European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure

This integrated version has been created for printing purposes only. Please refer to the individual question & answers as published in the pre-submission guidance for access to the hyperlinked information.

Questions and answers are being updated continuously, and will be marked by "NEW" or "Rev." with the relevant date upon publication.

This guidance document addresses a number of questions which users of the centralised procedure may have. It provides an overview of the European Medicines Agency’s position on issues, which are typically addressed during the course of pre-submission meetings.

It will be updated regularly to reflect new developments, to include guidance on further pre-authorisation procedures and to reflect the implementation of the new European legislation. Revised topics will be marked by "New" or "Rev" upon publication.

The EMA emphasises the importance of pre-submission meetings between applicants and the EMA/(Co-) Rapporteur. Pre-submission meetings (which should take place approximately 7 months prior to the anticipated date of submission of the application) are a vital opportunity for applicants to obtain procedural, regulatory and legal advice from the EMA. The product team is available to address any questions MAHs may have regarding their pre-authorisation application.

This guidance information and fruitful pre-submission meetings should enable applicants to submit applications, which are in conformity with the legal and regulatory requirements and which can be validated speedily. Pre-submission meetings will also enable applicants to establish contact with the EMA staff closely involved with the application as it proceeds.

Note:

It should be highlighted that this document has been produced for guidance only and should be read in conjunction with "The rules governing medicinal products in the European Union", Volume 2A, Notice to Applicants.
Applicants must in all cases comply with all requirements of Community Legislation. Provisions, which extend to EEA countries (i.e. the EU member states, plus Norway, Iceland and Liechtenstein) by virtue of the EEA agreement, are outlined in the relevant sections of the text.
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1. Is my medicinal product eligible for evaluation under the Centralised Procedure? *Rev. Feb 10*

Regulation (EC) No 726/2004 of the European Parliament and of the Council lays down a centralised Community procedure for the authorisation of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community.

A marketing authorisation granted under the centralised procedure is valid for the entire Community market, which means the medicinal product, may be put on the market in all member states.

**1.1. Article 3 of Regulation (EC) No 726/2004 defines the scope and eligibility of applications for evaluation under the centralised procedure through which medicinal products must ("mandatory scope") or may ("optional scope" or "Generic/Hybrid") be authorised by the Community.**

**1.1.1. Mandatory scope (Article 3(1)):**

For medicinal products falling within the mandatory scope of the Annex of Regulation (EC) No 726/2004, applicants are obliged to use the centralised procedure by submitting their marketing authorisation application to the EMA. Medicinal products under the mandatory scope belong to one of the following categories:

1. Medicinal products developed by means of one of the following biotechnological processes:
   - recombinant DNA technology;
   - controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells;
   - hybridoma and monoclonal antibody methods;

Similar biological ("biosimilar") medicinal products which are developed by one of the above biotechnological processes also fall under the mandatory scope of the centralised procedure.

1.1. Advanced therapy medicinal product as defined in Article 2 of Regulation (EC) No 1394/2007
   - Gene therapy medicinal products
   - Somatic cell therapy medicinal products
   - Tissue engineered products

   "Transitional period“ applies (Article 29):

Advanced therapy medicinal products, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.

Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 shall comply with this Regulation no later than 30 December 2012.
2. Medicinal products for human use containing a new active substance which, on the date of entry into force of the Regulation (20 November 2005), was not authorised in the Community and for which the therapeutic indication is the treatment of any of the following diseases:

- Acquired immune deficiency syndrome;
- Cancer;
- Neurodegenerative disorder;
- Diabetes;

And with effect from 20 May 2008

- Auto-immune diseases and other auto-immune dysfunctions;
- Viral diseases;

Clarifications on the working definitions of the diseases listed above are available in the "Scientific Aspects and Working definitions for the mandatory scope of the centralised procedure (EMEA/CHMP/121944/2007)".

3. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

1.1.2. Optional Scope (Article 3(2)):

For medicinal products falling under the optional scope, applications for the following categories may, at the request of the applicant, be accepted for assessment under the centralised procedure:

1. A medicinal product containing a new active substance which, on the day of entry into force of the Regulation (20 November 2005) was not authorised in the Community (Article 3(2)a).

A new chemical, biological or radiopharmaceutical active substance, as defined in Annex III to Chapter 1 of the Notice to Applicants, includes:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;
- a biological substance previously authorised as a medicinal product in the European Union, but differing in molecular structure, nature of source material or manufacturing process;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously the European Union;

2. A medicinal product, which constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation is in the interest of patients at Community level (Article 3(2)b).

For the purpose of determining whether “a medicinal product constitutes a significant therapeutic, scientific or technical innovation”, the Agency will consider if:

- the medicinal product provides a new alternative to patients in treating, preventing or diagnosing a disease, or,
the medicinal product development is based on significant new scientific knowledge or on the application of a new scientific knowledge, or,

• a new technology or a new application of technology is used for the development or the manufacture of the medicinal product.

Regarding the criteria of ‘interest of patients’, a medicinal product which does not constitute a significant therapeutic, scientific or technical innovation, can be of patient interest at Community level when it addresses a specific health issue, allows access to medicines, or provides another type of contribution to patient care in the Community.

1.1.3. Generic/Hybrid of centralised medicinal product applications (Article 3(3)):

A generic or hybrid medicinal product of a reference medicinal product authorised via the centralised procedure has ‘automatic’ access to the centralised procedure under Article 3(3).

1.1.4. Duplicate/multiple marketing authorisations

Multiple/duplicate or informed consent applications from the same or different marketing authorisation holder for a specific medicinal product with an active substance(s) already authorised via the centralised procedure, have automatic access to the centralised procedure.

1.2. Applications for certain medicinal products for paediatric use may also be eligible for evaluation through the centralised procedure in accordance with the Paediatric Regulation (Regulation (EC) No 1901/2006)

1.2.1. Marketing Authorisation application including paediatric indication(s) for a medicinal product which is not authorised in the Community (Article 28):

A marketing authorisation application for a medicinal product not authorised in the Community on the date of entry into force of the Paediatric Regulation (26 July 2008) and which includes one or more paediatric indication(s) on the basis of studies conducted in compliance with an agreed paediatric investigation plan (PIP).

1.2.2. Applications for a new paediatric indication, a pharmaceutical form and/or a route of administration for nationally authorised medicinal products (Article 29):

Applications for a new paediatric indication, a pharmaceutical form and/or a route of administration for a nationally authorised medicinal product falling under Article 8 of Regulation (EC) No 1901/2006 and which include results of studies conducted in compliance with an agreed PIP. Article 8 of Regulation (EC) No 1901/2006 applies to authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate.

1.2.3. Paediatric Use Marketing Authorisation (PUMA) application (Article 31):

Applications for a PUMA concerns only a medicinal product for human use which is not protected by a supplementary protection certificate under Regulation (EEC) No 1768/92 or by a patent which qualifies...
for the granting of the supplementary protection certificate, and which covers exclusively paediatric therapeutic indications, including the appropriate strength, pharmaceutical form or route of administration for that product.

In all cases listed above, the eligibility of a medicinal product for evaluation via the centralised procedure must be requested by the applicant by submitting a Pre-submission request form (Eligibility) to CPeligibility@ema.europa.eu.

References

- Regulation (EC) No 726/2004
- Regulation (EC) No 1394/2007
- “Scientific Aspects and Working definitions for the mandatory scope of the centralised procedure (EMEA/CHMP/121944/2007)”.
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1 on “Marketing authorisation”
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4 on “Centralised Procedure”
2. How and when should the eligibility request be sent to the EMA?  

**Rev. Feb 10**

Regardless of whether the product falls into the mandatory or optional scope, or would have "automatic access" or access in accordance with the Paediatric or Advanced Therapy Regulation, an "eligibility request" should always be submitted using the specific form and accompanied by a justification of eligibility for evaluation under the centralised procedure. The applicant should clearly address the specific criterion fulfilled by the product to be eligible for the centralised procedure (for eligibility criteria see Q1).

Please note that:

1. In cases where products fall under the **mandatory scope** criterion (**Art. 3(1)** of the Regulation (EC) No. 726/2004), the relevant justification should be provided.

   For Advanced Therapy Medicinal Products (ATMPs), the relevant justification and documentation (including EMA scientific recommendation on classification of ATMPs by the Committee for Advanced Therapies (CAT) if available) should be provided.

   **NB:** Only one criterion can be chosen

2. In cases where products fall under one of the **optional scope** criteria (**Art. 3(2)** of the Regulation (EC) No. 726/2004), the justification should consist of a concise summary document of preferably two pages stating why the product should qualify for evaluation through the centralised procedure. The applicant should clearly state in the request which criterion the appended justification concerns:

   - **Art. 3(2) a:** New active substance; or
   - **Art. 3(2) b** Significant therapeutic innovation, or
   - **Art. 3(2) b** Significant scientific innovation or
   - **Art. 3(2) b** Significant technical innovation; or
   - **Art. 3(2) b** Interest of patient at the community level.

   **NB:** Only one criterion can be chosen and must be adequately justified; e.g. eligibility in accordance with Art 3(2)b of Regulation (EC) No. 726/2004 – Significant therapeutic innovation

3. In the following cases where the medicinal product applied for may have **automatic access** to the centralised procedure, this should be the basis for the justification to be submitted. This is the case when the medicinal product applied for, is either:

   - A "**generic/hybrid**" (**Art. 3(3)** of the Regulation (EC) No. 726/2004); or
   - A **duplicate/multiple**; or
   - An **informed consent**

   to a centrally authorised medicinal product, adequate and relevant information on the already centrally authorised medicinal product should be provided as background information (such as invented name/INN/ Commission Decision date/ type of application submitted and criteria/ indent under which the medicinal product was eligible to access the centralised procedure at the time (EMA letter to be annexed)).
4. When the medicinal product applied for, is either:

- an application including paediatric indication(s) in compliance with an agreed PIP (Art. 28 of Regulation (EC) No 1901/2006); or

- an application consisting of a new paediatric indication, a new pharmaceutical form and/or a new route of administration in compliance with an agreed PIP for a nationally authorised medicinal product (Art. 29 of Regulation (EC) No 1901/2006); or

- an application for a Paediatric Use Marketing Authorisation (PUMA) (Art. 31 of Regulation (EC) No 1901/2006),

adequate and relevant information should be provided (such as copy of the EMA PIP decision to be provided in annex), details of the paediatric indication/form/route applied for and a listing of the study data collected in accordance with the PIP which will be submitted in the planned application).

When submitting a request, the applicant should use the Pre-submission request form (Eligibility) and send it electronically to: CPeligibility@ema.europa.eu, together with a separate Annex 1 (draft Summary of Product Characteristics) and Annex 2 (Justification for Eligibility) especially required for medicinal products falling under the optional scope of Article 3(2)b.

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 could be submitted as part of the "letter of intent to submit". For Eligibility requests submitted as part of the "letter of intent to submit", Rapporteurs will be automatically appointed following the confirmation of the eligibility to the centralised procedure provided that the planned submission date is within 6-7 months.

The eligibility request and supporting documentation should be submitted to the EMA 10 calendar days before the CHMP meeting (see enclosed table for submission deadlines), so as to ensure its inclusion in the next CHMP agenda.

Any request received after the deadline will be considered the following month.

The eligibility will be evaluated on a case-by-case basis by the EMA/CHMP. The applicant will, in all cases, be informed of the CHMP opinion, the week following the CHMP meeting where the discussion took place.

NB: Review of eligibility applications made under Article 3(2)b will take place over 2 consequent CHMP meetings because of the need to appoint a sponsor(s) to assess the request.

References

- Regulation (EC) No 726/2004
- Regulation (EC) No 1394/2007
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4 on "Centralised Procedure"
- "Scientific Aspects and Working definitions for the mandatory scope of the centralised procedure" (EMEA/CHMP/121944/2007)
3. What will be the legal basis for my application?

Rev. Feb 08

The applicant should clearly indicate the legal basis for the submission of their application in the EU Application Form, i.e. select one of the following articles of Directive 2001/83/EC:

- Article 8(3) - Full application
- Article 10 - Generic, hybrid or similar biological application
- Article 10a - Well-established use application
- Article 10b - Fixed combination application
- Article 10c - Informed consent application

At pre-submission meetings, it is strongly recommended to discuss the proposed legal basis in view of the available data, with the EMA in order to prevent difficulties at validation.

3.1. Article 8(3) - Full application:

For full applications according to Article 8(3) of Directive 2001/83/EC, the results of pharmaceutical tests (physico-chemical, biological or microbiological), pre-clinical tests (pharmacological and toxicological), and clinical trials need to be submitted. Detailed data requirements are set-out in Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC.

Any deviations from these requirements, in particular, absence of a study/test report, requires a justification as to why the results are not provided and whether the requirements as set out in the Annex I to Commission Directive 2001/83/EC, are considered fulfilled.

Justifications are to be provided in the respective non-clinical and clinical overviews in Module 2. Further guidance on the drafting of such justifications is provided below. There is a possibility to use “umbrella” justifications to cover absence of more than one study report or more than one indent provided that is clear that the justification applies to several study reports. There is no need, however, to create and include a document in Module 4 and 5 which (only) refers to the presence of a justification in Module 2.

3.1.1. ‘Full-mixed’ application:

Where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references this kind of application has also to be submitted according to Article 8(3) of Directive 2001/83/EC (So-called ‘full-mixed’ application - see also section on ‘mixed’ marketing authorisation application in Part II of Annex I to the Directive).

A justification for not having performed certain tests/trials and for providing literature references instead, should be provided as to why the references provided by the applicant can replace the study reports, and how the results presented fulfill the requirements as set out in the Annex I to Commission Directive 2001/83/EC. The general principles for ‘justifications’ as outlined above also apply to full-mixed applications.

Such literature references, when replacing required study reports, should be included in the relevant Module 4/5 indents and should be summarised in Module 2 as required for any other study report.
“Supportive-only” literature references (i.e. provided in addition to study reports), should be provided in the CTD sections for “references” and do not need to be summarized in Module 2.

3.1.2. Guidance for the preparation of the Non-clinical and/or clinical Overviews in case of Art 8.3 (Full or “Full-mixed”) marketing authorisation applications:

- For each item of section 4.1 and 5.1 of Part I of the Annex I to Dir 2001/83/EC, the Applicant should indicate whether the Application contains the results of pre-clinical tests or clinical trials in the format of detailed study reports (hereafter referred to as “study reports”), and/or in the format of bibliographical references, or no information at all.

- If study reports are provided and cover all the requirements for a specific section, no further justifications are required.

- If results are submitted in the form of bibliographical references for a specific item, a justification is required as to why the references provided by the applicant can replace the study reports, and how the results presented fulfill the requirements as set out in the Annex I to Commission Directive 2001/83/EC.

- If no results are provided for a certain test or trial, a justification is required as to why the results are not provided and whether the requirements as set out in the Annex I to Commission Directive 2001/83/EC, are considered fulfilled. A simple statement such as “Not Applicable” is not an acceptable justification.

Justifications for absence of study reports in each of the sections can be based, for example, on the following principles:

- Specific derogations foreseen in Directive 2001/83/EC;

- Specific derogations foreseen in CHMP Guidelines;

- Animal welfare¹ and ethical considerations² coupled with expert assessment that further tests or trials are unlikely to extend scientific knowledge of subject area;

- Expert assessment that repetition of certain tests or trials is unlikely to extend scientific knowledge of subject area (e.g., extent of clinical experience with active substance at the time of development to replace certain non-clinical tests);

- Scientific argumentation regarding inapplicability of such tests and trials;

- Inability to provide comprehensive data in accordance with Article 14(8) of Regulation (EC) No 276/2004 and as outlined in general provisions of Section 6 of Part II of the Annex to Commission Directive 2001/83/EC (applications in exceptional circumstances);


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2 Declaration of Helsinki
3.2. Article 10 - Generic, hybrid or similar biological applications

3.2.1. Generic applications:

According to Article 10(1) of Directive 2001/83/EC, the applicant is not required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a reference medicinal product which is or has been authorised under Article 6 of Directive 2001/83/EC for not less than 8 years in a Member State or in the Community.

A generic medicinal product is defined as a medicinal product that has:

- the same qualitative and quantitative composition in active substances as the reference product,
- the same pharmaceutical form as the reference medicinal product,
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

This type of application refers to information that is contained in the dossier of the authorisation of the reference medicinal product, for which a marketing authorisation has been granted in the Community on the basis of a complete dossier in accordance with article 8(3), 10a, 10b or 10c of Directive 2001/83/EC.

It should be noted that the period of 8 years from initial authorisation of the reference medicinal product, providing a period of so-called “data exclusivity”, only applies to those reference medicinal products for which the initial application for authorisation was submitted through the centralised procedure after 20 November 2005.

3.2.2. Hybrid applications:

Hybrid applications under Article 10(3) of Directive 2001/83/EC differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following three circumstances:

- where the strict definition of a ‘generic medicinal product’ is not met;
- where the bioavailability studies cannot be used to demonstrate bioequivalence;
- where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product.

In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC as amended by Directive 2003/63/EC.

These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data. Some guidance on the appropriate additional studies required is indicated in Annex IV of the Chapter 1 of the Notice to Applicants.

3.2.3. Similar biological application:

In Article 10(4) of Directive 2001/83/EC it is stated that where a biological medicinal product which is similar to a reference biological product, does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the similar biological medicinal product and the reference biological
medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I to Directive 2001/83/EC and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

The chosen reference medicinal product must be a medicinal product authorised in the Community, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC.

3.3. Article 10a - Well-established use application:

According to Article 10a of Directive 2001/83/EC, as amended it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substances of a medicinal product have been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

The following criteria for the demonstration of such well-established use should be taken into account:

- the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods;
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments;

For such applications, the provisions of the Annex I to Directive 2001/83/EC apply in like manner. They are considered as full and independent applications. Applicants should submit Modules 1, 2 and 3 as described in Part I of Annex I to Directive 2001/83/EC. For Modules 4 and 5, a detailed scientific bibliography shall address all required pre-clinical and clinical characteristics, and should be summarised in Module 2. As with any other full application, if parts of the dossier are incomplete, particular attention must be paid to justify such absences in the non-clinical/clinical overviews.

