial Applications
CTD	Common Technical Document
CTFG	Clinical Trials Facilitation Group
CTR	Clinical Trials Register
CVMP	Committee for Medicinal Products for Veterinary Use
DDPS	Detailed Description Pharmacovigilance System
DSUR	Development Safety Update Report
DVD	Digital Versatile Disc
EC	European Commission
e-CTD	Electronic Common Technical Document
EDQM	European Directorate for Quality of Medicines and Health Care
EEA	European Economic Area
EEC	European Compliance Academy
EMA	European Medicines Agency
EnprEMA	European Network of Paediatric Research at the European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
ESTRI	Electronic Standards for the Transfer of Regulatory Information
EU	European Union
EudraCT	European Clinical Trials Database
EudraGMP	European Database on Manufacturing and Import

[176] http://www.ema.europa.eu/ - Find a medicine / Human medicines / Medicines for use outside the EU
[177] http://www.ema.europa.eu/ - Regulatory / Human medicines (Veterinary medicines) / Referral Procedures
[178] http://www.ema.europa.eu/ - Find a medicine / Herbal medicines for human use

	Authorisations and Good Manufacturing Practice
EURDS	European Union Reference Dates and Frequency of Submission of Periodic Safety Update Reports
EVCODE	EudraVigilance Code
EVCTM	EudraVigilance Clinical Trial Module
EVCTM	EudraVigilance Clinical Trial Module
EVPM	EudraVigilance Post-authorisation Module
EVVET	EudraVigilance Veterinary
EVWEB	EudraVigilance web-based Tool
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMOs	Genetically Modified Organisms
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICTRP	International Clinical Trials Registry Platform
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
ISO	International Organisation for Standardisation
ITF	Innovation Task Force
IVMPs	Immunological Veterinary Medicinal Products
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRL	Maximum Residue Limit
MUMS	Minor Uses and Minor Species
NCA	National Competent Authority
No	Number
NRG	(Invented) Name Review Group
NTA	Notice to Applicants
OECD	Organisation for Economic Co-operation and Development
OJEU	Official Journal of the European Union
PASS	Post-Authorisation Safety Studies
PD/PK studies	Pharmacodynamics/Pharmacokinetic studies
PDCO	Paediatric Committee
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PM	Project Manager
PRAC	Pharmacovigilance Risk Assessment Committee
PRAC	Pharmacovigilance Risk Assessment Committee
PREA	Paediatric Research Equity Act

PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PTL	Product Team Leader
PTM	Product Team Member
PUMA	Paediatric Use Marketing Authorisation
Q&A	Questions & Answers
QPPV	Qualified Person for Pharmacovigilance
R&D	Research & Development
Rev.	Revision
RMP	Risk Management Plan
SAG	Scientific Advisory Group
SAWP	Scientific Advice Working Party
SAWP-V	Scientific Advice Working Party – Veterinary
SME	Micro, Small and Medium sized Enterprises
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Reactions
TSE	Transmissible Spongiform Encephalopathy
US(A)	United States (of America)
VHP	Voluntary Harmonisation Procedure
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organisation
xEVMPD	Extended EudraVigilance Medicinal Product Dictionary
XEVPRM	Extended EudraVigilance Product Report Message

8.3. Contact points at the EMA

SME office

The SME office has been set up within the Agency to address the particular needs of smaller companies. The office aims to facilitate communication with SMEs through dedicated personnel within the Agency who will respond to practical or procedural enquiries, monitor applications, and organise workshops and training sessions for SMEs. Any comments on the content of this SME user guide should also be forwarded to the SME office.

SME office contact point:

E-mail: smeoffice@ema.europa.eu
Direct telephone: (44-20) 74 18 85 75/86 43

Fax: (44-20) 75 23 70 40

Advanced therapies and technologies

General queries relating to advanced therapies and technologies can be sent to:

Innovation task force contact point: E-mail: ITFsecretariat@ema.europa.eu

ATMP secretariat contact point: E-mail: AdvancedTherapies@ema.europa.eu

Orphan designation

Requests for further information on orphan designation applications and requests to set up a free pre-submission meeting should be sent to:

Orphan medicines contact point: E-mail: orphandrugs@ema.europa.eu

Scientific advice

For queries relating to the procedure for scientific advice or to request a free pre-submission meeting, contact:

For medicinal products for human use: E-mail: ScientificAdvice@ema.europa.eu

For medicinal products for veterinary use: E-mail: vetscientificadvice@ema.europa.eu

Veterinary MUMS

General queries / requests for further information on MUMS classification should be sent to:
E-mail: VetMUMSapplications@ema.europa.eu

Documentation services

A wide range of documents is published by the EMA, including press releases, general information documents, annual reports and work programmes.