It should be noted that, if well-known substances are used for entirely new therapeutic indications, it is not possible to solely refer to a well-established use and additional data on the new therapeutic indication together with appropriate pre-clinical and human safety data should be provided. In such case, Article 8(3) of Directive 2001/83/EC should be used as legal basis.

3.4. Article 10b - Fixed combination application:

According to Article 10b of Directive 2001/83/EC, in the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i) of the same Directive, but it shall not be necessary to provide scientific references relating to each individual active substance.

The combination of active substances within a single pharmaceutical form of administration according to this provision is a so-called 'fixed combination'.

Applications for fixed combination medicinal products can be accepted and validated under Article 10b on condition that the individual substances have been authorised as a medicinal product in the EEA via a Community or national procedure.
It follows from the wording of Article 10b as well as from Part II.5 of Annex I to the Directive 2001/83/EC as amended, that a full dossier, comprising all the information of modules 1 to 5, has to be provided in relation to the fixed combination. Any absence of specific fixed combination data should be duly justified in the Non-clinical and/or clinical Overviews (see general guidance above).

Although there is no requirement for the inclusion of data on the individual active substances, it is possible to include information on the individual substances (literature or actual data), especially in order to justify the absence of certain specific data on the combination.

3.5. Article 10c - Informed consent application:

According to Article 10c of Directive 2001/83/EC as amended, following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, non clinical and clinical documentation contained in the dossier of the medicinal product for the purpose of examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

It is a prerequisite for the use of Article 10c as legal basis that consent has been obtained from the marketing authorisation holder of the reference product for all three modules containing the pharmaceutical, pre-clinical and clinical data (modules 3, 4 and 5), and the applicant of the informed consent application should have permanently access to this documentation or should be in possession of the information.

For such informed consent applications, only a complete module 1 should be submitted, including the Application Form with relevant Annexes (e.g. copy of correspondence with the European Commission for multiple applications, if applicable, see also Q9 – multiple applications, and the letter of consent from the MAH of the authorised medicinal product allowing access to modules 2, 3, 4, 5 of the initial dossier and any subsequent documentation submitted)

If the dossier of the authorised medicinal product includes an ASMF, a new letter of access should be included in module 1 of the informed consent application.

References

- Regulation (EC) No 726/2004
- Directive 2001/83/EC, as amended
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1
- EMEA guidance for users of the Centralised Procedure for generic/hybrid applications (CHMP/225411/2006)
- CHMP Guideline on similar biological medicinal products (CHMP/437/04)
4. How will I know if the proposed (invented) name of my medicinal product is acceptable from a public health point of view? Rev. Jan 13

In accordance with Article 6 of Regulation (EC) No 726/2004, “each application for the authorisation of a medicinal product for human use (...), otherwise than in exceptional cases relating to the application of the law on trademarks, shall include the use of a single name for the medicinal product.” The Centralised Procedure therefore requires one single name for the medicinal product to be authorised.

According to Article 1(20) of Directive 2001/83/EC, as amended, the name of the medicinal product “may be either an invented name not liable to confusion with the common name, or a common name or scientific name accompanied by a trademark or the name of the Marketing Authorisation Holder”. It is also understood by legislation that a common name is according to Article 1(21) of Directive 2001/83/EC, as amended, “The international non-proprietary name (INN) recommended by the World Health Organisation, or, if one does not exist, the usual common name”.

Although it is not mandatory under Community legislation, in practice, many companies submitting marketing authorisation applications under the Centralised Procedure wish to use invented names for their medicinal products.

As part of the EMA’s role in evaluating the safety of medicinal products in the centralised procedure, it is obliged to consider whether the (invented) name proposed for a medicinal product could create a public-health concern or potential safety risks.

In particular, the (invented) name of a medicinal product:

- should not convey misleading therapeutic or pharmaceutical connotations;
- should not be misleading with respect to the composition of the product;

In order to identify, at an early stage, potential difficulties presented by the (invented) name(s) proposed by an applicant, the EMA/CHMP set up the Name Review Group (NRG), to perform the review of names. The NRG is also responsible for updating the "Guideline on the acceptability of names for human medicinal products processed through the centralised procedure" (CPMP/328/98).

4.1. The Name Review Group (NRG)

The NRG is composed of representatives of EU Member States and is chaired by an EMA representative. Representatives of the European Commission and the EMA Secretariat also participate in the work of the group. Other relevant experts (e.g. WHO experts) are consulted on a case-by-case basis.

The NRG meets 6 times a year (approximately every 2 months). Its conclusions are presented for adoption at the subsequent CHMP plenary meeting.

The criteria applied by the NRG when reviewing the acceptability of proposed invented names are detailed in the “Guideline on the acceptability of names for human medicinal products processed through the centralised procedure” (CPMP/328/98), hereafter referred to as the ‘Guideline’.
4.2. The EMA procedure for checking proposed (invented) names

4.2.1. Submission of the (invented) name request by the Applicant/MAH

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 and preferably 4-6 months prior to the planned submission date of the marketing authorisation application. See also Question 4a. What are the dates for submission of invented name requests for the deadlines for submission of Proposed (Invented) Names.

The ‘Proposed (Invented) Name request form’, along with either a draft Summary of Product Characteristics (SmPC) or a product profile and any other relevant information, should be sent to the EMA at the e-mail address: NRG@ema.europa.eu. An electronic request form (in pdf format) has been developed and replaces the current form in word format.

The applicant is advised to propose up to four invented names per marketing authorisation application. All proposed names are reviewed independently of the company’s preference.

Applicants should follow the criteria described in the ‘Guideline’ when proposing (invented) names and would be expected to review the proposed (invented) name, applying the criteria before requesting that an invented name be considered. Where the applicant deviates from these criteria, justification should be provided.

Where the applicant submits proposed (invented) names intended to be used in the context of multiple marketing authorisations/applications, it shall specifically request the NRG to consider whether the proposed (invented) names cannot be considered potentially confusing with each other (see also question on Multiple Applications).

4.2.2. Consultation with the Member States and WHO and NRG discussion/CHMP adoption

The proposed (invented) name(s) and all the background information provided by the applicant(s)/MAH(s) are sent to every NRG contact point nominated by National Competent Authorities (NCAs) of EU Member States, the European Commission (EC) and the World Health Organisation (WHO) for their review and will subsequently be discussed at the NRG meeting. The detailed procedure is described in the ‘Guideline’.

The NRG conclusions/recommendations are presented for adoption to the subsequent CHMP plenary meeting, after which the applicant will be informed of the outcome of the discussion on the acceptability of the proposed (invented) name(s) for their medicinal product together with the reasons and source for the objections(s) raised, where applicable. See also Question 4a. What are the dates for submission of invented name request for the dates of NRG discussion/CHMP adaption.

4.2.3. Rejection by NRG/CHMP of a proposed (invented) name

In case of rejection of a proposed (invented) name by NRG/CHMP, the applicant/MAH has got the following possibilities:

- To submit new (invented) names proposals, which are checked through the same procedure as described above.
- To provide a justification to retain the (invented) name (addressing specifically all the objections raised) using the ‘Proposed (Invented) Name Request form’ and selecting ‘Justification Form’ in the
‘Form Type’ area. Such justification will be reviewed as described in the ‘Guideline’. If the proposed (invented) name cannot be accepted prior to submission, the Marketing authorisation application can be submitted under either any of the proposed (invented) names or the common name or scientific name accompanied by a trademark or the name of the MAH.

At the latest one month prior to the adoption of the CHMP opinion on the concerned MAA, the applicant will in such case have to inform the EMA and the NRG Secretariat on the acceptable invented name of their choice.

- If no suitable invented name has been identified at that stage, the opinion will be adopted using the common name or scientific name accompanied by the name of the MAH. Applicants are hereby reminded that such name also needs NRG review and acceptance by the CHMP prior to the adoption of the opinion. In this case, as soon as the Commission Decision is granted, the MAH may submit a variation to introduce an invented name, on the condition that such name has been considered acceptable by the NRG.

- Exceptionally, provided all means have been exhausted, the applicant/MAH may request the matter to be presented to the CHMP within the context of the evaluation of the medicinal product (e.g. oral explanation).

**4.2.4. Change of the (invented) name after the marketing authorisation is granted**

In accordance with Commission Regulation (EC) No 1234/2008, the (invented) name of a medicinal product may be changed after a marketing authorisation is granted through a Type IAIN (No A.2) variation procedure.

This can be done either in case of a marketing authorisation being granted under INN or common name together with a trademark or the name of the MAH or in case the MAH wants to change the initial invented name.

Such Type IAIN variation is possible provided that the check by the Agency on the acceptability of the new name had been finalised and was positive before implementation of the new name. Immediately upon implementation of the change, the MAH must submit a Type IAIN variation notification to the Agency for review (see the EMA Post-Authorisation Procedural Advice on Type IA variations).

Taking into account that the MAH will be required to submit the EMA letter of acceptance of the concerned (invented) name as part of the variation application, it is recommended that the proposed invented name be submitted at least 4-6 months in advance of the foreseen implementation date and submission of the Type IAIN variation notification.

**References**

- Regulation (EC) No 726/2004
- Directive 2001/83 EC as amended
- "Centralised Procedure", The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4
- "Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure” (CHMP/328/98)
- Regulation (EC) No 1234/2008
- "Post-Authorisation Procedural Advice Human Medicinal Products" (EMEA-H-19984/03)
5. How shall I compose the complete name of my medicinal product? *Rev. May 11*

Each medicinal product should be placed on the market under a name and in a package suitable to ensure identification and differentiation. A medicinal product authorised under the Centralised Procedure must have the same name in all EU Member States.

The medicinal product should be identified in the product information according to the following rule: the name of the medicinal product should be followed by the strength and the pharmaceutical form. However, when otherwise referring to the medicinal product throughout the product information text, the strength and the pharmaceutical form do not have to be mentioned in the name.

In the SPC, the INN or the common name of the active substance should be used when referring to properties of the active substance(s) rather than the invented name. The use of pronouns (e.g. “it”) is encouraged whenever possible.

Thus, whenever the “name of the medicinal product” is specifically required to be provided in the SPC, labelling (on the outer or immediate packaging or on blisters) or the Package Leaflet, it should be written in the following order as:

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{(invented) name strength pharmaceutical form}, whereby
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- **invented name:** no ® ™ symbols attached
- **Pharmaceutical form:**
  The pharmaceutical form should be stated according to the full “Standard Terms” published by the Council of Europe, in the singular (except for tablets and capsules). Where the Council of Europe short standard term is used on small immediate packaging materials (blisters, strips, small immediate packaging units) in case of space limitation, the short term should be added in brackets in section 3 of the SPC.

  E.g.  
  (invented name) X mg hard capsules  
  (invented name) Y mg/g cream

- The different strengths of fixed-combination products should be presented separated by a “/”.

  E.g.  
  (invented) name 150 mg/12.5 mg tablets

For mock-ups and specimens, this information may be presented on different lines of text or in different font sizes if necessary, provided that the appearance of the name is as an integrated item.

E.g.  
(invented) name Z mg/ml  
Solution for injection

Where the INN or the common name is to be provided in addition to an invented name, this should preferably be given on the line of text directly below the complete name.
References

- Directive 2001/83/EC title I, II and V, as amended
- "Guideline on the readability of the label and package leaflet of medicinal products for human use", the Rules governing Medicinal products in the European Community, Volume 2C, Notice to applicants
- "Guideline on Summary of Product Characteristics", the Rules governing Medicinal products in the European Community, Volume 2C, Notice to applicants
- QRD Product Information Template with explanatory notes
6. What legal status can I obtain for my medicinal product?  
*Rev. July 06*

In accordance with Article 9(4)(b) of Regulation (EC) No 726/2004, the documents annexed to the CHMP favourable opinion to the granting of a Marketing Authorisation for a medicinal product shall include “details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, in accordance with the criteria laid down in Title VI of Directive 2001/83/EC, as amended”.

The classification for the supply of the medicinal product to the patient is also referred to as ‘Legal Status’.

6.1. Categories for the Legal Status of a medicinal product

At the first level, ‘main categories’, the medicinal product is classified either as:

- subject to medical prescription or
- not subject to medical prescription

To this end, the criteria laid down in Article 71(1) of Directive 2001/83/EC, as amended, should be taken into account.

For products subject to medical prescription, where applicable, there is a second level and the EMA may have to apply one of the following additional ‘sub-categories’, in accordance with Article 70(2) of Directive 2001/83/EC as amended:

- Medicinal product subject to special medical prescription
- Medicinal product on restricted medical prescription, reserved for use in certain specialised areas

To this end, the factors laid down in Article 71 paragraphs 2 and 3 should be taken into account.

Medicinal products, which meet the criteria for both above-mentioned ‘sub-categories’, will be subject to special and restricted medical prescription.

There is another ‘sub-category’ foreseen in Article 70(2) of Directive 2001/83/EC, as amended, i.e.: ‘medicinal products on medical prescription for renewable or non-renewable delivery’. The definition and therefore also the implementation may vary in those Member States where the ‘sub-category’ exists. Therefore it has been decided that for centrally authorised products such ‘sub-category’ will not be explicitly mentioned in the Opinion/Decision, leaving for Member States the possibility of the implementation of the ‘sub-category’ in accordance with national measures and in compliance with the content of the SPC.

6.2. Implementation of the Legal Status in the CHMP Opinion

At the pre-submission stage applicants should include a proposed classification for the supply of the medicinal product in their “notification of intention to submit an application” to be sent to the EMA at least 7 months before submission. At the time of the submission of the application applicants should indicate their proposal for Legal Status in the section 2.3 of the Module 1 application form (available in the Notice to Applicants (NTA) Volume 2B - Application Form: Module 1.2 Application form).
The CHMP refers to the above-mentioned criteria and factors where it comes to take a decision on the Legal Status.

The Legal Status will be mentioned in the CHMP opinion and in the Commission decision.

In the CHMP opinion, the Legal Status will be reflected in the following annexes:

- Annex I of the CHMP opinion (Summary of Product Characteristics)

Wherever appropriate, the SPC will include in section 4.2 an explanation on how the medicinal product should be supplied to patients (e.g. to be administered in a hospital setting or prescribed by specialists only, or specific type of care during the treatment of a chronic disease).

- Annex II.B of the CHMP opinion (Conditions or restrictions regarding supply and use) should mention one of the categories below:
  - medicinal product not subject to medical prescription
  - medicinal product subject to medical prescription
  - medicinal product subject to special medical prescription
  - medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)
  - medicinal product subject to special and restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- Annex III.A of the CHMP opinion (Labelling)

The outer packaging should mention either “medicinal product not subject to medical prescription” or “medicinal product subject to medical prescription” (without specifying "restricted" and/or "special")

As regards mock-ups and specimens, the use of any 'sub-category' at national level (e.g. renewable/non-renewable) and the information required to express this, should be addressed in the blue box (see also "When shall I submit mock-ups and/or specimens?").

This information may concern either one, or more, 'sub-categories' listed in Article 70(2) of Directive 2001/83/EC as amended, or a specific way of conveying particular information about the Legal Status. Some Member States use symbols or expressions/specific wordings. Such symbols or expressions are set out in the Annex to the "Guideline on the packaging information of medicinal products for human use authorised by the Community". The EMA strongly advises Applicants to follow this guideline since compliance with the guideline ensures compliance with Community legislation.

### 6.3. Change of Legal Status

According to Article 74 of Directive 2001/83/EC as amended, when new facts are brought to its attention, the EMA shall examine and, as appropriate, amend the classification of a centrally authorised medicinal product, by applying the criteria listed in Article 71 of that Directive.

The data requirements for an application to change the classification for the supply of a medicinal product from to prescription to non-prescription ("Switch") are outlined in Part 2 of the "Guideline on changing the classification for the supply of a medicinal product for human use".

In addition, according to Article 74a of the same Directive, a change of classification may benefit from one year of protection. This 1-year period of protection covers significant pre-clinical tests or clinical trials carried out for the purpose of substantiating an application for a change of classification.
Commission decisions authorising a change of classification will contain a clear statement of whether the change is based on significant pre-clinical tests or clinical trials. A change of classification authorised after 20 November 2005 may benefit from this year of protection.

Further information on Legal Status is provided in the “Guideline on Legal Status for the supply to the patient of centrally authorised medicinal products” (EMEA/186279/2006).

References

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- Guideline on Legal Status for the supply to the patient of centrally authorised medicinal products (EMEA/186279/2006)
- “Guideline on the packaging information of medicinal products for human use authorised by the Community” the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
- “Guideline on changing the classification for the supply of a medicinal product for human use” the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
7. What is the procedure for appointment of CHMP Rapporteur/Co-Rapporteur and their assessment teams?

Rev. May 10

7.1. Overview of the appointment procedure

For any scientific evaluation in respect of a procedure, a Rapporteur, and if relevant a Co-Rapporteur, shall be appointed from amongst the members of the CHMP (including co-opted members) and CHMP alternate members. For Advanced Therapy Medicinal Products, a Rapporteur, and if relevant a Co-Rapporteur, shall be appointed from amongst the members of the Committee for Advanced Therapies (CAT) and alternate members. In addition up to two CHMP Co-ordinators will be appointed (one supporting the CAT Rapporteur assessment team and another supporting the CAT Co-Rapporteur assessment team).

- The Rapporteur/Co-Rapporteur is supported by a team of assessors/experts (assessment team) during the various phases of the assessment of the application.
- In the pre-authorisation phase of the Marketing Authorisation Application (MAA), two Rapporteurs (i.e. a Rapporteur and a Co-Rapporteur) are appointed.
- Normally, the Rapporteur (and her/his assessment team) would be the leader in the centralised post-authorisation phase.

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 European Economic Area (EEA) on the relevant scientific area.

7.1.1. Methodology regarding the appointment of Rapporteur/Co-Rapporteur and their assessment teams

Applicants are strongly advised to notify the EMA of their intended marketing authorisation application submission date, by sending the Pre-submission request form (Intent to submit MA) to pubs@ema.europa.eu. Submission dates must be as realistic and accurate as possible. Such information is crucial to the EMA and to the future appointed (Co) Rapporteurs and their assessment teams for planning purposes.

The appointment procedure for the CHMP Rapporteur/Co-Rapporteur and their assessment teams is usually initiated following the receipt of the letter of intention to submit the MAA and their request to assign Rapporteurs. However, the appointment procedure will not be initiated until 7 months prior to the Marketing Authorisation Application intended submission date at the earliest.

For further information on the content of the letter of intent see Chapter 4 (Centralised Procedure) of Volume 2A (Notice to Applicants). Such appointment is not always connected to a possible earlier request for eligibility for assessment via the centralised procedure.

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3 The involvement of the Co-Rapporteur is deemed necessary in: a) the centralised pre-authorisation phase b) the assessment of a Type II variation application concerning new indication(s) c) renewals of centrally authorised medicinal products and d) referral procedures. The involvement of the Co-Rapporteur in other variations/post-authorisation procedures will be agreed by the CHMP on a case-by-case basis.
The deadline for Applicant’s to send their letter of intention to submit the MAA and their request to assign Rapporteurs is 7 months prior to the MAA submission intended date (see also question "What are the submission dates for Rapporteur appointment requests?").

The actual appointment takes place 6 months prior to the intended submission date.

Please note that the Applicant’s proposals/preferences will not be considered for the appointment of Rapporteur/Co-Rapporteur.

Example:

If the intended submission date is 4th January 2011 (i.e. recommended submission date for a new application), then the Applicant should notify the EMA/CHMP secretariat 7 months in advance, i.e. by 11th June 2010. The Pre-submission request form (Intent to submit MA) and the request to assign Rapporteurs should be received by the EMA by Agency no later than Friday 11th June 2010.

Appointment of Rapporteurs shall take place at the July 2010 CHMP meeting.

7.1.2. Methodology regarding the appointment of Rapporteur/Co-Rapporteur and their assessment teams for Advanced Therapy Medicinal Products

Applicants are strongly advised to notify the EMA of their intended marketing authorisation application submission date by sending the Pre-submission request form (Intent to submit MA) to pa-bus@ema.europa.eu. Submission dates must be as realistic and accurate as possible. Such information is crucial to the EMA and to the future appointed (Co) Rapporteurs and their assessment teams for planning purposes.

The appointment procedure for the CAT Rapporteur/Co-Rapporteur and their assessment teams and CHMP Co-ordinators is usually initiated following the receipt of the Pre-submission request form (Intent to submit MA) and their request to assign Rapporteurs. However, the appointment procedure will not be initiated until 7 months prior to the Marketing Authorisation Application intended submission date at the earliest.

For further information on the content of the letter of intent see Chapter 4 (Centralised Procedure) of Volume 2A (Notice to Applicants). Such appointment is not always connected to a possible earlier request for eligibility for assessment via the centralised procedure.

The deadline for Applicant’s to send their letter of intention to submit the MAA and their request to assign CAT Rapporteurs and CHMP Co-ordinators is 7 months prior to the MAA submission intended date (see also submission dates for Rapporteur appointment requests)

The actual appointment takes place 6 months prior to the intended submission date.

Please note that the Applicant’s proposals/preferences will not be considered for the appointment of Rapporteur/Co-Rapporteur.

7.2. Appointment of Rapporteur/Co-Rapporteur and their assessment teams for generic/hybrid medicinal products

7.2.1. Principles

Due to the particularities of generic/hybrid applications (e.g. legal basis, data requirements), the following principles are considered for the appointment of Rapporteur/Co-Rapporteur and their assessment teams:
• A Rapporteur is appointed for the scientific evaluation of a generic/hybrid medicinal product.
  – Rapporteurships are open to all CHMP delegations. The scope of these Rapporteurships relate to the pre-authorisation phase and the introduction of quality changes in the post-authorisation maintenance phase.
  – For the scientific evaluation of a hybrid medicinal the appointment of a Co-Rapporteur is considered on a case-by-case basis (depending on the particularity of the applied hybrid medicinal product).
• For pharmacovigilance surveillance activities of a generic/hybrid medicinal product, a pharmacovigilance (PhV) Rapporteur is appointed.
• The PhV Rapporteur is the same as previously appointed for the reference medicinal product. The reference medicinal product of a generic/hybrid medicinal product can be authorised through a centrally authorised procedure, a Mutual Recognition/ Decentralised procedure (MRP/DCP) or a national procedure.

7.2.2. Methodology

Applicants are strongly advised to notify the EMA of their intended submission date, by sending the Pre-submission request form (Intent to submit MA) to pa-bus@ema.europa.eu. Submission dates must be as realistic and accurate as possible. Such information is crucial to the EMA and to the future appointed (Co) Rapporteurs and their assessment teams for planning purposes.

The appointment procedure for the CHMP Rapporteur/Co-Rapporteur and their assessment teams is usually initiated following the receipt of the Pre-submission request form (Intent to submit MA) and their request to assign Rapporteurs. Such appointment is not always connected to a possible earlier request for eligibility for assessment via the centralised procedure.

The deadline for Applicants to send their letter of intention to submit the MAA and their request to assign Rapporteurs is 7 months prior to the MAA submission intended date (see also submission dates for Rapporteur appointment requests:(q07a)). The actual appointment takes place 2-6 months prior to the intended submission date. At the same time the PhV Rapporteur will be identified.

Please note that the Applicant's proposals/preferences will not be considered for the appointment of Rapporteur/Co-Rapporteur

7.3. Appointment of Rapporteur/Co-Rapporteur and their assessment teams for similar biological medicinal products

7.3.1. Principles

Due to the particularities of the similar biological medicinal products applications (e.g. legal basis, data requirements), the following principles shall be considered on the appointment of CHMP Rapporteur/Co-Rapporteur and their assessment teams:

• For the scientific evaluation of a similar biological medicinal product a Rapporteur and a Co-Rapporteur will be appointed.
• The EMA Secretariat shall handle and finalise all other post-authorisation activities (i.e. "administrative" harmonisation between the reference (see below) and the similar biological medicinal product). The reference medicinal product of a similar biological medicinal product can
be authorised through a centrally authorised procedure, an Ex-concertation/Mutual Recognition/Decentralised procedure (MRP/DCP) or a national procedure.

7.3.2. Methodology

Applicants are strongly advised to notify the EMA of their intended submission date, by sending the Pre-submission request form (Intent to submit MA) to pa-bus@ema.europa.eu. Submission dates must be as realistic and accurate as possible. Such information is crucial to the EMA and to the future appointed (Co) Rapporteurs and their assessment teams for planning purposes.

The appointment procedure for the CHMP Rapporteur/Co-Rapporteur and their assessment teams is usually initiated following the receipt of the Pre-submission request form (Intent to submit MA) and their request to assign Rapporteurs. Such appointment is not always connected to a possible earlier request for eligibility for assessment via the centralised procedure.

The deadline for Applicants to send their letter of intention to submit the MAA and their request to assign Rapporteurs is 7 months prior to the MAA submission intended date. The actual appointment takes place 6 months prior to the intended submission date.

Please note that the Applicant’s proposals/preferences will not be considered for the appointment of Rapporteur/Co-Rapporteur.

7.4. Appointment of Rapporteur/Co-Rapporteur and their assessment teams for non-prescription medicinal products

7.4.1. Principles

Due to the particularities of non-prescription medicinal products (e.g. self-care environment, data requirements), the following principles are considered for the appointment of Rapporteur/Co-Rapporteur and their assessment teams:

- For the scientific evaluation of a non-prescription medicinal product a Rapporteur and a Co-Rapporteur shall be appointed.
  
  - In the pre-authorisation phase both the Rapporteur and Co-Rapporteur shall be involved. The appointment process shall be open to all CHMP delegations however specific experience in non-prescription medicinal product assessments shall be sought. Additional experience with change in legal status from prescription to non-prescription will also be requested. Experience in communication with patients is also foreseen.
  
  - In the post-authorisation phase, when a change in legal status is foreseen (e.g. switch from prescription to non-prescription), a peer reviewer shall be appointed to work with the existing Rapporteur and Co-Rapporteur already in place for the given medicinal product. The suitable candidate for peer review should have relevant knowledge of the area of non-prescription medicinal products and if possible previous experience in changing the legal status of a medicine/active substance from prescription to non-prescription.

7.4.2. Methodology

Applicants are strongly advised to notify the EMA of their intended submission date by sending the Pre-submission request form (Intent to submit MA) to pa-bus@ema.europa.eu. Submission dates must be as realistic and accurate as possible. Such information is crucial to the EMA and to the future appointed (Co) Rapporteurs and their assessment teams for planning purposes.
The appointment procedure for the CHMP Rapporteur/Co-Rapporteur and their assessment teams is usually initiated following the receipt of the Pre-submission request form (Intent to submit MA) and their request to assign Rapporteurs. Such appointment is not always connected to a possible earlier request for eligibility for assessment via the centralised procedure.

The deadline for Applicants to send their letter of intention to submit the MAA and their request to assign Rapporteurs is 7 months prior to the MAA submission intended date (see also submission dates for Rapporteur appointment requests:(q07a)).

The actual appointment takes place 6 months prior to the intended submission date.

In case of a change in legal status (prescription to non-prescription), the appointment of a peer reviewer will be initiated at a CHMP meeting prior to the intended submission date.

Please note that the Applicant’s proposals/preferences will not be considered for the appointment of Rapporteur/Co-Rapporteur

7.5. Appointment of Rapporteur/Co-Rapporteur for re-examination of a CHMP opinion

7.5.1. Principles

In cases of re-examination of a CHMP opinion a Rapporteur and a Co-Rapporteur shall be appointed. For CHMP opinions where the Co-Rapporteur was not involved in the evaluation, no Co-Rapporteur needs to be appointed. In cases of re-examination of a CHMP opinion for an advanced therapy medicinal product, a different CAT Rapporteur and a different CAT Co-Rapporteur shall be appointed together with two new CHMP Co-ordinators.

A different Rapporteur and, where applicable, a different Co-Rapporteur from those appointed for the initial evaluation shall be appointed in order to adequately assess the grounds for the re-examination of the CHMP opinion. These Rapporteurs will coordinate the evaluation for the duration of the re-examination procedure only.

7.5.2. Methodology

The Rapporteur, Co-Rapporteur (if applicable) appointment process will be initiated as soon as the EMA/CHMP receives written notice that the applicant/MAH wishes to request a re-examination of the CHMP opinion.


References

- Regulation (EC) No 726/2004
“Centralised Procedure”, the Rules governing Medicinal Products in the European Community, Volume 2A, Notice to Applicants, Chapter 4
8. Is my product eligible for an Accelerated Assessment

Rev. Feb 10

8.1. Legal basis and general principles

According to Articles 6(3) and 7c of Regulation (EC) No 726/2004, the maximum timeframe for the evaluation of a marketing authorisation application under the Centralised Procedure is 210 days, excluding clock stops when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP.

However, according to Recital 33 and Article 14(9) of Regulation (EC) No 726/2004, the applicant may request an accelerated assessment procedure in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, for medicinal products of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.

Applicants requesting an accelerated assessment procedure should justify that the medicinal product is expected to be of major public health interest. Based on the request, the justifications presented, and the recommendations of the Rapporteurs, the CHMP will formulate a decision. Such a decision will be taken without prejudice to the CHMP opinion (positive or negative) on the granting of a marketing authorisation.

If the CHMP accepts the request, the timeframe for the evaluation will be reduced to 150 days.

8.2. Request for an accelerated assessment: timing and justification

Any request for accelerated assessment should be made as early as possible before the actual submission of the marketing authorisation application. The request, including the justification, should be sent electronically to the EMA product team leader and all CHMP members at least 10 working days in advance of the CHMP meeting preceding the intended start of the centralised procedure. In practice, submission of the request will generally occur at least between 10 to 30 days before the intended start of the procedure.

Applicants requesting an accelerated assessment procedure should duly substantiate the request and in particular, justify their expectation that the medicinal product is of major public health interest particularly from the point of view of therapeutic innovation. There is no single definition of what constitutes major public health interest. This should be justified by the applicant on a case-by-case basis.

The justification should include the major benefits expected and present the arguments to support the claim that the medicinal product introduces new methods of therapy or improves on existing methods, thereby addressing to a significant extent the greater unmet needs for maintaining and improving public health.

The key items to be described in the justification, and the appropriate level of detail, should be evaluated on a case-by-case basis. The request should be presented as a short but comprehensive document (ideal length 5-10 pages). The following list of key items would normally be addressed in the justification:

- the unmet needs and the available methods of prevention, diagnosis or treatment
• the extent to which the medicinal product is expected to have major impact on medical practice, its major added value, and/or how it addresses the greater unmet needs

• a brief outline of the main available evidence on which the applicant bases its claim of major public health interest

When submitting an accelerated assessment request, the applicant should use the [Pre-submission request form](#) (Accelerated Assessment) and Applicant’s justifications, which should be sent electronically, to: [pa-bus@ema.europa.eu](mailto:pa-bus@ema.europa.eu).

Alternatively, a paper version can be sent to the following mailing address:

Product and Application Business Support (PA-BUS)
European Medicines Agency EMA
7 Westferry Circus
Canary Wharf
London, E14 4HB
UK

Following receipt of the request, the Rapporteurs will produce a briefing note including the Rapporteurs’ recommendations as to the appropriateness of an accelerated assessment. The CHMP will consider the request submitted by the applicant, the Rapporteurs’ recommendations and the views of other CHMP members, in order to conclude on the acceptability or not of the request. If necessary, the CHMP may request clarifications from the applicant about the request. The CHMP conclusions will be communicated to the applicant. The reasons for accepting or rejecting the request will also be summarised in the CHMP assessment report.

If a request for an accelerated assessment procedure is granted, the CHMP will take into consideration the standard timetable agreed for the accelerated assessment procedure (see Section 6 of the “Guideline on the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004” (EMEA/419127/05)).

**References**

• [Regulation (EC) No 726/2004](#)

• "Guideline on the procedure for accelerated assessment pursuant to article 14 (9) of Regulation (EC) No 726/2004" (EMEA/419127/05)

• "Centralised Procedure“, the Rules governing Medicinal Products in the European Community, [Notice to Applicants, Volume 2A, Chapter 4](#)
9. If I intend to submit multiple applications for a specific medicinal product? Rev. Feb 12

The EMA is regularly approached by applicants wishing to obtain, either simultaneously or successively, more than one Marketing Authorisation for a specific medicinal product, under different invented names.

According to Article 82(1) of Regulation (EC) No 726/2004, the Commission may authorise applicants to submit more than one application to the EMA, when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health care professionals and/or patients or for co-marketing reasons.

Therefore, applicants will be asked to explain and justify the motives behind multiple applications and their intentions as far as the exploitation of the marketing authorisation is concerned.

In the framework of the article 82(1) of the Regulation, a specific procedure has been agreed between the EMA and the European Commission. Under this procedure Applicants should, approximately four months prior to the anticipated date of submission, notify the Commission of their motives for submitting multiple applications and provide the necessary explanation and justification addressing the article 82(1) of the Regulation (EC) No 726/2004 criteria, with a copy to the EMA, addressing either public health reasons or co-marketing reasons.

Such notification should be sent to the following address:

European Commission
Health and Consumers Directorate-General
Public Health and Risk Assessment
Unit C8, Pharmaceuticals
BREY 10/106
Avenue d'Auderghem, 45
B - 1040 Brussels
Belgium

The Commission will consider the situation, liaise with the Applicant(s) where appropriate and inform the Applicant(s) as to whether it would have specific objections to the granting of multiple Marketing Authorisations or not. The company will always need to include this Commission response as Annex 5.16 to the application form, as otherwise the Agency cannot validate such applications.

Procedural aspects

Multiple/duplicate applications for a specific medicinal product with an active substance(s) already under assessment via the centralised procedure have automatic access to the centralised procedure. Nevertheless, in all cases the eligibility of a medicinal product for evaluation via the centralised procedure needs to be requested by the applicant by submitting an eligibility request to the EMA. For details see Question 2. This has to be done prior to submission of any dossier and should also include the request for Rapporteur assignment.
For the assessment procedure, the objective is to ensure the adoption of a CHMP Opinion for a multiple application at the same time when the CHMP Opinion for the initial application is adopted. Therefore, for practical reasons, the EMA strongly recommends the following time points for the time for submission of the multiple application(s):

a. In parallel with the initial application submission (day 0)

b. Submission before the adoption of the list of questions (before the day 120) for the initial application

c. Submission at the time of the response to list of questions (day 121) for the initial application

It should be noted that multiple applications are subject to a full validation as they are stand-alone applications. Therefore, the validation outcome may differ from the one of the original application. Following the positive outcome of the validation, the evaluation of the multiple application(s) will be aligned with that of the ongoing initial application, in case the above timeframes have been duly observed by the applicant. The submission of the multiple application(s) should be done in advance, to allow sufficient time for the validation to be completed by D120 or D121 of the ongoing initial application. The validation period between submission date and start date is 13 EMA working days. Please observe the EMA procedural timetables.

Relevant aspects of the Paediatric legislation should be considered as appropriate for each of the multiple applications submitted. The Risk Management Plans for multiple applications should be product specific and reflect the particulars of each specific application (e.g. product details including differences in indication(s) in case of patent issues, RMP version number and date).