These and other documents are available:

on the internet at www.ema.europa.eu

by email request to info@ema.europa.eu

by fax to (44-20) 7418 8670

by writing to the:

EMA Documentation service

European Medicines Agency

7 Westferry Circus, Canary Wharf

London, E14 4HB

UK

Annex 1

National provisions for SMEs applicable to the pharmaceutical sector

National provisions for SMEs applicable to the pharmaceutical sector (last update December 2012)

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
Austria	Human & Vet	AGES Austrian Medicines and Medical Devices Agency LCM Traisengasse 5 1200 Vienna Austria www.ages.at	Information on fee reductions for: Veterinary medicinal products: Mag. Eugen Obermayr Phone: +43 50 55 53 66 70 E-mail: eugen.obermayr@ages.at Medicinal products produced in pharmacies: Mag. Helga Lacina Tel.: +43 50 55 53 66 40 E-mail: helga.lacina@ages.at	No specific provisions for SMEs applicable to pharmaceutical sector. There are general provisions for fee reductions for the authorisation and life-cycle management for veterinary medicinal products and medicinal products produced in local pharmacies. More detailed information about the Austrian fee levels is available on the Agency's website[179].
Belgium	Human & Vet	Federal Agency for Medicines and Health Products Eurostation bloc II Place Victor Horta 40 Boîte 40 1060 Brussels Belgium www.fagg.be	Phone: +32 2 524 80 68 or 8228 E-mail: info.dgm@fagg-afmps.be/ sta@fgg-afmps.be	No specific provisions for SMEs applicable to pharmaceutical sector. In the future there will be the possibility to have assistance for applications for specific medicinal products, for example, those for the treatment of minor species.

[179] Information on AGES Austrian Medicines and Medical Devices Agency fees: http://www.basg.gv.at/en/about-us/fees/

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
Bulgaria	Human	Bulgarian Drug Agency 8 Damyan Gruev Str. 1303 Sofia Bulgaria www.bda.bg	Phone: +359 28 90 35 55 E-mail: bda@bda.bg	No specific provisions for SMEs for human medicines.
	Vet	National Veterinary Service 15A 'Pencho Slaveykov' Blvd 1606 Sofia Bulgaria www.nvms.government.bg	Dr Krasimir Zlatkov Head of Control of VMP and Feeds Safety Department Phone: +359 29 15 98 69 E-mail: krasimir.zlatkov@nvms.government.bg	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.
Cyprus	Human	Ministry of Health Pharmaceutical Services 7 Larnacos Avenue 1475 Lefkosia Cyprus http://www.moh.gov.cy	Mr Ioannis Kkolos Pharmaceutical Services Phone: +357 22 40 71 32 E-mail: jkkolos@phs.moh.gov.cy	*Cyprus research promotion foundation* The Cyprus research promotion foundation is an independent establishment that promotes scientific and technological research in Cyprus. Its main measures include three packages: measures on health research, measures on SME research and measures relating to the development of research infrastructures. *Measures on health research* This scheme includes the program on "biological sciences health". The main target of this scheme is the design of high quality research in the fields of public health, biomedical sciences and biotechnology and food science and biotechnology. Grants under this scheme may be up to 160.000 Euros. *SME research* This is a new scheme that includes the "development of research and innovation in businesses" program. The main aim of the scheme is to improve the competitiveness, viability and development of Cypriot enterprises and the creation of new work posts in research and