Multiple applications can also be submitted after the Commission Decision on the initial application as stand-alone applications or Informed Consent applications. Again, requirements for eligibility and Rapporteur assignment remain. However, as a rule, an abridged timetable for assessment will be adopted in line with a 60 days procedure. Submission of the application(s) should be done in advance to allow the completion of the validation before the intended start date of the procedure.

Applicants are reminded that multiple applications of the same marketing authorisation holder will be covered by the notion of “global marketing authorisation”.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1 and Chapter 4.
- EC communication on ‘Handling of Duplicate Marketing Authorisation Applications’ (March 2010) and Update 1 (October 2011)
- EMA procedural timetables

4 Later submission of the dossier is not recommended due to difficulties with its alignment with the original application.
10. What fee do I have to pay and how is the appropriate fee for my application calculated? Rev. Dec 10

Fees for obtaining and maintaining a Community authorisation to market medicinal products for human use are levied in accordance with Regulation (EC) No 297/95.

Since 1 December 2005, the EMA will issue an invoice on the date of the notification of the administrative validation to the applicant and fees will be payable in EURO within 45 calendar days of the date of the said notification. The invoice is sent to the billing address indicated by the Applicant, and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment.

Where more than one procedure is processed in a given month a summary invoice or statement is issued at the end of each month for payment within 30 days of the end of the month.

If the application cannot be validated, the EMA will issue an invoice on the date of the notification of the administrative non-validation to the applicant for an administrative charge to cover administrative costs.

Further details on EMA fees can be obtained in the "Explanatory Note on fees payable to the European Medicines Agency" (EMA/348317/2010)

Where an applicant disagrees on the classification by the EMA of an application under one of the fee categories described in the 'Fee Regulation’, the following procedure may apply:

• Any disagreement should be sent to the Executive Director accompanied by the appropriate justification, at the latest two weeks after receipt of the invoice indicating the fees payable to the EMA.

• The Executive Director will take a decision following consultation with the competent committee.

The EMA contacts point for queries on Fees, Procedures or Application numbers, are:

Product and Application Business Support (PA-BUS) or e-mail address: pa-bus@ema.europa.eu

References

• Regulation (EC) No 297/95

• "Centralised Procedure”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4

• “Explanatory Note on fees payable to the European Medicines Agency”

• European Medicines Agency Management Board "Rules for the implementation of Regulation (EC) No 297/95 as amended on fees payable to the European Medicines Agency and other measures” (EMA/MB/818152/2009)
11. What definition of strength is used for the calculation of fees? Rev. Oct 12

The “Guideline on the categorisation of New Applications versus Variation Applications” describes the agreement reached as to the use of the same definitions of strength in case of applications submitted through the Centralised Procedure and the Mutual Recognition Procedure.

This definition will be taken into account for the calculation of fees as well as for the numbering system used by both the EMA and the Commission (see "Payment of fees" and "Management of applications").

The following definitions therefore apply:

- For single-dose preparations, total use, the strength is defined as the amount of active substance per unit dose
- For single-dose preparations, partial use, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m², in percentage as appropriate
- For multi-dose preparations, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m², as appropriate
- For powder for reconstitution (powder for oral solution or suspension, powder for solution for injection, etc.) the strength is defined as the concentration after dissolution or suspension (reconstitution) to the volume and liquid recommended
- For concentrates for solutions (for injection or for infusion) the strength is defined as the concentration of the concentrate before dilution
- For transdermal patches, the strength is defined as the amount of active substance released form the patch in 24h

Please note that no additional strengths or presentations can be applied for by the applicant after the validation of the application and payment of the fee. Such changes can be introduced after the marketing authorisation has been granted through a variation procedure.

References

- “Guideline on the categorisation of New Applications versus Variation Applications”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
12. **What is the fee for a GMP/GCP inspection?** Rev. Dec 10

For all inspections requested by the CHMP in respect of an application under the Centralised Procedure fees are payable by the applicant under Regulation (EC) No 297/95, as amended.

For information on the fee applicable for inspections, please refer to the [Explanatory note on fees payable to the European Medicines Agency](#).

Invoices are issued within 20 days of the confirmation of the inspection dates by the relevant inspectors and are sent by registered post to the applicant. Applicants for marketing authorisations under the centralised procedure are required to pay the total fee charged within 45 days from the date on which the inspection is carried out. (Important: Invoice reference number to be mentioned with each payment).

For inspections outside the EEA/European Union the applicant is also required to pay the travel and accommodation expenses of the Inspector(s) and any Experts or Rapporteur involved in carrying out the inspection(s). These expenses are to be paid directly by the applicant to the inspector’s Authorities.

In the case of concurrent multiple applications for exactly the same medicinal product, the applicants may agree between themselves that one of them will be regarded as the “lead” applicant for the purpose of inspections. The identity of the “lead” applicant must be notified in writing to the EMA at the pre-submission stage. In such a case, the multiple applications will be treated as a single one and the total fee(s) will be charged to the “lead” applicant.

Where an inspection that has been formally notified to the applicant (and an invoice has been issued) is cancelled due to the withdrawal of or change to an application at any stage in the processing of the application, the applicant will be liable for 50% payment of inspection fee(s) as follows:

- Applicant decides to withdraw the application.
- In the context of GMP inspection, change to manufacturing arrangements by the manufacturer necessitating cancellation of the inspection, agreed at any time before the inspection is carried out.
- In the context of GCP inspection, change to the scope of the application or submitted data, or access to, ownership of, or location of facilities or data necessitating cancellation of the inspection, agreed at any time before the inspection is carried out.

Where the cancelled inspection was to take place outside the EEA/European Union, the applicant will be liable for any travel expenses already incurred by the inspectors at the date of cancellation for which they are not able to obtain reimbursement.

For more information on inspection fees, please refer to the EMA website: [Regulatory\Human medicines\Fees](#)

**References**

- [Regulation (EC) 297/95](#), as amended
- [Explanatory note on fees payable to the European Medicines Agency](#)
- [Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures](#)
13. When could a fee waiver / fee reduction be granted?

Rev. Oct 12

Applicants may benefit from fee incentives if at the time of the administrative validation the application or the applicant itself meets the criteria for fee reduction or deferral. Any changes which may take place after validation, would not retrospectively affect the levied fee.

Under article 7(2) of Regulation (EC) No 141/2000 on orphan medicinal products, total or partial fee exemptions may be granted by the EMA, for medicinal products designated as "orphan" by the European Commission on recommendation from the Committee on Orphan Medicinal Products. This includes fees for pre-authorisation activities such as protocol assistance (scientific advice), and for products using the centralised procedure: the application for marketing authorisation, inspections and post-authorisation activities such as variations, annual fees, etc.

Each year funds are made available by the EU Budgetary Authority to grant fee exemptions for designated orphan medicinal products. Subject to the availability of funds, the Executive Director will decide at the beginning of each year on the percentage of fee reductions to be granted that year.

Sponsors of orphan medicinal products wishing to request a fee reduction should address a letter of intent to the EMA, to the attention of the Head of Scientific Advice and Orphan Drug Sector.

The letter of intent to request a fee reduction should be received by the EMA not more than 2 months and not less than 2 weeks prior to the planned protocol assistance/centralised application/variation. For inspections, the letter requesting a fee reduction should be sent out as soon as the CHMP inspection request is issued.

It should be noted that fee reductions can only be considered once a decision on orphan medicinal product designation has been granted by the European Commission. In addition, the application should fall within the scope of the orphan condition. The applicant or marketing authorisation holder requesting the fee reduction must be the sponsor of the designation. If this is not the case, the sponsorship of the designation should be transferred prior to submitting the request.

Further information on how to apply for a fee reduction for an orphan medicinal product is provided in the EMA Public Statement on Fee reductions for Designated Orphan Medicinal Products (EMEA/63200/2009).

Applicants which meet the definition of a micro, small or medium-sized enterprise (SMEs) as set out in Commission Recommendation 2003/361/EC of 6 May 2003, are eligible for certain fee reductions from the EMA. This includes fee reductions for scientific advice, pre- and post-authorisation inspections, scientific services, and a full fee waiver for administrative services (with the exception of parallel distribution).

SMEs may also request deferral of the fee payable for the application for marketing authorisation or related inspection.

It should be noted that fee reductions and deferrals can only be considered once the applicant has been assigned SME status by the EMA. SME applicants wishing to request a fee reduction and/or deferral should address a letter of such intent to the EMA, to the attention of the SME Office.

The letter of intent should be received by the EMA 2 months prior to the centralised application. For inspections, the letter requesting a fee reduction should be sent as soon as the CHMP inspection request is issued. For scientific advice, the letter should be submitted as early as possible, at least 2 weeks in advance of the scientific advice request.
Further information on the level of fee reductions/deferrals available to SME applicants and how to request them is available in the EMA document 'Fee reductions/deferrals for micro, small and medium-sized enterprises (SMEs)' (EMEA/366526/2005).

Fee reductions may also be granted by the EMA Executive Director in exceptional circumstances and for imperative reasons of public or animal health, after consultation of the competent committee, in accordance with Article 9 of Regulation (EC) No 297/95, as amended. In such circumstances applicants should liaise with their Product Team Leader (PTL).

References

- Regulation (EC) No 297/95, as amended
- Regulation (EC) No 141/2000
- Regulation (EC) No 2049/2005
- Commission Recommendation 2003/361/EC
- “Centralised Procedure”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4
- EMEA Public Statement on Fee Reductions for Designated Orphan Medicinal Products (EMEA/63200/2009)
14. When shall I submit mock-ups and/or specimens?

*Rev. Dec 08*

Mock-ups and specimens of the outer and immediate packaging together with the package leaflet must be submitted by the applicant/MAH to the EMA for review, before commercialisation of the medicinal product.

A "Mock-up" is a copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging, so that the three dimensional presentation of the labelling text of the medicinal product is clear. It is generally referred to as a "paper copy" or "computer generated version".

A "Specimen" is a sample of the actual printed outer and inner packaging materials and package leaflet.

The fact that the mock-up has to be a real example of the sales presentation implies that the mock-up should indicate how the information specifically required by Member States (such as price, reimbursement, legal status, identification and authenticity) will be presented in the ‘blue box’. This means that if at the time of submission of the mock-ups this specific information is not yet known, at least an indication should be given of the way in which this information will be printed in the ‘blue box’ on the outer packaging. Details on the ‘blue box’ content, for each Member States, are given in the Annex of the “Guideline on the Packaging Information of Medicinal Products for Human Use Authorised by the Community”. EMA can also accept the inclusion of a national barcode on the immediate packaging (e.g. for traceability purposes), where space and readability permit.

In January 2007, a revised checking process of mock-ups and specimens in the Centralised Procedure was introduced, based on the following general principles:

- The EMA, through the revised translations checking policy, will ensure that high-quality product information in all EU languages, as prepared by the MAH and checked by the Member States prior to the granting of the MA, is included in Commission Decisions on centrally authorised medicinal products;

- MAHs are responsible for the correct implementation of the agreed product information texts in their printed packaging materials, in line with the Commission Decision and relevant EU legislation;

- The EMA will no longer perform a detailed linguistic check of mock-ups and specimens, but rather a general check from the viewpoint of readability in order to contribute to the safe use of medicines;

- The EMA can, at any time, request specific specimens from the MAH for review (e.g. further to a safety-related or product defect issue).

Applicants should provide the EMA with mock-ups and/or specimens for new applications in accordance with the following requirements:

- At **day -10** of the submission of the application, one English colour full-size mock-up and one multi-lingual colour full-size mock-up ("worst-case") of the outer and inner packaging for each pharmaceutical form in each container type in the smallest pack-size must be included in Module 1.3.2 of the application. Mock-ups of the package leaflet may be included (optional).

- By **day 121, at submission of the answers to the list of questions**, revised mock-ups of labelling and package leaflet need to be provided in case of comments or in case the applicant has changed the overall design.
At the latest 15 working days before marketing, specimens of printed outer and immediate packaging materials and package leaflet for each strength and each pharmaceutical form in each container type need to be provided to the EMA (using the “Specimen Submission Form” (see EMEA/305821/2006):

- when first marketed in the EU,
- when first marketed as a multi-lingual pack (if different from the first specimens sent to the EMA),
- when any other multi-lingual pack is marketed with a higher number of languages than the multi-lingual pack(s) previously reviewed.

The EMA will perform a general check from the viewpoint of readability within 15 working days, and will check if any previous comments on mock-ups/specimens have been duly implemented. The applicant will be informed about the outcome of the check.

For any questions on the checking process or to discuss upcoming mock-up/specimen submissions please contact the EMA Medical Information Sector on: muspecimens@ema.europa.eu.

References

- Directive 2001/83/EC, as amended
- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure (EMEA/305821/2006)
- “Guideline on the packaging information of medicinal products for human use authorised by the Community”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
- “Centralised Procedure”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4 and Chapter 7
- The Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02)
15. Do I have to submit samples together with my application? *Rev. May 06*

Samples for testing the proposed medicinal product are not required at time of submission of the application.

The CHMP may however request the testing of samples of the medicinal product and/or its ingredients during the assessment of the application in accordance with the provisions of Article 7 (b) of Regulation (EC) No 726/2004.

In this case the Rapporteur and/or Co-Rapporteur will specify a test protocol (type of samples, number of samples, number of batches, testing to be performed and methods and specifications to be used) and agree with the EMA which Official Medicines Control Laboratory (OMCL) or other laboratories designated for this purpose by a Member State will carry out the required testing.

Sampling and testing will be co-ordinated by the EMA in collaboration with the European Directorate for the Quality of Medicines and Healthcare (EDQM).

The results of the tests are reported to the EMA, Rapporteur and Co-Rapporteur and the CHMP for consideration in finalising the CHMP Assessment Report.

**References**

- Regulation (EC) No 726/2004
- The Rules governing Medicinal Products in the European Community, Volume 2A, *Chapter 4* and *Chapter 7*
16. Am I, as applicant, duly established in the EEA?

Rev. Feb 12

The Marketing Authorisation Holder (MAH) is the person who holds the authorisation to place a medicinal product on the market and is legally responsible for marketing the medicinal product. The granting of a marketing authorisation by a competent authority does not discharge the holder from civil and criminal liability as provided for by the Union law.

The MAH may be a natural or legal person.

The MAH of a centralised marketing authorisation must be established within the EEA (Norway, Iceland, Liechtenstein and the Member States of the European Union).

In order to fulfil this requirement the MAH must have a permanent legal structure which is formed in accordance with the law of an EEA Member State and which allows the concerned holder to assume the duties and responsibilities as well as to perform the tasks laid down by Union law.

Companies or firms formed in accordance with the law of a Member State and having their registered office, central administration or principal place of business within the EEA shall be treated in the same way as natural persons who are nationals of Member States. An applicant should demonstrate that it is duly established in the EEA. A proof of establishment from the applicant company is required by the EMA in order for an application to be validated (e.g. UK: Certificate of incorporation issued by the Registrar of Companies, FR: Extrait du registre du commerce et des sociétés). This proof of establishment should be included in Annex 5.3 of the Application Form (Available in the Notice to Applicants (NTA) Volume 2B - Application Form: Module 1.2)

It should be emphasised that while the Marketing Authorisation Holder may delegate certain activities to third parties, the MAH remains responsible for assuring all the obligations imposed on Marketing Authorisation Holders by the European legislation and by national law, as applicable.

References

- Regulation (EC) No 726/2004
- The Rules governing Medicinal Products in the European Community Volume 2A, Notice to Applicants, Chapter 1
- Directive 2001/83/EC
17. What information relating to the manufacture and batch release should be provided as part of my application?

Rev. Feb 12

The EMA requires the applicant to provide background information in support of the application relating to the manufacture (including packaging), batch testing and batch release by the Qualified Person in the European Economic Area (EEA). This should be sent to the EMA along with the application dossier.

The EEA includes European Union Member States plus Iceland, Norway and Liechtenstein. Switzerland is not part of the EEA.

Once validated, it is normally not permitted to add a new site or to change the steps of manufacture/batch release described under Module 1.2 (i.e. Application Form) of the application during the 210-day review period. Any additional site or change in the manufacturing or batch release arrangements should be submitted as a variation after the granting of the Marketing Authorisation.

The information on manufacturing/batch release sites submitted in Module 1.2 of the application must be consistent with module 3. All the manufacturing/batch release sites mentioned in module 3 must be listed in Module 1.2 and the activities carried out at each site must be described in Module 1.2 consistently with the information provided in module 3.

17.1. Manufacturing sites:

All sites involved in the production of the finished medicinal product and of the active substance must be described (name and detailed address, including building reference) in Module 1.2 of the application for a marketing authorisation together with a description of the steps performed. This should include:

- active substance manufacture and packaging
- any contract laboratories used for testing the active substance (including ongoing stability monitoring)
- bulk medicinal product manufacture
- diluent/solvent manufacture (if any)
- manufacture of any other associated medicinal product (if any)
- finished product manufacture and packaging
- batch release
- any contract manufacturing sites
- any contract laboratories used for testing the finished product
- Official Medicines Control Laboratory (OMCL) for blood products/vaccines if “Official Batch Release” is a requirement for the product in question.

For third country manufacturers, information about any previous EEA inspection in the last 2-3 years and/or any planned EEA inspection(s) should be provided and should include details of the inspection dates, product category inspected and the name of the inspecting competent authority.
17.2. **Documents to be attached to Module 1.2 of the application:**

The following documents should be attached to Module 1.2 of the application:

- For all sites in the EEA, other than active substance manufacturers, copies of the "Manufacturing Authorisation" authorising the sites involved in the manufacture, importation, control and/or testing and Qualified Person release of batches of the medicinal product. Alternatively, a reference can be made to the appropriate entry in the EudraGMP database.

(Note: for sites in the EEA, GMP Certificates are not an acceptable alternative to a Manufacturing Authorisation. However, GMP certificates can be useful additional information. Also, particular attention should be paid that the scope of the Manufacturing Authorisation for a given manufacturer covers the activities proposed as part of the Marketing Authorisation Application.)

- For all sites other than active substance manufacturers, located in third countries where a Mutual Recognition Agreement or other relevant agreement is in place, MRA certificate, not older that 3 years, from the local competent authority that carried out the inspection and/or GMP certificate from the EEA inspecting competent authority if the site has been inspected by an EEA competent authority in the last 2/3 years. Where the MRA partner has placed the certificate in the EudraGMP a reference to the entry will suffice. For the countries which have operational Mutual Recognition Agreements (MRA) with the EU, please consult the EMA website on Mutual Recognition Agreements.

- For all sites other than active substance manufacturers, located in third countries with no Mutual Recognition Agreement, GMP certificate from the EEA inspecting competent authority if the site has been inspected by an EEA competent authority in the last 2/3 years. Alternatively, a reference can be made to the appropriate entry in the EudraGMP database.

- In addition to the above, copy of the registration or other document analogous to a manufacturing authorisation from the local competent authority demonstrating that the site is authorised for manufacture of the product/pharmaceutical form and details of any inspection performed other than by EEA authorities (e.g. GMP certificate or similar statement from the competent authority which carried out the inspection).

- For the sites that have not been inspected by an EEA competent authority in the last 2/3 years, it might be useful to provide copy of the annual registration or other document from the local competent authority demonstrating that the site is authorised for manufacture of the product/pharmaceutical form.

- A flow-chart describing all the main steps involved in the manufacture of the active substance and finished product.

- For each active substance, a declaration from the Qualified Person(s) of all the finished product manufacturer(s) located in Module 1.2 where the active substance is used as a starting material and from the Qualified Person(s) of the batch release site(s) in the EEA that the active substance manufacturer(s) listed in Module 1.2 operate in compliance with the detailed guidelines on Good Manufacturing Practice.

17.3. **Contact person in the EEA for product defects/recalls:**

A proposed contact point/person in the EEA for Quality problems and defective batches of product must also be provided in Module 1.2 of the application (name, full address, 24 hour emergency phone and fax numbers + e-mail address, and mobile phone number if available).
References

- Directive 2003/94/EC
- Directive 2001/83/EC
18. What batch release arrangements in the EEA are required for my medicinal product? Rev. Feb 12

18.1. Importing site/Supervisory Authority:

According to Article 51(1) of Directive 2001/83/EC each batch of a medicinal product must be certified by a Qualified Person prior to release to the market in the EEA.

In the case of products imported from a third country, and for the purpose of Article 51(1)(b) of Directive 2001/83/EC the site where the certification of batches by the Qualified person occurs is considered to be the importing site in the EEA (and not necessarily the site through which the batch first physically enters the EEA).

The EEA includes European Union Member States plus Iceland, Norway and Liechtenstein. Switzerland is not part of the EEA.

In accordance with the provisions of Article 18 of Regulation (EC) No 726/2004 the Supervisory Authority(ies) shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation provided for in article 40(1) of Directive 2001/83/EC in respect of the manufacture of the medicinal product. In the case of products imported from third countries, the Supervisory Authority(ies) shall be the competent authority(ies) of the Member State(s) which granted the manufacturing authorisation provided in Article 40(3) of Directive 2001/83/EC to the importer, unless a Mutual Recognition Agreement (MRA) or other relevant agreement covering GMP for the product under consideration is operating with the country where the medicinal product is manufactured.

In the exceptional circumstances where a valid manufacturing authorisation is not in place at the time of the marketing authorisation submission for any finished product manufacturer/importer/batch release site located in the EEA, EMA will consult the Supervisory Authority and a request for inspection may be triggered. The marketing authorisation procedure will require the inspection outcome before opinion and in particular confirmation of the grant of the manufacturing authorisation.

For any finished product manufacturer that is not in possession of a GMP certificate at the time of the marketing authorisation submission located in third countries with no Mutual Recognition Agreement, a request for inspection will normally be triggered. The marketing authorisation procedure will require the inspection outcome before opinion.

18.2. Batch testing upon importation:

For medicinal products imported from third countries, retesting of each batch within the EEA upon importation is required unless a Mutual Recognition Agreement (MRA) or other relevant agreement covering GMP for the product under consideration is operating with the country where the medicinal product is manufactured. If such MRA is in operation, batch controls/tests carried-out in the country where the product is manufactured are acceptable.

It should be noted that MRAs cover batch control/testing and do not cover batch release. Batch release must take place in the EEA territory for every production batch released to market in the EEA, regardless of if a MRA with the exporting country is in place or not.
For the countries which have operational Mutual Recognition Agreements (MRA) with the EU, please consult the EMA website on Mutual Recognition Agreements.

Batch release of an imported medicinal product from a third country without re-testing is a serious failure of a qualified person’s legal obligations. According to Article 52 of Directive 2001/83/EC it is expected that Member States’ Supervisory Authorities will launch appropriate administrative measures and may withdraw the product concerned from the market (Article 117(1)(e) of Directive 2001/83/EC).

18.3. Contracting out of certain controls:

The provisions of Article 20(b) of Directive 2001/83/EC allows certain of the controls required under the provisions of Article 51(1) of Directive 2001/83/EC to be contracted out to third parties, if justified, and provided that the laboratories have been verified by the Competent Authorities. Laboratories used for contract testing upon importation of medicinal products manufactured in third countries may be located in any EEA country.

The Qualified Person of the Manufacturing Authorisation Holder named in the Application is however responsible for certifying that any contract laboratory used carries out the controls in accordance with Good Manufacturing Practice, as applicable and with the requirements of the Marketing Authorisation once granted.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Annex 16 to GMP Certification by a Qualified person and Batch Release (July 2001), Volume 4 of the rules governing medicinal products in the European Union
19. How shall I submit an Active Substance Master File (ASMF)? *Rev. Feb 12*

Annex I to Directive 2001/83/EC describes the concept of an open and closed Active Substance Master File (ASMF) and specifies that:

“For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the:

i) Detailed description of the manufacturing process

ii) Quality control during the manufacture, and

iii) Process validation

to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.

In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take the responsibility for the medicinal product...”

It should be emphasized that the concept of the ASMF shall only apply to a well-defined active substance and cannot be used for excipients, finished products and biological active substances. The information related to excipients, finished products and biological active substances shall be provided within the Marketing Authorisation Application (MAA) by the applicant.

In case an application under the Centralised Procedure includes the submission of an Active Substance Master File (previously referred to as European Drug Master File (EDMF)), applicants should be aware of the fact that, as mentioned in the Guideline on Active Substance Master File Procedure (CPMP/QWP/227/02), an ASMF consists of 2 parts:

- An ASMF Applicant’s Part, also referred to as Open Part, which shall be at the disposal of the applicant.
- An ASMF Restricted Part, also referred to as Closed Part, which is a confidential document closed to the applicant.

Both parts need to be separated and follow the structure of the Module 3.2.S. of the CTD. A table of content and a separate Quality Overall Summary for each part must also be provided as part of the ASMF.

The content requirements, as described in the above mentioned Guideline should be followed.

The applicant should submit the Applicant’s Part of the ASMF. It should be included in their application within Module 3.2.S. of the dossier. The ASMF holder should submit both the Applicant’s Part (which should be identical to the one provided by the applicant) and the Restricted Part. Both parts should be the latest versions available of the ASMF. It is recommended to include a table summarising those changes made to the ASMF compared to the previous version.

Applicants should note that the ASMF constitutes an integral part of the dossier and therefore it should be always submitted as part of a new MAA.

The applicant is responsible for the submission of all necessary documents to the EMA.
It should be noted that although the ASMF procedure is developed to keep intellectual property confidential, it is also permitted to use the procedure when the applicant is also the manufacturer of the active substance.

The ASMF holder should submit the full ASMF to the EMA accompanied by the following documents:

- A cover letter, in accordance with the template provided in Annex 3 of the above mentioned Guideline.

- A "Letter of Access", to be included in Annex 5.10 of the application form, Module 1.2. According to the template provided in Annex 2 of the above mentioned Guideline, the letter must contain:
  - The number, version and issue date of the ASMF, when possible. This number is internally assigned by the ASMF holder.
  - The name and address of the manufacturing site
  - The name and address of the ASMF holder
  - The name of the applicant
  - The name of product and Marketing Authorisation (MAA) number
  - The planned date of submission of the Marketing Authorisation Application
  - A statement that the ASMF holder gives permission to the EMA including all CHMP Members and their experts to refer to and review the ASMF

- A commitment to inform the applicant and the EMA of any change in the ASMF to be provided either as a separate letter included in Annex 5.11 or within the letter of access provided in Annex 5.10 to the application form.

The Letter of Access and the Letter of Commitment to inform the applicant about any changes in the ASMF should be included both in the AP submitted by the applicant (Annexes 5.10 and 5.11) and also in the ASMF submitted by the ASMF holder.

The contact details of the ASMF holder contact person must be the same in the Cover Letter of the ASMF, in the Letter of Access and the Application Form (Module 1.2).

It is necessary for the applicant and the ASMF holder to liaise to ensure that the ASMF including these documents are synchronized to arrive at ideally the same time as the planned MAA to be submitted by the applicant, although an interval of some days may be allowed. Note that the marketing authorisation application cannot be validated until all the necessary documents are received in a satisfactory form. This also applies to the ASMF-related responses to Day 120 LoQ and Day 180 LoOI. Applicants should be aware that the procedure cannot re-start until the responses from the ASMF holder are received by the Agency.

At Day 120 of the scientific assessment timetable of the application, a list of questions is sent to the applicant. It is to be noted that the Rapporteur, the Co-Rapporteur and the CHMP will define those questions which refer to the closed part of the ASMF, and therefore in order to respect the confidentiality of the information included in this part, the scientific assessment of the restricted part and its questions will only be sent to the ASMF holder. The applicant will receive the scientific assessment and questions concerning the applicant’s part of the ASMF.
Non applicability of ASMF concept to biological active substances

Further to clarifications from the European Commission on the interpretation of Directive 2001/83/EC as amended, and the subsequent announcement in the October 2004 CHMP Monthly report, the ASMF concept is not acceptable for biological medicinal products.

The characterisation and determination of biological active substances requires not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control.

The MAH/applicant for a biological medicinal product could therefore not comply with the requirement to ‘take responsibility for the medicinal product’ without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and should therefore not be allowed for biological active substances.

In addition, active substances, which are present in certain medicinal products such as vaccines or cell therapy medicinal products, do not fit with the concept of a ‘well-defined’ active substance.

Non applicability of ASMF concept of open and closed parts to Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF)

The concept of the ASMF does not apply to blood derived medicinal products and vaccine antigens. In this context, the manufacturer can submit a PMF or a VAMF.

Regarding the VAMF, the legislation specifies that the VAMF holder cannot differ from the MAH/applicant for the concerned medicinal product: there is hence no rationale for an open/closed parts system.

For VAMF linked MAs, if a particular MAH name and address are not identical to the name and address of the proposed VAMF certificate holder, a relevant declaration should be provided attached to the application form, stating that the MA applicant and the MAH belong to the same mother group of companies, which share the same data package.

For the PMF the legislation specifies that where the MAH/applicant differs from the holder of the PMF, the PMF shall be made available to the MAH/applicant for submission to the competent authority.

References

- Annex I to the Directive 2001/83/EC, as amended
- Guideline on Active Substance Master File Procedure (CPMP/QWP/227/02)
- CMD(h) – Overview of Biological Active Substances of non-recombinant origin
- Guideline on requirements for Vaccine Antigen Master File (VAMF) certification (EMEA/CPMP/4548/03/Final/Rev1)
- Guideline on requirements for Plasma Master File (PMF) certification (CPMP/BWP/4663/03).
20. What shall I submit if my medicinal product contains or consists of genetically modified organisms (GMOs)?

Potential applicants are advised to discuss their future applications which consists or contains of GMOs well in advance (6 months – 1 year) of their submission with the EMA.

Applicants may also find it useful to apply for scientific advice during the development of their medicinal product. For any scientific advice questions relating to the Environmental Risk Assessment (ERA), the necessary consultations will be held with the designated GMO Competent Authorities (CAs).

With the letter of intent to submit an application for a Marketing Authorisation under the Centralised Procedure for a medicinal product containing or consisting of Genetically Modified Organisms (GMOs) within the meaning of Article 2 of Directive 2001/18/EC, the applicant will be required to provide a confirmation that all obligations have been complied with. It is necessary to ensure the traceability at all stages of the placing on the markets of GMOs as or in products authorised under part C (article 12) of the above-mentioned Directive.

Article 6 of Regulation (EEC) No 2309/93 specifies the documents to be presented in Module 1.6.2 for a Marketing Authorisation Application (MAA) for a medicinal product consisting of or containing GMO(s):

- A copy of the CA’s written consent to the deliberate release into the environment of the GMOs for research and development purposes. Although already appearing in Modules 1 (annex to the application form), this information should be repeated in Module 1.6.2.

- The technical and scientific information on the GMO specified in Annexes III and IV to Directive 2001/18/EC. As the Directive qualifies this point with a statement to the effect that not all listed points may be applicable to particular GMOs or GMO categories, the list in these Annexes should be understood to be a compilation of points to consider which is subject to justified deletions and/or additions, depending on the nature of the medicinal product. The information also needs to take into account, inter alia, the diversity of sites of use of the GMO and the results of research and trials already completed on the GMO.

- The ERA dossier. The content of this dossier should follow the order of headings and requirements specified within Annex II to Directive 2001/18/EC and expanded upon in Commission Decision 2002/623/EC.

- The results of any investigations performed for the purposes of research or development.

In addition and in analogy with the requirements of Article 6 of Regulation (EEC) 2309/93, it is recommended to complete M1.6.2 with the following:

- Information on the proposed product information (including proposed conditions of use and handling) and on the packaging of the product. Although already appearing elsewhere in the MAA, this information should be repeated in Module 1.6.2 for the benefit of the lead consulted CA which will not receive the full MAA dossier.

- A plan for monitoring, in accordance with Council Decision 2002/811/EC, during the period of use and beyond, of the product, or a justification for the omission of such a plan.


- Bibliographical references.
The module section 1.6.2, presenting all these particulars, should be bound separately from the remainder of the dossier. Moreover, there is no provision for a summary to be included in Module 2 of the dossier.

The fundamental dossier requirements for ERAs for GMOs proposed to be placed on the market as or in products are included in Directive 2001/18/EC and in Commission Decision 2002/623/EC.

Technical and scientific information presented in the ERA will overlap with items of information presented in other sections of Module 1, and other Modules of the MA application dossier. Applicants are reminded to ensure full consistency of all data throughout the dossier, bearing in mind that variability, reflecting different origins (medicinal product regulatory versus environmental regulatory texts) may occasionally be encountered in the official terminology describing GMO attributes.

This Directive 2001/18/EC shall not apply to GMOs as or in products as far as they are authorised by the Council Regulation (EEC) No 2309/93 provided a specific environmental risk assessment is carried out in accordance with the principles set out in Annex II to this Directive and on the basis of the type of information specified in Annex III to this Directive.

Council Regulation (EEC) 2309/93, as amended, requires that the Rapporteur hold necessary consultations with the Competent National Authorities under Directive 2001/18/EC, where the medicinal product contains or consists of GMOs.

To accelerate the consultation process, the CHMP rapporteur may appoint one of the national GMO CAs to act as lead consulted CA. This lead consulted CA will liaise with its fellow GMO CAs on the review of the documentation forwarded to it by the applicant.

The assessment report on the module 1.6.2 data, prepared by the lead consulted CA and including any comments received from the fellow CAs, will be sent to the Rapporteur for CHMP consideration. The CHMP Members will subsequently have the opportunity to comment on all aspects of the scientific assessment. The environmental assessment is an integral part of the assessment report, and is done accordingly to the same timelines.

It should be highlighted that current experience under the Centralised Procedure with medicinal products containing or consisting of GMOs is rather limited. Once more experience is accumulated, an SOP will be prepared by the EMA for discussion and adoption by the CHMP.

References

- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2B, Presentation and content of the dossier
- Environmental Risk Assessments for Medicinal products containing, or consisting of, Genetically Modified Organisms (GMOs) (Module 1.6.2) (EMEA/CHMP/BWP/135148/2004) (CHMP released for consultation on EMA website, January 2005)
21. What information shall I provide if my medicinal product contains or uses in the manufacturing process materials of animal and/or human origin? Rev. July 06

The applicant must comply with the Part I Module 3.2 (9) “Content: basis and principle” of the Annex I to Directive 2001/83/EC, as amended, which requires that “The applicant must demonstrate that the medicinal product is manufactured in accordance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products (...)” and its updates.

Demonstration of compliance with “the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products” can be done by submitting Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) (in Annex 6.12 of the Application form), or by inclusion in module 3.2 of the dossier of scientific data to substantiate this compliance. In the latter situation, this data should be reviewed in Module 2.3 (expert reports).

For all applications, the table A on ‘Materials of animal origin covered by the Notice for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products’ should be completed and included in Module 3.2.R.

For materials from animals not covered by the Notice for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products and the Annex I to Directive 2001/83/EC as amended, applicants are requested to complete the table B on ‘Other materials of animal origin’, and include it in Module 3.2.R.

Materials of human origin

If an application relates to a medicinal product, which contains or uses in the manufacture materials of human origin, applicants are requested to complete the table C ‘on albumin and other human tissue derived materials’ and include it in Module 3.2.R.

References

- Directive 2001/83/EC
- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products (EMEA/410/01)
22. Where on my medicinal product information can I mention a local representative? **Rev. Jan 06**

Some Holders of Community Marketing Authorisations have requested that there be a contact point identified in the Package Leaflet and on the label. This would normally be the Holder of the Community Marketing Authorisation. However, a Marketing Authorisation Holder may wish to add the name of another (local) contact point, the "local representative".