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
				development. Grants under this scheme may be up to 170.000 Euros. *Measures relating to the development of research infrastructures* The aim of the scheme is to help develop research infrastructures by upgrading current infrastructures and the creation of new ones with emphasis on innovative scientific sectors. Grants under this scheme may be up to 800.000 Euros. *Measures relating to research infrastructure* The provisions of directive 2001/20/EC are fully transposed into the national legislation of Cyprus. Sponsors and investigators may utilise the current infrastructure to conduct paediatric clinical trials.
	Vet	Ministry of Agriculture, Natural Resources & Environment Veterinary Services 1417, Nicosia Cyprus http://www.moa.gov.cy/vs	Ioanna Talioti Veterinary Services Phone: +357 22 80 51 12 E-mail: italioti@vs.moa.gov.cy	There is the Cyprus research promotion foundation which is an independent establishment which also promotes scientific and technological research in Cyprus. Additionally, there is a reduction of fees in the national legislation for VMPs [VMPs (fees) regulations 132/2006] for the following case: "If a VMP is necessary for the public health and the volume of sales will not cover the expenses of the marketing, the competent authority may reduce the fees for the assessment and issue of the marketing authorisation or may not require any fees from the applicant".
Czech Republic	Human	State Institute for Drug Control Šrobárova 48 100 41 Praha 10 Czech Republic www.sukl.cz	Phone: +420 27 21 85 11 1 E-mail: posta@sukl.cz	Under government decree no. 427/2008 coll., SMEs are eligible to 50% reduction of fees charged by the State Institute for Drug Control (SUKL) for expert activities and annual fees. All applications filed by SMEs in 2010 and 2011 were granted. Apart from that no specific provisions for SMEs apply to human pharmaceuticals sector.

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
	Vet	Ústav pro státní kontrolu veterinárních biopreparátu a léciv Hudcova 56a 621 00 Brno - Medlánky Czech Republic www.uskvbl.cz	Phone: 420 54 12 10 02 20 24 E-mail: uskvbl@uskvbl.cz	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.
Denmark	Human & Vet	Danish Health and Medicines Authority Axel Heides Gade 1 2300 Copenhagen Denmark www.dkma.dk	Phone: +45 72 22 74 00 E-mail: sst@sst.dk	The national fee structure and service/administrative offers are adjusted to the fact that the national legislation is adapted to the special needs of Danish SME enterprises. In addition, fee exemptions are also available in specific circumstances e.g. that the medicinal product is essential to the patient's treatment. For more detailed information about the Danish fee levels a total list of current fees charged in Denmark can be found on the Danish Medicines Agency website under the heading medicinal products, fees payable. In addition, the website contains information on how to obtain administrative and procedural assistance, and information about the supervision of medicinal products and medical devices, including possibilities to obtain scientific advice.
Estonia	Human & Vet	State Agency of Medicines 1 Nooruse Street 50411 Tartu Estonia www.ravimiamet.ee	Phone: +372 73 74 14 0 E-mail: info@ravimiamet.ee Mrs Kaili Lellep Phone: +372 73 74 14 0 E-mail: kaili.lellep@ravimiamet.ee	The support of enterprise and state loan guarantees act (RT I 2003, 18, 96 as amended[180]) entered into force in Estonia on 1 May 2003 and contains some provisions for SMEs, applicable to the pharmaceutical sector. The act sets out the bases, principles and organisation of state support for enterprises and the grant of state guarantees for loan agreements and leasing contracts.

[180] http://www.legaltext.ee/text/en/X70025K1.htm

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
Finland	Human & Vet	Finnish Medicines Agency P.O. Box 55 (Mannerheimintie 103b) 00301 Helsinki Finland http://www.fimea.fi	Phone: +358 9 4733 4 1	Regulatory advice is given on an *ad hoc* basis and also more specific advice upon request for the SMEs. Scientific advice fee exemption is possible.
France	Human	Agence française de sécurité sanitaire des produits de santé (Afssaps) 143-147 Blvd Anatole 93285 Saint-Denis CEDEX France www.afssaps.sante.fr	Phone: +33 1 55 87 30 00 Dr Pascale Maisonneuve E-mail: pascale.maisonneuve@afssaps.sante.fr Phone: + 33 1 55 87 43 30 Mr Stéphane Paliès E-mail: Stephane.palies@afssaps.sante.fr	No specific financial provisions for SMEs applicable to human health products. However, various procedures are in place in order to help development of innovative health products: • early meeting with Afssaps; • scientific advice during medicinal product development or before submission of marketing authorisation; • pre-submission procedure for clinical trials . These procedures are free of charge for all structures, SME or not. For more information see: http://www.afssaps.fr/Activites/Accompagnement-de-l-innovation/Afssaps-et-innovation/(offset)/0
	Vet	Agence Nationale du Médicament Vétérinaire Anses-ANMV 8 rue Claude Bourgelat Parc d'Activités de la Grande Marche BP 90203 35302 Fougères France www.anmv.anses.fr	Phone: +33 2 99 94 78 71 E-mail: sylvie.goby@anses.fr	No specific provisions for SMEs applicable to veterinary pharmaceutical sector. But specific fees for marketing authorisation for MUMS and homeopathic veterinary medicinal products. Also, the annual fees take into account and are proportionate to the turnover of the company for each medicinal product. There is no fee where the turnover is less than 50000 euros and progressive annual fee until 10 000 000 euros (article D. 5141-60 of public health code)