"Local representative" shall be taken to mean: any private or legal person established in the Community charged, through a civil contract with the Marketing Authorisation Holder, with representing him in a defined (geographical) area; this contract excluding any transfer of any responsibility imposed on the Marketing Authorisation Holder by Community law and by national law, regulation and administrative action implementing such Community law.

The "local representative" may be indicated:

- In the Package Leaflet, under heading 6 as detailed in the QRD Product information Template, by name, telephone number and electronic e-mail address (optional) only. Postal address may be added space permitting,
  
  and

- By name in the blue box on the label, as long as not interfering with the legibility of the EU text on the outer packaging, and if mentioned in the leaflet.

All telephone numbers should be accessible when dialled from abroad (e.g. when a toll free number is given which is not accessible from abroad, an alternative international number may have to be added).

Reference to website addresses or to e-mails linking to websites are not allowed, neither for the marketing authorisation holder nor for the local representative.

Designation of a local representative cannot be a requirement but, when the Holder of a Community Marketing Authorisation wishes to identify a local representative in the Leaflet, all of the Community must be covered so that the consumer in each Member State and EEA country has equivalent access to a local representative. A local representative may be designated for more than one Member States or EEA country and may be also the Marketing Authorisation Holder when no other local representative is indicated.

Moreover it is reminded that, in principle, only one local representative should be indicated per Member State or EEA country. Local representatives should be able to address queries in the local official EEA language(s) of the country for which he or she is designated.

There has been some confusion with regard to terms such as 'exploitant', 'technical director', 'distributor' etc. Since there is neither a commonly agreed understanding of these terms nor equivalent legal definitions of these terms amongst the Member States, and in the absence of any reference or definition in Community law, reference to such terminology will not be accepted for a medicinal product authorised by the Community.

It must be recalled that Member States may not require that a local representative of the Marketing Authorisation Holder be appointed for their territory. Therefore, the arrangements outlined above are purely optional for Holders of the Community Marketing Authorisations.
References

- "Guideline on the packaging information of medicinal products for human use authorised by the Community" the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
- QRD Templates with Explanatory Notes
23. How and to whom shall I submit my dossier? **Rev. Feb 12**

In order to fulfil EU dossier requirements applicants must submit new Marketing Authorisation Applications (MAA) as follows:

**Languages to be used:**

All applications have to be submitted in English.

**Format and number of copies:**

From 1 January 2010, eCTD is the only acceptable electronic format for all applications and all submission types in the context of the centralised procedure (e.g. new applications, variations, renewals). Any other electronic format, including NeeS, will be automatically rejected and the submission receipt will not be acknowledged. Additionally, if the eCTD submission results in a Technical Validation Report that indicates an invalid submission the submission receipt will not be acknowledged.

The latest version of the ICH M2 eCTD specification can be found at [http://www.ich.org](http://www.ich.org), and the current version of the eCTD EU Module 1 specification can be found in the Rules governing Medicinal Products in the European Community, *Notice to Applicants, Volume 2B*, more specifically: *Electronic Common Technical Document, eCTD EU Module 1 (version 1.4)*.

For further information regarding the current policy and requirements for the eCTD in the context of the Centralised Procedure, please refer to the question-and-answer document regarding strategic aspects of the Agency’s plans to implement electronic, and specifically eCTD submission or contact the Agency.

Applicants should submit only 1 full electronic copy of the Marketing Authorisation Application (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, preferably in the ‘subject’ line. Additional cover letters arriving together or separately from the submission of media will create delays in processing, therefore we ask the applicants to avoid sending multiple copies of the same cover letter, even if the letter is addressed to multiple recipients.

The European Medicines Agency is standardising the administrative information required in cover letters for any submission concerning centralised procedures. This is in line with changes to the internal financial system and quality improvements to distribution workflows. The Summary Table should be incorporated in the cover letter of each submission in the Centralised Procedure (see explanatory notes in the template).

Replacement sequences of a previously submitted eCTD application (e.g. following corrections) are not acceptable. Instead corrected eCTD applications should always be submitted as a new eCTD sequence. Replacements should always be accompanied by an updated cover letter explaining the reason of the re-submission.

Further detailed practical guidance on eCTD submissions is also available in the TIGes Harmonised Guidance for eCTD Submissions in the EU.

In those cases where a Active Substance Master file (ASMF) exists, the applicant should ensure that the Active Substance Master File is submitted by the ASMF holder to the Agency, at around the same time as the main application (see also question "Submission of a ASMF").
As per eCTD requirement, the Product Information (SmPC, PIL and labelling) has to be submitted within the module 1 of the eCTD structure in PDF format. Additionally, this information should also be submitted in Word format outside the eCTD structure but in the same CD-ROM or DVD within a folder called “working documents”

**European Medicines Agency delivery address:**

All applications should be sent to the attention of the Product and Application Business Support (PA-BUS):

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
London E14 4HB
UK

In the exceptional case of a paper submission, applicants are advised to contact PA-BUS in advance (PA-BUS@ema.europa.eu) for information on dossier delivery requirements

**Submission requirements for (Co-)Rapporteur and CHMP members:**

In parallel to submitting the application to the Agency, applicants must submit the application to both the Rapporteur and Co-Rapporteur; otherwise there may be a delay in the start of the procedure because of the time lapse between the validation by the Agency and the confirmation from the (Co-)Rapporteur that they have received the dossier.

**Validation of the application:**

In the event that the Agency requires additional data, information or clarification in order to complete its validation of the dossier, it will contact the applicant requesting supply of this information within a specific time limit. When supplying the Agency with this information, the applicant should also send a copy of this information to the Rapporteur and Co-Rapporteur. In this case, the validation can only be completed after receipt and verification of the information submitted.

If the (Co-)Rapporteur have not received their copies of the dossier and/or additional validation information on the day where the dossier is validated by the Agency, the start of the procedure may be delayed until the procedural starting date of the next month. Applicants should therefore provide a proof of delivery of the application to the (Co-)Rapporteur, to the Agency before start of the procedure.

After positive validation of the application, the Agency will notify the applicant accordingly in writing, together with the names of CHMP members to whom full or partial copies of the dossier should be sent (including any additional information supplied during the validation phase).

For a full overview of the submission requirements for (Co-)Rapporteur and all CHMP members – see: list of CHMP members/dossier requirements).

**Submission of responses:**

The above requirements also apply to the submission of responses to List of Questions / List of Outstanding Issues from CHMP.

**References**
• “Centralised Procedure”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4

• The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2B, Electronic Technical Document (eCTD)

• Official Website for ICH

• eSubmission Website
24. How shall I present my new MAA dossier? *Rev. Dec 08*

Answer integrated in Q&A 23 “Dossier submission requirements“.
25. When to submit the Marketing Authorisation Application?

Rev. Oct 12

In the same way as it is important for applicants to plan their application strategies for an efficient use of their resources, it is important for the European Medicines Agency, CHMP members and Experts to be able to plan and allocate their workload efficiently. If the actual submission date is several months after the date originally indicated, Rapporteur and Co-Rapporteur may find it difficult to provide the necessary expertise and re-appointment could be necessary.

The European Medicines Agency advises applicants to consider the date of submission very carefully and to notify the Agency, Rapporteur and Co-Rapporteur of a 'real' submission date.

At least seven months before submission, applicants should notify the European Medicines Agency of their intention to submit a MAA and provide the intended date of submission. This should be done by using the Pre-submission request form Pre-submission request form (Intent to submit MA), selecting as a scope of request: Centralised Procedure-Intent to submit a MAA; this should be sent electronically to pa-bus@ema.europa.eu. The appointment procedure for Rapporteur will be initiated 7 months prior to the Marketing Authorisation Application intended submission date (see question "What is the procedure for appointment of CHMP Rapporteur/Co-Rapporteur and their assessment teams?").

Furthermore applicants are requested to notify the European Medicines Agency, Rapporteur and Co-Rapporteur as soon as possible when the previously notified submission date cannot be met, by re-sending an updated Pre-submission request form Pre-submission request form, selecting as a scope of request: Notification of change-applicant/contact person details.

Applicants are finally requested, if they no longer wish to pursue the submission of their application, to notify the European Medicines Agency of their intention to withdraw the request for submission of a MAA. This should be done by using the Pre-submission request form, selecting as a scope of request: Withdrawal of request; this should be sent electronically to pa-bus@ema.europa.eu. Please note that this will close the case procedure and the whole pre-submission history.

The submission deadlines and full procedural detailed timetables are published as a generic calendar (see submission deadlines and full procedural timetables). The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

In order to accelerate and facilitate the procedure, applicants must submit, in parallel to the European Medicines Agency, the required number of copies of the dossier to both the Rapporteur and the Co-Rapporteur, as stated in the published Dossier requirement table.

Soon after the notification of a valid application, the Agency will send an invoice to the Applicant. The fees should be paid within 45 days of the receipt of this invoice. For more information regarding the applicable fee, see question “What fee do I have to pay and how is the appropriate fee for my application calculated?”. 
The address for submission of the application is:

Product and Application Business Support (PA-BUS)
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
London E14 4HB
UK

(located at the rear of the European Medicines Agency premises)
(6:00 – 18:00 hours Monday to Friday)

For more information on the complete set of documents that need to be submitted and for the addresses of CHMP members for submission of the application, see question "How and to whom shall I submit my dossier and how many copies?".

References

- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 4 and Chapter 7
26. How shall my application be evaluated (timetable)?

Rev. Jan 06

Once the application is validated and provided the Rapporteur and Co-Rapporteur have confirmed that they have received the dossier, the EMA starts the procedure at the monthly starting date published on the EMA website. If, within a month from the start of the procedure, any other member of the CHMP has not received the requested parts of the dossier from the applicant, the EMA will stop the clock until confirmation is received that each member of the CHMP has been delivered the requested documentation. It is therefore important that applicants are able to provide a proof of delivery to Rapporteur, Co-Rapporteur and to CHMP members (upon request) to the EMA.

A timetable is prepared by the EMA in consultation with Rapporteur and Co-Rapporteur. This timetable is then proposed to the CHMP for adoption.

In order to allow the CHMP to adopt a timetable at the first CHMP meeting after submission of the valid MAA, applicants are advised to submit the MAA accordingly to the published EMA calendar (See "Dates for CHMP meetings").

The submission deadlines and full procedural detailed timetables are now published as a generic calendar on the EMA website (see: "submission deadlines and full procedural timetables").

The published timetables identify the submission, start and finish dates of the procedures as well as other interim dates/milestones that occur during the procedure.

The EMA shall ensure that the opinion of the CHMP is given within 210 days (less any clock-stops for the applicant to provide answers to question from the CHMP) in accordance with the following standard timetable, which can be shortened in exceptional cases (see Request for accelerated assessment).

<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
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<tbody>
<tr>
<td>1*</td>
<td>Start of the procedure</td>
</tr>
<tr>
<td>80</td>
<td>Receipt of the Assessment Report(s) or critique from Rapporteur and Co-Rapporteur(s) by CHMP members (which includes the peer reviewers) and EMA. EMA sends Rapporteur and Co-Rapporteur Assessment Report/critique to the applicant making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CHMP.</td>
</tr>
<tr>
<td>100</td>
<td>Rapporteur, Co-Rapporteur, other CHMP members and EMA receive comments from Members of the CHMP (including peer reviewers).</td>
</tr>
<tr>
<td>115</td>
<td>Receipt of draft list of questions (including the CHMP recommendation and scientific discussions), from Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members and EMA</td>
</tr>
<tr>
<td>120</td>
<td>CHMP adopts the LoQ as well as the overall conclusions and review of the scientific data to be sent to the Applicant by the EMA. Clock stop. At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).</td>
</tr>
<tr>
<td>121*</td>
<td>Submission of the responses, including revised SPC, labelling and package leaflet texts in English. Restart of the clock.</td>
</tr>
</tbody>
</table>

* Target dates for the submission of the responses are published on the EMA Website CHMP meeting
After receipt of the responses, the CHMP will adopt a timetable for the evaluation of the responses. In general the following timetable will apply:

<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
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<tr>
<td>150</td>
<td>Joint Response Assessment Report from Rapporteur and Co-Rapporteur received by CHMP members and the EMA. EMA sends this joint Assessment Report to the applicant making clear that it is sent for information only and does not yet represent the position of the CHMP. Where applicable inspection to be carried out. EMA/QRD sub-group meeting for the review of English product Information with participation of the applicant (optional) around day 165.</td>
</tr>
<tr>
<td>170</td>
<td>Deadline for comments from CHMP Members to Rapporteur and Co-Rapporteur, EMA and other CHMP members</td>
</tr>
<tr>
<td>180</td>
<td>CHMP discussion and decision on the need for adoption of 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. Submission of final inspection report to the EMA, Rapporteur and Co-Rapporteur by the inspection team (at the latest by day 180).</td>
</tr>
<tr>
<td>181</td>
<td>Restart of the clock and oral explanation (if needed).</td>
</tr>
<tr>
<td>181 to 210</td>
<td>Final draft of English SPC, labelling and package leaflet sent by applicant to the Rapporteur and Co-Rapporteur, EMA and other CHMP members.</td>
</tr>
<tr>
<td>By 210</td>
<td>Adoption of CHMP Opinion + CHMP Assessment Report. Adoption of a timetable for the provision of product information translations</td>
</tr>
</tbody>
</table>

After adoption of a CHMP opinion, the preparation of the annexes to the Commission Decision are carried out in accordance with the following timetable:

<table>
<thead>
<tr>
<th>DAY</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>215 at the latest</td>
<td>Applicant provides to the EMA the product information and Annex A in the 20 languages (all EU languages including Norwegian) and the “QRD Form 1” by e-mail* or on CD Rom for review by Member States.</td>
</tr>
<tr>
<td>229</td>
<td>Member States will send linguistic comments on the product information by e-mail with a copy to the EMA together with QRD Form 1</td>
</tr>
<tr>
<td>232 at the latest</td>
<td>Applicant provides EMA with final translations of SPC, Annex II, labelling and package leaflet in the 20 languages (+ &quot;QRD Form 2&quot;)</td>
</tr>
<tr>
<td>237</td>
<td>Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland.</td>
</tr>
<tr>
<td>239-261</td>
<td>Draft Commission Decision Standing Committee Consultation</td>
</tr>
<tr>
<td>By 277</td>
<td>Finalisation of EPAR in consultation with Rapporteur, Co-Rapporteur, CHMP and Applicant (the latter for confidentiality aspects)</td>
</tr>
<tr>
<td>277</td>
<td>Final Commission decision</td>
</tr>
</tbody>
</table>

*By e-mail: grd@ema.europa.eu or on CD-Rom

References
European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure
EMA/339324/2007
• Regulation (EC) No 726/2004

• “Centralised Procedure”, the Rules governing Medicinal Products in the European Community, Volume 2A, Notice to Applicants, Chapter 4 and Chapter 6

• The new Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02)
27. How is an EMA Application Number attributed?  
*Rev. July 06*

On submission of an application, details of the product are entered into SIAMED, the EMA tracking system.

### 27.1. Procedures

The name and the active substance(s) of the product primarily identify applications for the granting of a Community Marketing Authorisation (MA) for a medicinal product. However, for administrative purposes, each application is also given a core number, EMEA/H/C/xxxxxx, where H stands for Human and C for Centralised Procedure, with the remainder corresponding to a sequentially allocated and unique number identifying the whole of the application. This core number, which is provided after the submission of the application and communicated to the applicant at the start of the procedure, is retained throughout the life cycle of the product.

In every case of an administrative procedure relating to the product, an additional marker denoting the nature of the procedure is appended to this core number, i.e. for the first application for the granting of the MA, any extension, variation, transfer or renewal of MA. A sequential number is added, too. The markers currently used are as follows:

<table>
<thead>
<tr>
<th>Marker</th>
<th>Procedure</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>/0000</td>
<td>First new application</td>
<td>EMEA/H/C/000789/0000</td>
</tr>
<tr>
<td>N/xxxx</td>
<td>Notification Art. 61(3)</td>
<td>EMEA/H/C/000789/N/0001</td>
</tr>
<tr>
<td>IA/xxxx</td>
<td>Type IA variation</td>
<td>EMEA/H/C/000789/IA/0002</td>
</tr>
<tr>
<td>IB/xxxx</td>
<td>Type IB variation</td>
<td>EMEA/H/C/000789/IB/0003</td>
</tr>
<tr>
<td>II/xxxx</td>
<td>Type II variation (regardless of procedural length)</td>
<td>EMEA/H/C/000789/II/0004</td>
</tr>
<tr>
<td>X/xxxx</td>
<td>Annex II application</td>
<td>EMEA/H/C/000789/X/0005</td>
</tr>
<tr>
<td>S/xxxx</td>
<td>Annual Re-assessment</td>
<td>EMEA/H/C/000789/S/0006</td>
</tr>
<tr>
<td>T/xxxx</td>
<td>Transfer of MA</td>
<td>EMEA/H/C/000789/T/0007</td>
</tr>
<tr>
<td>R/xxxx</td>
<td>Renewal of MA</td>
<td>EMEA/H/C/000789/R/0008</td>
</tr>
<tr>
<td>Z/xxxx</td>
<td>(Renewal of) Suspension of MA</td>
<td>EMEA/H/C/000789/Z/0009</td>
</tr>
</tbody>
</table>

These numbers are used as a reference by the EMA and should be used by the Applicant in all correspondence relating to a certain procedure.