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
Germany	Human	Federal Institute for Drugs and Medical Devices (BfArM) Kurt-Georg Kiesinger-Allee 3 53175 Bonn Germany www.bfarm.de	Phone: +49 22 82 07 30 E-mail: info@bfarm.de Dr Sabine Mayrhofer Phone: +49 22 82 07 31 22 E-mail: s.mayrhofer@bfarm.de	There is one specific provision aimed at SMEs presently implemented in Germany: the possibility for a reduction of fees for licensing activities. According to art. 3, paragraph 2 of the German regulation on fees for the licensing of medicinal products, the fee can be reduced by up to 50 % if justified by the related operating expense of the authority on one hand and the relevance, economical value or other benefit for the applicant on the other hand.
	Human - sera, vaccines, blood preparations	Paul Ehrlich Institut Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel Paul Ehrlich Str. 51-59 63225 Langen Germany www.pei.de	Bettina Ziegele, M.A. Deputy Head Innovation Office Phone: +49 61 03 77 10 12 E-mail: innovation@pei.de	The Paul-Ehrlich-Institut has established an innovation office. Information and details about the innovation office of the PEI can be found on the Paul-Ehrlich-Institut website.
	Vet	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) Mauerstr. 39 - 42 10117 Berlin Germany www.bvl.bund.de	Phone: +49 30 18 44 57 100 E-mail: poststelle@bvl.bund.de Dr Anton Dotter, Ref. 301 301@bvl.bund.de	The German fee regulation offers the possibility to reduce the fee normally charged for a marketing authorisation to such a degree that only 25% of it has to be paid. However, this only applies to products for which the expenses outweigh the expected profit and public interest can be identified (no alternative) or which will be used in rare cases. If the authorisation is refused it is possible to refrain from charging a fee. There is no possibility for fee deferral according to German fee regulation.

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
Greece	Human & Vet	EOF – National Drug Organisation Mesogion Avenue 284 Holargos Athens 15562 Greece www.eof.gr	Phone: +30 2132040297 E-mail: relation@eof.gr	No specific provisions for SMEs applicable to pharmaceutical sector.
Hungary	Human	EOF – National Drug Organisation Mesogion Avenue 284 Holargos Athens 15562 Greece www.eof.gr	Phone: +30 2132040297 E-mail: relation@eof.gr	No specific provisions for SMEs applicable to pharmaceutical sector.
	Vet	National Food Chain Safety Office Directorate of Veterinary Medicines Szállás utca 8. 1107 Budapest Hungary http://www.nebih.gov.hu	Dr Gábor Kulcsár Phone: +36 14 33 03 30 Email : kulcsarg@nebih.gov.hu	No specific provisions for SMEs applicable to pharmaceutical sector.

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
Ireland	Human & Vet	Irish Medicines Board The Earlsfort Centre Earlsfort Terrace Dublin 2 Ireland www.imb.ie	Information on fees is available from IMB website: www.imb.ie Phone: +353 16 76 49 71 Email: imb@imb.ie Specific queries on service item fees can be directed to accounts@imb.ie	No specific provisions for SMEs applicable to pharmaceutical sector. There is a service item fee (reduced fee) that relates to the market segment/use of the product (not to the size of the individual pharmaceutical company).
Italy	Human	Agenzia Italiana del Farmaco Via del Tritone 181 00187 Roma Italy http://www.agenziafarmaco.gov.it/	Dott.ssa Gabriella Conti g.conti@aifa.gov.it Alternate: Dr Daniela Salvia d.salvia@aifa.gov.it	According to art. 4 of the decree of the ministry of health, together with the minister for public administration and the simplification and the minister of economy and finance of 29 March 2012, no. 53 (amendment to the regulation and operation of the Italian Medicines Agency), which was adopted in order to enforce the provisions of art. 17, paragraph 10, of decree law, 06 July 2011, no. 98, which became law with amendments by law 15 July 2011, no. 111, for SMEs the amounts of payments of services provided by AIFA and annual fees are reduced by 25%. Moreover assistance is available for promoting exports. In addition, general provisions exist, such as legislative decree 297/1999 (financing of industrial research) which handles funds from FAS (the fund for underutilised areas of the ministry for universities and research) and foresees increased funding for SMEs compared to large companies, or tax credits for new research, grants and contributions to universities.

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
	Vet	Ministero della Salute Via G. Ribotta 5 00144 - Rome Italy http://www.salute.gov.it	Dr Daniela Raneri d.raneri@sanita.it Phone: +39 06 59 94 37 34 Alternate: Dr Virgilio Donini v.donini@sanita.it Phone: +39 06 59 94 65 90	No specific provisions for SMEs applicable to pharmaceutical sector.
Latvia	Human	State Agency of Medicines Jersikas iela 15 1003 Riga Latvia www.zva.gov.lv	Ms Ludmila Romanova Phone: +371 67 07 84 44 E-mail: ludmila.romanova@zva.gov.lv	There are no specific provisions for fee reductions for SMEs. There is specific provision for exemption from the annual fee for post-registration surveillance of the relevant medicine unless the turnover of the said medicine for the previous calendar year exceeded LVL 1500. This provision ensures the availability of medicines which are manufactured or distributed in a limited amount.
	Vet	Assessment and Registration Agency 30 Peldu Street 1050 Riga Latvia www.pvd.gov.lv	Mr Gatis Ozoliņš Phone: +371 29229686 E-mail: gatis.ozolins@pvd.gov.lv	No specific provisions for SMEs applicable to pharmaceutical sector. Medicines, which are not widely marketed within year of taxation, can be released from yearly post authorisation fee.
Lithuania	Human	State Medicines Control Agency Žirmūnų str. 139A 09120 Vilnius Lithuania www.vvkt.lt	Phone: +370 5 263 92 64 Mrs Irena Vaketaite Head of Inspections Unit Phone: +370 5 263 98 91 E-mail: irenavaketaite@vvkt.lt	Currently no specific provisions for SMEs applicable to pharmaceutical sector. There are some proposals for general provisions for fee reductions for the authorisation and life-cycle management of medicinal products under evaluation at governmental level.

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
	Vet	National Food and Veterinary Risk Assessment Institute J. Kairiūkščio str. 10 08409 Vilnius Lithuania nmvrvi@vet.lt	Phone: +370 5 278 04 84 E-mail: nmvrvi@vet.lt Dr Mačiulskis Petras Deputy Director Phone: +370 5 278 04 84 E-mail: pmaciulskis@vet.lt	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.
Luxembourg	Human & Vet	Direction de La Santé Villa Louvigny Division de la Pharmacie et des Medicaments Allée Marconi 2120 Luxembourg www.ms.etat.lu	Human E-mail: lHuman: uxdpm@ms.etat.lu Veterinary Email: luxvet@ms.etat.lu	No specific provisions for SMEs applicable to pharmaceutical sector.
Malta	Human	Medicines Authority 203, Level 3 Rue D'Argens Gzira GZR 03 Malta www.medicinesauthority.gov.mt	Medicines Authority Phone: +356 23 43 90 00 E-mail: info.medicinesauthority@gov.mt Malta Enterprise Phone: +356 2542 0000 E-mail: info@maltaenterprise.com	In Malta companies engaged in the production of pharmaceuticals (including the packaging of such products) qualify for assistance under incentives and schemes. This is subject to approval of the activity by Malta Enterprise – the Maltese entity responsible for foreign direct investment, internalisation of companies and the promotion of entrepreneurship and business start-ups. Further information is available on the Malta Enterprise website: http://support.maltaenterprise.net/
	Vet	Ministry for Resources and Rural Affairs Fish and Farming Regulation and Control Division	Ministry for Resources and Rural Affairs Phone: +356 2590 5100 Email: vafd.mrra@gov.mt	In Malta companies engaged in the production of pharmaceuticals (including the packaging of such products) qualify for assistance under incentives and schemes. This is subject to approval of the activity by Malta Enterprise – the Maltese entity responsible for foreign direct