### 27.2. Presentations

In addition, the numbering system covers all presentations (pharmaceutical forms, strengths and pack sizes) of the product. This is mainly relevant during evaluation of the procedure and for the purpose of identifying single presentations in lists such as the Annex A to the opinion. (For correspondence, it is sufficient to indicate the procedural number as above.)
A sequential three-digit number for each presentation is added to the procedural number (core number plus procedural marker). An example is given below for a product consisting of three different presentations, with two ensuing procedures creating new presentations:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Example</th>
<th>Numbers in Annex A</th>
</tr>
</thead>
<tbody>
<tr>
<td>First new application</td>
<td>EMEA/C/H/000789/0000</td>
<td>EMEA/H/C/000789/0000/001&lt;br&gt;EMEA/H/C/000789/0000/002&lt;br&gt;EMEA/H/C/000789/0000/003</td>
</tr>
<tr>
<td>Type II variation creating three new presentations</td>
<td>EMEA/C/H/000789/II/0004</td>
<td>EMEA/H/C/000789/II/0004/004&lt;br&gt;EMEA/H/C/000789/II/0004/005&lt;br&gt;EMEA/H/C/000789/II/0004/006</td>
</tr>
<tr>
<td>Annex II application creating a further three new presentations</td>
<td>EMEA/C/H/000789/X/0005</td>
<td>EMEA/H/C/000789/X/0005/007&lt;br&gt;EMEA/H/C/000789/X/0005/008&lt;br&gt;EMEA/H/C/000789/X/0005/009</td>
</tr>
</tbody>
</table>

NB: For all procedures creating new presentations, this numbering system is superseded after MA by the EU numbers, which would from then onwards appear in the Annex A to opinions. The EU number is allocated independently of the EMA number, but retains the principle of identifying each single presentation by ending in a three-digit sequential number.
28. When can I expect a pre-approval GMP inspection and how are they conducted? *Rev. May 06*

### 28.1. Legislative Basis

Directive 2001/83/EC as amended states that Manufacturing Authorisation Holders are obliged to comply with the Good Manufacturing Practice (GMP) for medicinal products and to use as starting materials only active substances that have been manufactured in accordance with the detailed guidelines on Good Manufacturing Practice for starting materials.

The principles and guidelines for GMP for medicinal products for human use are stated in Directive 2003/94/EC. Compliance with these principles and guidelines is mandatory within the European Economic Area (EEA), interpretation of these requirements is provided in part I of the Guide to Good Manufacturing Practice, published in Volume 4 of Eudralex. Part II of this guide provides for the detailed guidelines on Good Manufacturing Practice for active substances used as starting materials.

The guide to Good Manufacturing Practice consists of detailed guidelines (part I and part II) which are supplemented by a series of annexes specific for certain types of product, or for a particular topic.

The ad hoc GMP Inspection Services Group within the EMA is in charge to publish a “compilation of procedure” on behalf of the European Commission to gather all these guidelines, outlining the quality system requirements for National GMP Pharmaceutical inspectorates. The compilation is published on the [Inspections page of the EMA website](http://www.ema.europa.eu) and, according to Directive 2003/94/EC, Member States shall take it into account.

### 28.2. Pre-submission notification:

In their notification of intention to submit, Applicants should mention:

- The name (including contact point), and the address of the proposed manufacturer(s) of the active substance(s) and finished product
- The name and address of the proposed site(s) in the EEA responsible for batch release of the medicinal product
- If the medicinal product is imported from a third country, it should also include information on GMP inspections of the site(s) concerned carried out in the last 2-3 years by EEA competent authorities and/or by competent authorities of countries where a Mutual Recognition Agreement (MRA) is in operation, as applicable.
- Final manufacturing and batch release arrangements will have to be provided when submitting the application
- A description of the sequence of all different sites involved

The manufacturing sites mentioned should be in compliance with Good Manufacturing Practice (GMP) and hence be “inspection ready” at the time of submission of the application and throughout the assessment.

Manufacturing sites in third countries should be aware of European Community GMP requirements as mentioned below.
Once the application is received, it is normally not permitted to add a new site or to change the steps of manufacture/release described in the dossier during the 210-day assessment procedure. Any additional site should be submitted as a variation after the granting of the marketing authorisation.

At reception of application, the EMA determines if satisfactory inspections information is available. If not, the EMA with the Rapporteur and co-Rapporteur asks the CHMP to make a request for inspection of the manufacturer of either the active substance or the medicinal product in order to complete the assessment.

The performance of these inspections by the EEA competent authorities will be co-ordinated by the EMA taking into account:

- Inspections carried out of the same manufacturers by the EEA Countries
- Inspections carried out of the same manufacturers by competent authorities of countries where a MRA is in operation, when applicable
- The advice of the Rapporteur/Co-Rapporteur
- Specific issues and questions raised during the assessment of the application

**28.3. Inspection Team:**

The team required to perform the inspection will be proposed and co-ordinated by the EMA Secretariat. The team will be drawn from the inspection services of the Supervisory and other competent authorities of the EEA. On the advice of the Rapporteur and/or Co-Rapporteur the Inspection Team may include scientific experts and/or a Rapporteur for the Inspection as referred to in the provisions of Article 8 of Regulation (EC) No 726/2004.

**28.4. Type of inspection:**

Inspections may be carried out to verify compliance with European Community Good Manufacturing Practice principles and guidelines and/or to cover product or process related issues arising from the assessment of the application. Inspections may cover the following activities:

**28.4.1. Manufacture of the Active Substance:**

The detailed guidelines on Good Manufacturing Practice adopted by the EEA for the manufacture of the active substance, are contained in part II of the EU Guide to Good Manufacturing Practice (Good Manufacturing Practice for Active Pharmaceutical Ingredients) in "The Rules Governing Medicinal Products in the European Union - Volume 4". Inspectors of the competent authorities in the EEA will inspect against the requirements of this guideline.

**28.4.2. Manufacture of the Finished Product:**

The GMP principles and guidelines applying to the manufacture of medicinal products for the EEA are laid down in Commission Directive 2003/94/EC, which are restated along with part I of the EU Guide to Good Manufacturing Practice in "The Rules Governing Medicinal Products in the European Union - Volume 4".

Where a manufacturing site is located in the EEA it is normally not necessary to request an inspection to confirm its GMP status as it is required by the above-mentioned Directive to be regularly inspected by the relevant authorities.
An inspection will normally be requested to confirm the GMP compliance status of manufacturing sites in third countries unless satisfactory information is available from an inspection of the same or similar category of product carried out during the last 2-3 years by an EEA competent authority or by the competent authority of a country where a MRA is in operation, as applicable.

In all cases (for sites in the EEA and third countries), an inspection may be requested to cover product or process related issues arising from the assessment of the application. In this case the Rapporteur and/or Co-Rapporteur will provide the Inspection Team with a list of questions/issues, which should be addressed during the inspection.

28.4.3. Importing Site - Site located in the EEA:

Importing sites in the EEA are required by the provisions of title III of Directive 2001/83/EC as amended, to hold a manufacturing authorisation. Inspections of importing sites to confirm their GMP compliance status are not normally requested in connection with applications for marketing authorisations. Inspections may however be requested to cover product or process related issues arising from the assessment of the application. In this case the Rapporteur and/or Co-Rapporteur will provide the Inspection Team with a list of questions/issues, which should be addressed during the inspection.

28.5. Timetable for Inspections:

Inspection(s) requested in connection with an application for a marketing authorisation must be carried out and the final report(s) sent to the EMA and submitted to the CHMP in accordance with the 210 day time limit for the evaluation of the application by the CHMP.

Once an inspection request is adopted by the CHMP the Inspection Sector of the EMA will write within 5 working days to:

- the applicant explaining that an inspection(s) will take place, giving details (target date for carrying out the inspection, inspection team, scope of the inspection, contact person in the relevant authority responsible for arranging the inspection)
- the Rapporteur and Co-Rapporteur for information.

The Inspection Team will contact the Company to agree inspection dates within the agreed target date. Inspections usually take place in parallel with the “clock stop” period and will approximately be conducted within two months from the adoption of the inspection request.

If the manufacture of the product is carried out infrequently or is not scheduled to take place during the period when the assessment of the application is to take place, the Inspection Team and the Rapporteur/Co-Rapporteur may agree to inspect the manufacture of a similar product or process.

Regarding the fees to be paid, details can be found in the question “What is the fee for a GMP/GCP inspection?”.

28.6. Inspection Reports:

Inspectors will send the draft Inspection Report to the manufacturer within fifteen days of the Inspection for comments on major factual errors, point of disagreement or remedial actions. Where necessary, the manufacturer should respond within a further fifteen days to provide comments and, if necessary, an action plan with a timetable for implementation. This will be considered during the finalisation of the Inspection Report and, if necessary, attached to it.
The timing of any discussions, further actions and/or the provision of additional information arising from the inspection will be agreed with the Inspectors and communicated by the Inspectors to the Rapporteur, the Co-Rapporteur and the EMA.

Inspectors finalise the report and send to the EMA inspections sector by Day 180 at the latest, which circulate to the Rapporteur, Co-Rapporteur and CHMP. In case of a non-satisfactory inspection report, which cannot lead to a positive opinion, discussions between the EMA, the Rapporteur, the Co-Rapporteur and the applicant should take place.

28.7. **Documents for inspection:**

It is helpful to have a site/plant master file for use in preparing and carrying out the inspection. The preferred format is that recommended by the Pharmaceutical Inspection Co-operation Scheme (PIC/PICS). The Applicant should supply this document directly to the Inspection Team as far in advance of the inspection as possible. The site/plant master file is however not required to be submitted to the EMA.

**References**

- Regulation (EC) No 726/2004
- Directive 2003/94/EC
- Directive 2001/83/EC
- The rules governing medicinal products in the European Community, Good Manufacturing Practice, *Volume 4*
- The Rules Governing Medicinal Products in the European Community, the *Notice to Applicants, Volume 2A, Chapter 4*
29. When can I expect a pre-approval GCP inspection and how are they conducted? *Rev. May 06*

Clinical trials included in any marketing authorisation application (MAA) in the EU and in any subsequent application to the initial one are required to be conducted in accordance with Good Clinical Practices (GCP). GCP inspections are conducted in accordance with Article 15 of Directive 2001/20/EC. The requirements which apply for the conduct of clinical trials included in a MAA are set out in Recital 16 and Article 6(1) of Regulation (EC) No 726/2004 as well as in Annex I to Directive 2001/83/EC, as amended (Introduction and general principles - sections 4 and 8 - and Part I - Module 5). Requirements for the conduct of clinical trials and GCP inspections are published in Volume 10 of the Rules governing Medicinal Products in the European Community.

The EMA relies for the scientific review of centralised applications for marketing authorisations for medicinal products on the expertise located in the Member States. The same approach exists in the area of inspections, where inspections are conducted by Member States’ inspectorates if requested by the CHMP. These inspections are co-ordinated by the EMA if they pertain to centralised applications and in the case of GCP inspections, they are conducted by Member States’ inspectorates in accordance with Article 15 of Directive 2001/20/EC. There is a GCP Inspection Services Group, composed of inspectors from the Member States, which meets quarterly at the EMA.

EMA inspection sector reviews all new applications for evidence of GCP compliance and other validation aspects. All new applications are examined to assess the need for GCP inspection(s). The EMA Inspections Sector liaises closely with the Product Team Leader, Rapporteur and Co-Rapporteur during the pre-submission phase and in the period during and after validation to discuss the need to request GCP inspection(s). A need for inspection(s) may be identified at this stage, based on previous relevant experience of the Inspections Sector and the Member States’ national inspectorates. In addition, a need for GCP inspection(s) may also be identified during the review by the assessors, in particular during the initial assessment phase up to day 120.

GCP inspection issues are usually addressed in the List of Questions (although the inspection may commence earlier once adopted by CHMP), and therefore are usually adopted at Day 120. The GCP inspection(s) of the concerned site(s) can then take place in parallel with the “clock stop” period. However, GCP inspection(s) may be requested by CHMP at any stage of the assessment.

It should be noted that clinical data submitted as a result of specific obligations/follow-up measures, or within variations, extensions or other information received after the initial authorisation (e.g. in relation to safety updates, risk management plan etc...) may also trigger a GCP inspection request.

The Reporting Inspector appointed is usually from the inspectorate of the Member State of the CHMP Rapporteur or Co-rapporteur unless the site(s) to be inspected are located in a single EEA state (or small number (3 or less) of EEA states), in which case that Inspectorate is usually designated as the Reporting Inspectorate.

In addition to the Reporting Inspector, one Lead Inspector is designated per site to be inspected. The Lead Inspector is usually from the Inspectorate of the Member State where the site to be inspected is located (for inspections in the EEA). The Reporting Inspector may also be the Lead Inspector for one or more sites.

In the case of third country inspections, the Reporting Inspectorate and the inspectors are usually from the Rapporteur/Co-Rapporteur country inspectorates.
The applicant is asked to provide information in the application in order to facilitate the review and where needed the preparation of GCP Inspections. This information should be provided in the Individual Clinical Study Reports and their Appendices (Module 5) in line with the “Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications” (CHMP/EWP/2998/03), and the “Note for Guidance on Structure and Content of Clinical Study Reports” (CPMP/ICH/137/95). Some of the key information to be provided for each study, are listed below with the specific references to the section numbers given in the “Note for Guidance on Structure and Content of Clinical Study Reports” (CPMP/ICH/137/95):

- A clear description of the study administrative structure (clear identification of the sponsor and of the parties who have performed the monitoring, data management, statistics, laboratory assessments, randomization, site(s) of manufacture, site of release in Europe, medical writing, other applicable activities and the location of the trial master file) preferably in a tabular form and indicating name and address of the site where each activity was performed, responsibilities and scope of each activity. These should be identified in the clinical study report of each study, for instance in section 6, or appendix 16.1.4.

- A list of investigators (name, address, country), preferably in a tabular form, showing the number of patients enrolled by each site, and the total number of sites. In addition a table with the number of patients enrolled per country should be included. These should be identified in the clinical study report of each study, for instance in section 10.1 or appendix 16.1.4.

- Audit certificates (indicating the sites audited, the dates of audit, the type of audit and the auditor). These should be identified in the clinical study report of each study, for instance in appendix 16.1.8.

- Signature of the principal or coordinating investigator(s) according to Annex I to Directive 2001/83/EC as amended and in line with the “Note for Guidance on Structure and Content of Clinical Study Reports” (CPMP/ICH/137/95), and not only the signature of the sponsor’s responsible medical officer. These should be identified in the clinical study report of each study, for instance in appendix 16.1.5.

A list of inspection(s) conducted or planned by other regulatory authorities, related to the product and trial sites involved, should also be provided, preferably attached to the Application cover letter.

Each clinical study report should contain a statement indicating whether the study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

According to the Notice to Applicant, Volume 2B, the clinical overview (Module 2), should assess the quality of the design and performance of the studies and also include a statement regarding GCP compliance.

In addition, in accordance with Article 6(1) of Regulation (EC) No 726/2004, a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC should be provided, where applicable, in Module 1.9. This statement should indicate that “clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC” together with a listing of all trials (protocol number) and countries (outside the EU) involved.
References

- “Centralised procedure” the Rules governing Medicinal Products in the European Community, *Volume 2A, Notice to Applicants, Chapter 4*
- Directive 2001/20/EC
- Directive 2001/83/EC as amended
- Regulation (EC) No 726/2004
- “Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications” (CHMP/EWP/2998/03)
- “Note for Guidance on Structure and Content of Clinical Study Reports” (CPMP/ICH/137/95)
- “Clinical trials”, The Rules governing Medicinal Products in the European Community *Notice to Applicants, Volume 10*
30. Which tools are used by the EMA to facilitate the streamlining of the European Decision making process / What is the QRD product information? Rev. Jan 06

The Quality Review of Documents group (QRD) was established in June 1996 and operates under the mandate adopted by the EMA Management Board on 3 December 1997.

The QRD Group is composed of representatives of the Member State’s national authorities with experience in regulatory affairs and product information and representatives of the EMA (which also chairs the Group and provides secretariat facilities). The European Commission as well as observers from candidate EU countries and the Commission “Centre de Traduction” are invited to participate.

The main task of this group is to ensure clarity, consistency and accuracy of the medicinal product information (summary of product characteristics (SPC), labelling and package leaflet) and of its translations, which will be attached to scientific CHMP opinions. The mandate sets out a series of other tasks, namely:

- Verification of terminology used in translations of Opinions and their consistency with the original version of documents
- Ensuring linguistic and other formal coherence and consistency between different terminology used in scientific Opinions, and promotion of initiatives towards the standardisation of terminology
- Review and update of Opinion templates
- Promotion of legibility of patient information and verification of specimens of sales presentations/mock-ups in all EU official languages
- Consideration of issues which could lead to delays in the Commission’s decision-making process and possible development, on request, of advice (particularly with a view to contribute to the development of common understanding on the implementation of legislation and guidelines)

The mandate also provides that "the Group shall develop its own working methods" and will consider "how best it may be associated with the different stages of the evaluation and Decision-making process".

In this regard, a New Linguistic Review Process of Product Information has been developed and adopted, providing a more streamlined and more efficient review of the Product Information in all EEA languages.

The new process can be summarised as follows:

Pre-opinion:

Before Day 210 two reviews of the English Product Information are performed.

Between Day 80 and 110, a first review is done by the EMA Product Information Quality Group (PIQ) followed by a second review by the QRD group between Day 121 and 165.

The new process also foresees the possibility for one or two Applicant representative(s) to participate to a meeting around Day 165 to discuss the comments and the English Product Information with representatives from the EMA and the QRD.
Post-opinion:

Between Day 215 and 229, a detailed review of all translations of the Product Information is made by the Member States coordinated by the national QRD members concerned.

Between Day 232 and 237, the PIQ reviews the implementation of Member States comments made by the applicants in the final texts.

By Day 237, the final translations are sent to the European Commission to start the external Standing Committee consultation.

As part of a Marketing Authorisation Application, Applicants must submit proposals for SPC, Labelling and Package Leaflet texts in module 1.3.1. using the QRD Product Information Templates.

The Templates:

- are intended to provide applicants with practical advice on how to draw up the product information, but without prejudice to any final position of the EMA, CHMP and European Institutions as to the contents of the document
- set out the standard headings and indicate the most commonly used standard phrases and terms in the 20 official EU languages (with addition of Icelandic and Norwegian)
- define the format and layout for Summary of Product Characteristics (SPC); labelling and Package Leaflet (see also "Convention" to be followed for QRD templates in order to ensure absolute consistency between all language versions)
- provide useful guidance as to the content of the information to be supplied, in the QRD template with explanatory notes

In addition, QRD Reference Documents provide more detail guidance on various aspects concerning terminology and style.