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
		The Abattoir, Albert Town Marsa MRS 1123 Malta	Malta Enterprise Phone: +356 2542 0000 E-mail: info@maltaenterprise.com	investment, internalisation of companies and the promotion of entrepreneurship and business start-ups. Further information is available on the Malta Enterprise website: http://support.maltaenterprise.net/
Netherlands	Human & Vet	College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board Kalvermarkt 53 P.O.Box 16229 2511 CB Den Haag The Netherlands www.cbg-meb.nl	Phone: +31 70 35 67 40 0 E-mail: info@cbg-meb.nl	No specific provisions for SMEs applicable.
Poland	Human & Vet	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products 41 Zabkowska Str. 03-736 Warsaw Poland www.bip.urpl.gov.pl	Phone: +48 22 49 21 10 0 E-mail: bip@urpl.gov.pl	No specific provisions for SMEs applicable to pharmaceutical sector.

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
Portugal	Human	INFARMED - Instituto Nacional da Farmácia e do Medicamento Parque da Saúde de Lisboa Avenido do Brasil, n° 53 1749-004 Lisboa Portugal www.infarmed.pt	Ms Maria Morais Phone: +351217987246 E-mail: mjoao.morais@infarmed.pt	There is one specific provision aimed at SMEs presently implemented in Portugal: the system of incentives to small entrepreneurial initiatives (SIPIE). This incentive was created by portaria no. 317-A/2000 of 31 May. SIPIE is a program that applies to all the economic sectors, including the pharmaceutical sector, through incentives given to specific projects. The above-mentioned program and project description can be found on the webpage of the Institute that supports SMEs in Portugal, the IAPMEI[181] INFARMED, I.P. provides scientific and regulatory advice to the applicants, during initial development stages of medicinal products, medical devices and cosmetic products (pre-submission) and also during post-marketing. Scientific and regulatory advice requests are subject to payment of fees in accordance with nos. 12 and 13 of the annex to portaria no. 377/2005 of 04 April (available at INFARMED's website). Upon duly justified request, a fee exemption or a fee reduction may be granted on grounds of public health and/or company category (SMEs).
	Vet	DGAV – Direção-Geral de Alimentação e Veterinária Largo da Academia Nacional de Belas Artes nº 2 1249-105 Lisboa Portugal www.dgv.min-agricultura.pt	Head of Vet Medicines Agency Prof Dr Nuno Vieira e Brito Phone: +351213239655/6 E-mail nuno.brito@dgv.min-agricultura.pt	Portaria no. 317-A/2000 of 31 May and the SIPIE (IAPMEI) also applies to the veterinary sector. DGAV provides scientific and regulatory advice to the applicants, during initial development stages of veterinary medicinal products (pre-submission) and also during post-marketing. Scientific and regulatory advice concerning an application for the purpose of subsequent evaluation by MRP or DCP is subject to payment of fees in accordance with nº 21 of the annex to portaria n. º 27/2011 of 10

[181] IAPMEI website: http://www.iapmei.pt/index.php and specific information on SIPIE: http://www.iapmei.pt/iapmei-art-02.php?id=76&temaid=13

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
				January. Upon duly justified request, a fee reduction may be granted namely in case of lack of availability and limited use of veterinary medicines in accordance with nº 5, of article 2º, (available at DGAV's website).
Romania	Human	National Agency for Medicines and Medical Devices 48, Av. Sanatescu Str. Sector 1 011478 Bucharest Romania www.anm.ro/en/home.html	Mrs Victoriţa Ivascu Pharmaceutical Inspection Phone: +40213161102 E-mail: victorita.ivascu@anm.ro	No specific provisions for SMEs applicable to human pharmaceutical sector.
	Vet	Institutul pentru Controlul Produselor Biologice si Medicamentelor de Uz Veterinar Str. Dudului 39 Sector 6 060603 Bucharest Romania www.icbmv.ro/	-	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.
Slovak Republic	Human	State Institute for Drug Control Kvetná 11 825 08 Bratislava 2 Slovak Republic www.sukl.sk	Phone: +42 1 2 50 70 11 11 E-mail: sukl@sukl.sk Dr Dana Vyskočilová Public Relations Manager vyskocilova@sukl.sk	The State Institute for Drug Control offers administrative and procedural assistance to applicants upon request, in line with standard procedures and in accordance with the state drug policy. There are no fee waivers applicable specifically for SME applications.

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
	Vet	Institute for State Control of Veterinary Biologicals and Medicaments Biovetska 34 949 01 Nitra Slovak Republic www.uskvbl.sk	Phone: +421 37 65 15 50 6 E-mail: uskvbl@uskvbl.sk	No specific provisions for SMEs applicable to pharmaceutical sector.
Slovenia	Human & Vet	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia Ptujska cesta 21 1000 Ljubljana Slovenia www.jazmp.si	Mrs Barbara Kovač Phone: +38 6 8 2000500 E-mail: Barbara.Kovac@jazmp.si	No specific provisions for SMEs applicable to pharmaceutical sector.
Spain	Human & Vet	Agencia Española del Medicamento y Productos Sanitarios Parque Empresarial Las Mercedes Edificio 8 C/Campezo 1 28022 Madrid España www.aemps.es	Ms Belén Crespo Sánchez-Eznarriaga Phone: +34 91 82 25 02 0 E-mail: sgaem@aemps.es	No specific provisions for SMEs applicable to pharmaceutical sector.
Sweden	Human & Vet	Medical Products Agency Dag Hammarskjölds väg 42 751 03 Uppsala Sweden	Phone: +46 18 17 46 00 E-mail: registrator@mpa.se SME-guide:	The regulatory advice office will assist especially small, new, national companies with regulatory queries although queries from all kind of companies are accepted. Scientific advice may be requested for all medicinal products from all

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
		www.lakemedelsverket.se	http://www.lakemedelsverket.se/malgrupp/Foretag/SME-guiden/ Mrs Ylva Satrell Regulatory-Advice@mpa.se Mrs Susanne Baltzer Sme-guiden@mpa.se	kind of companies, irrespective of subsequent choice of procedure for approval. The Medical Products Agency has established a web function, "SME-guide", where the users will be guided through the web pages and information related to regulatory issues can be found.
United Kingdom	Human	Medicines and Healthcare Products Regulatory Agency Market Towers 1 Nine Elms Lane London SW8 5NQ United Kingdom www.mhra.gov.uk	Phone: +44 20 70 84 20 00 E-mail: info@mhra.gsi.gov.uk Ms Kirsten Padgham Policy Division Kirsten.padgham@mhra.gsi.gov.uk Mrs Margaret Haynes Finance Division Margaret.haynes@mhra.gsi.gov.uk	The MHRA offers a number of easements to SMEs to aid their ability to pay the fee due. These easements include: • 25% of the application fee for a new active substance at the time of the application with the remaining 75% payable within 30 days of the marketing authorisation being determined; • 50% of most other marketing authorisation applications fee at the time of application and 50% within 30 days of the application being determined; • 25% of the fee relating to outgoing mutual recognition applications for new active substances at time of application and 75% once that procedure has been completed; • 50% for most other outgoing mutual recognition applications and 50% once that procedure has been completed; • 50% at the time of applications for manufacturers' or wholesale dealers' licences with 50% payable when the applications have been determined; The 50% 'rule' also applies to the payment of: • all inspection fees, including those relating to registrations for traditional herbal medicines;

Country	Human & Veterinary medicines	National competent authority	Contact point	Existing national provisions for SMEs applicable to pharmaceutical sector
				• applications for traditional herbal medicines registrations and applications for complex variations to traditional herbal registrations; • applications for registrations under the homeopathic registration schemes. In addition to these easements, there are some lower fees that reflect the size of a company. For example, wholesale dealers meet certain criteria including low turnover of licensed products, are eligible for lower application, inspection and annual fees. Also the annual fees for marketing authorisations are set with a sliding scale relating to turnover of the product. The MHRA offer pre-application scientific advice meetings at which companies can seek advice on the development of a product, but there is currently no easement of payment for fees relating to these meetings. Companies must meet certain criteria and need to make applications in writing.
	Vet	Veterinary Medicines Directorate Woodham Lane New Haw Addlestone KT15 3LS United Kingdom www.vmd.gov.uk	Phone: +44 93 23 36 91 1 E-mail: postmaster@vmd.defra.gsi.gov.uk Mr Gavin Hall g.hall@vmd.defra.gsi.gov.uk	No specific provisions for SMEs in veterinary medicines legislation.