While the templates and guidance notes aim to provide practical hints to the applicants, in particular in relation to how to address common problem areas, they are by no means a comprehensive guide to the information required to be included in the product literature. Thus applicants must also refer to the current EU legislation, guidelines, CHMP notes for guidance etc, when drawing up their drafts in order to be able to fully comply with the legal requirements in respect to product information.

For more details, please visit the QRD Website for all information relating to Product Information and all useful References Documents.

References

- The new Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02)
- QRD Templates with Explanatory Notes
31. How is a MAA pre-submission meeting conducted at the EMA? Rev. Oct 12

31.1. General principle

The pre-submission meetings represent important points in the product development and regulatory approval process, and relate to the preparatory steps in advance of submitting a request for marketing authorisation application (MAA). Successful pre-submission meetings should enable applicants to submit applications, which are in conformity with the legal and regulatory requirements and which can be smoothly evaluated. These meetings will also enable applicants to establish contact with the EMA Product Team Members who will be closely involved in the centralised evaluation procedure of their medicinal product.

31.1.1. Purpose/scope of meeting

a. MAA pre-submission meetings are aimed at providing applicants with information that will assist them in the finalisation of their upcoming marketing authorisation application. Such meetings typically address product-specific legal, regulatory and scientific issues in order to facilitate subsequent validation and assessment of the application. Pre-submission meetings can be especially helpful to SMEs / other companies that may have limited experience of interaction with the EMA or are unfamiliar with the centralised procedure. However, experience has shown the usefulness of pre-submission meetings even for applicants that already have experience with the centralised procedure, to address issues specific to their upcoming application in view of the constantly evolving regulatory framework and its application.

b. The MAA pre-submission meeting request form provides an overview of the most relevant topics (checklist) that applicants are advised to consider when preparing their upcoming application, and which will be discussed at a MAA pre-submission meeting. For each topic, a reference is included to the corresponding ‘question and answer’ in the EMA Pre-Submission Guidance for Users of the Centralised Procedure (PSG), which is available on the EMA Website. The PSG addresses a number of questions, which users of the centralised procedure may have, together with hyperlinks to relevant legislative documents and procedural guidelines which further complement the advice given in the PSG. The EMA considers that the information provided answers the majority of applicants’ queries. As EMA commits to keeping the pre-submission guidance document updated, there should not be a need to check or confirm the answers given in the PSG document at a pre-submission meeting. A topic should therefore only be proposed for discussion at a pre-submission meeting, in case the applicant’s questions are not fully answered by the PSG or other available guidance documents, due to certain particularities of the upcoming application and/or nature of the product. In that case, applicants are advised to clearly describe the issues in the ‘comments’ box under the topic concerned, and to provide relevant background information. Other topics not listed in the form may be added.

31.2. Timing of MAA pre-submission meetings

Pre-submission meetings for marketing authorisation applications (MAA) usually take place 6-7 months before submission. The MAA pre-submission meeting request form should be sent at least 6 weeks before the proposed meeting date or 3 months in advance if sent together with the Request of Eligibility, so that the meeting can be set-up at a mutually agreed date taking into account availability of EMA participants and meeting rooms. The meeting will start with the applicant’s 20-30’ presentation
followed by a discussion on the presentation and the topics ticked in the pre-submission request form. The total meeting duration should not exceed 2 hours.

### 31.3. Who is involved in a MAA pre-submission meeting?

EMA participants at MAA pre-submission meetings are the product Team Members i.e. the Product Team Leader (PTL) together with the Product Team Members (PTM) from the Quality / Safety-Efficacy sector and Regulatory Affairs. Depending on the topics to be discussed, other EMA attendees from the following sectors may attend parts of the meeting: Orphan Drugs, SME, Paediatrics, Inspections, Medical Information, Risk Management, Product and Application Business Support (PA-BUS).

Please note that the PTL will be chairing the meeting and will remain the primary contact point between the applicant and the rapporteurs during the life cycle of your product.

Applicant’s representatives should not exceed 7 to 8 participants. If needed, additional participants can join via teleconference.

### 31.4. Documents to be prepared for a MAA pre-submission meeting

- The [MAA pre-submission meeting request form](#) needs to be filled in electronically and send to PA-BUS at pa-bus@ema.europa.eu. This form includes topics and questions to be addressed at the pre-submission meeting.

- One of the key-documents to be provided with the [MAA pre-submission meeting request form](#) is an overview of the product and its development programme (quality, non-clinical and clinical) together with a draft Table of Contents of the Application, listing the studies performed for each EU-CTD heading and the draft product information.

- Applicants will need to provide a number of documents in relation to the product and the application with the [MAA pre-submission meeting request form](#). In addition, depending on the topics to be discussed, the applicant should provide additional topic-specific information (e.g. draft justification for accelerated review).

- Another important document to be provided is a [draft MA Application Form (EU-CTD Module 1.2)](#), which should be completed as far and accurate as possible. The form will provide important information on the product and the type of application (e.g. legal basis, reference product details, manufacturing sites, conditional approval) in relation to the topics to be discussed at the meeting. It will also allow EMA to identify topics, other than those requested by the applicant, for discussion/clarification at the meeting, and thereby preventing issues to be raised at validation. In order to avoid duplication of information, the topics in the pre-submission meeting request form will not require the inclusion of the detailed elements which are already to be provided in the application form (e.g. tick-boxes for legal basis, eligibility for centralised procedure).

- Following receipt of the pre-submission meeting request form and annexed documents, the EMA Product Team Leader (PTL) will review the topics proposed for discussion. He/she may consider that certain proposed topics would not need to be discussed at the meeting, as they are sufficiently addressed in existing guidance documents or as they could be easily clarified by phone or e-mail, in order to focus the meeting on particular product-specific issues. The applicant will be informed accordingly in advance of the meeting.

**Note:** Applicants must in all cases comply with all requirements of Community Legislation. Provisions, which extend to EEA countries (i.e. the EU member states, plus Norway, Iceland and Liechtenstein) by virtue of the EEA agreement, are outlined in the relevant sections of the text.
31.5. How are MAA pre-submission meetings conducted?

At the start of the meeting, the applicant will be invited to give a 20-30’ presentation on the product development. The applicant’s presentation should include the following topics:

- Company’s participants and contact points during the evaluation
- Brief description of the product
- Brief summary of the dossier content
- Particular EU guideline deviations

On the basis of the information provided, EMA participants will discuss with the applicant the appropriateness of the chosen legal basis in view of the available data, highlight elements to be specifically addressed in the CTD Overviews (e.g. missing data, deviations from scientific advice), will provide an EMA view on the possibility for requesting approval under exceptional circumstances or conditional approval if applicable, etc. EMA may also draw attention to relevant scientific and regulatory guidelines, in particular the CHMP ‘clock-stop’ rules in case of a potential premature submission, recommend (further) scientific advice and suggest improvements to the product information.

The MAA pre-submission meeting request form will serve as the agenda for the remaining of the meeting. The topics listed in the pre-submission meeting request form are grouped according to the following areas:

- Quality + GMP
- Non-clinical + Clinical + GLP + GCP
- Pharmacovigilance
- Regulatory + procedural
- Product information + transparency
- Administrative

It is envisaged that the issues will be addressed in this order at the pre-submission meeting. This will allow a sequential discussion of all the applicant’s questions on topics related to the same area, with involvement of relevant EMA staff with expertise in the area concerned (e.g. Medical Information Staff members will attend the discussion on the topics dealing with product information and transparency etc).

Note: Applicants wishing to meet with their appointed (Co-) Rapporteur and assessment teams at national level should also inform the EMA PTL who will try to participate to such a meeting via teleconference. In any case, minutes of such meetings should be provided to the EMA PTL.

31.6. Follow up of MAA pre-submission meetings

Detailed meeting minutes should be prepared by the applicant and provided to the EMA PTL within 2 weeks after the meeting. EMA Product Team Members will subsequently review the minutes within 2 weeks and agree the final (amended) minutes with the applicant.

31.7. Flow-chart summary
32. Is my medicinal product eligible for approval under exceptional circumstances? *New Jan 06*

### 32.1. Legal basis and Criteria

The legal basis for the marketing authorisation (MA) under exceptional circumstances is the Article 14 (8) of the Regulation (EC) No 726/2004, and the relevant documentation for applications in exceptional circumstances are laid down in Part II of Annex I of Directive 2001/83/EC, as amended.

Products for which the applicant can demonstrate in this application that he 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,

may be eligible for marketing authorisation under exceptional circumstances.

Consequently, the authorisation under exceptional circumstances is granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken.
32.2. **Prior to submission**

As early as possible during drug development, the applicant is encouraged to seek scientific advice from the EMA about the justification for applying for a marketing authorisation under exceptional circumstances, especially on the inability to provide comprehensive data.

Any further discussion on the appropriateness should preferably occur in the context of the presubmission meeting.

32.3. **Timing of the submission and Documentation to be supplied**

- First of all, the applicant should submit a statement on the appropriateness of the granting of a marketing authorisation under exceptional circumstances in the notification to the EMA of their intention to submit a marketing authorization application (at least 6 months before submission).
- Then, if the applicant considers that the grounds for approval under exceptional circumstances should apply, the applicant should tick the box 1.5.2 of the application form and include its justification in module 1, covering the following aspects:
  1. A claim that the applicant can show that he is unable to provide comprehensive non-clinical or clinical data on the efficacy and safety under normal conditions of use
  2. A listing of the non-clinical or clinical efficacy or safety data that cannot be comprehensively provided
  3. Justifications on the grounds for approval under exceptional circumstances
  4. Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information).

The proposals for detailed information on the specific procedures/obligations to be conducted shall also be written in accordance with the “Guideline on risk management systems for medicinal products for human use”.

32.4. **Assessment of the justification for exceptional circumstances**

The Rapporteur, Co-Rapporteur and the other CHMP members will assess the justification/data submitted for exceptional circumstances as part of the overall assessment of the benefit/risk of the application.

It is up to the CHMP, during the review, to ultimately decide on the type of the marketing authorisation.

32.5. **Differences between Exceptional circumstances and conditional marketing authorisation**

<table>
<thead>
<tr>
<th>Conditional Marketing Authorisation</th>
<th>Marketing Authorisation under Exceptional Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrate positive benefit-risk balance, based on scientific data, pending confirmation</td>
<td>Comprehensive data cannot be provided (specific reasons foreseen in the legislation)</td>
</tr>
<tr>
<td>Authorisation valid for one year, on a renewable basis</td>
<td>Reviewed annually to reassess the risk-benefit balance, in an annual re-assessment procedure-</td>
</tr>
</tbody>
</table>
A marketing authorisation under exceptional circumstances should not be granted when a conditional marketing authorisation is more appropriate. A conditional marketing authorisation is for example granted in the absence of comprehensive clinical data when it is likely that the applicant will be in the position to provide such data in a short timeframe, whereas the fulfilment of any specific procedures/obligations imposed as part of the marketing authorisation under exceptional circumstances is aimed at the provision of information on the safe and effective use of the product and will normally not lead to the completion of a full dossier.

32.6. **Particularities of the marketing authorisation under exceptional circumstances**

- It should be noted that designated orphan products are eligible for approval under exceptional circumstances only if the criteria considered for the approval under exceptional circumstances are fulfilled.

- The summary of product characteristics and package leaflet should mention that a marketing authorisation has been granted subject to certain specific obligations to be reviewed annually.

- The renewal of the marketing authorisation of a medicinal product under exceptional circumstances follows the same rules as a "normal" marketing authorisation. After 5 years, the marketing authorisation will then be renewed under exceptional circumstances for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. ([See the renewal guidance](#)).

**References**

- Regulation (EC) No 726/2004
- Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14 (8) of Regulation (EC) No 726/2004
- Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005)
33. Do I need to perform User Consultation? / When and how to submit information on User Consultation? New July 06

Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended, require that the package leaflet reflects the results of consultations with target patient groups (‘user consultation’) to ensure that it is legible, clear and easy to use and that the results of assessments carried out in cooperation with target patient groups are provided to the competent authority.

A user consultation is always required in the following situations:

- First authorisation of a medicinal product with a new active substance,
- Medicinal products which have undergone a change in legal status,
- Medicinal products with a new presentation,
- Medicinal products with particular critical safety issues.

However, reference to already approved package leaflets may be acceptable where appropriate, based on a sound justification by the applicant. Examples of when this may be considered acceptable as well as the considerations to be taken into account when choosing the types of ‘reference’ package leaflets are detailed in the “Guidance concerning consultations with target patient groups for the package leaflet”.

If user consultation has been performed on a package leaflet in the old QRD templates, there is no need to be retested when updating according to the new QRD templates. However, it should be noted that compliance with the QRD templates does not exempt from the obligation to undertake a user test or other form of user consultation. See also “What is the QRD product information?”

The package leaflet should be legible, clear and easy to read in all EEA languages, but it is normally sufficient to undertake user consultation in one EEA language. However, results of user consultation should be presented in English in order to allow assessment.

33.1. Methods of user consultation

The legislation does not define a precise method to be used for user consultation.

One of the possible ways of complying with the new legal requirement is by performing a ‘user testing’ of the package leaflet, i.e. to test the readability of a specimen with a group of selected test subjects. It is a development tool which is flexible and aims to identify whether or not the information as presented, conveys the correct messages to those who read it. Testing itself does not improve the quality of the information but it will indicate where there are problem areas which should be rectified.

Other methods than user testing may be acceptable provided that the outcome ensures that the information is legible, clear and easy to use so that patients can locate important information within the package leaflet, understand it and enables the user to act appropriately. Such alternative methodology will have to be justified by the applicant and will be considered on a case-by-case basis.

An example of a method for user testing of a package leaflet is provided in the Annex 2 of “A Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use”.

European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure EMA/339324/2007 Page 82/127
Further guidance on one way of user testing is also provided in the "EFPIA General Recommendations for Readability User Testing of Package Leaflets for Medicinal Products for Human Use Submitted or Approved under the European Centralised Procedure" and its Annexes (www.efpia.eu).

33.2. Submission and assessment of information on user consultation

During the pre-submission phase the applicant may discuss how to address 'user consultation' with EMA and (Co-) Rapporteur, if necessary. This discussion may indicate whether new 'user consultation' would be necessary or whether a justification for its absence or 'focused' user testing could be acceptable.

At the time of submission of the application, information regarding the ‘user consultation’ performed together with a presentation of its results, or a justification for not performing such consultation, is to be included in Module 1 (Section 1.3.4) of the dossier. The presentation of results should be shortened to a summary explaining how the consultation was executed and how the resulting package leaflet accommodated any need for change. The recommended structure of such a summary is provided in the "Guidance concerning consultations with target patient groups for the package leaflet".

In their assessment reports, the (Co-) Rapporteur will include the assessment of the results of user consultation or of the justification for its absence as well as a conclusion on the overall readability of the package leaflet. It should be noted that, if not included in the initial submission, the results of user consultation or any further clarification, as requested, will have to be submitted as part of the answers to the list of questions at Day 121.

The user consultation results and the (Co-) Rapporteur’s assessment will also be forwarded to QRD Group, as useful information when reviewing the draft product information.

Further details on the assessment of information on user consultation can be found in the EMA Operational Procedure on Handling of “Consultation with target patient groups” on Package Leaflets (PL) for Centrally Authorised Products for Human Use (EMEA/277378/2005).

References

- Directive 2001/83/EC, as amended
- "Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use", the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
- "Guidance concerning consultations with target patient groups for the package leaflet", the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
- EMEA Operational Procedure on Handling of "Consultation with target patient groups" on Package Leaflets (PL) for Centrally Authorised Products for Human Use (EMEA/277378/2005)
34. Do I need to include Braille on the Packaging of my Medicinal Product? *New July 06*

Braille is the internationally widespread reading and writing system for blind and partially sighted people. It consists of arrangements of dots which make up the letters of the alphabet, numbers and punctuation marks.

The revised legislation requires that the name of the medicinal product is expressed in Braille format on the packaging of the medicinal product. In addition, Marketing Authorisation Holders must ensure that the package leaflet is made available on request from patients’ organisations in formats appropriate for the blind and partially sighted.

These new requirements apply to new marketing authorisations with Commission Decisions as of 20 November 2005. Nevertheless, companies are encouraged to apply the provision to all centrally authorised medicinal products as soon as possible.

### 34.1. Packaging requirements

The *(invented) name* of the medicinal product followed by its *strength* should be put in Braille on the packaging of the product. The uncontracted Braille system should be used. For medicinal products authorised only in a single strength, it is acceptable that only the invented name in Braille is put on the packaging.

The name in Braille should only appear on the outer/secondary packaging (usually a carton). In case where there is no secondary packaging, it is possible to fix an adhesive Braille label around the bottle. On a volunteer basis, the name in Braille can be expressed on all packaging components.

It is also possible for companies to include, on a voluntary basis, further information in Braille on bigger volume packages (e.g. pharmaceutical form, expiry date, etc).

In case of multilingual packaging, the name in Braille has to be printed in all the different languages concerned.

It should be noted that there is no need to put the name in Braille on the packaging of products which are only intended for administration by health care professionals.

In case of small volume packages (up to 10 ml) with limited space capacity, alternative means of providing Braille information may be considered, e.g. use of contracted Braille system or certain defined abbreviations or addition of a supplementary “tab” label.

At the time of submission of the application, applicants should address in Module 1 - section 1.3.6 of the application dossier the proposed implementation of the Braille requirements on the packaging of the medicinal product. In addition, the information that will appear in Braille on the printed outer packaging should be mentioned, if applicable, as normal text in section 16 of the outer packaging labelling (Module 1 - section 1.3.1 – Annex IIIA) and, where applicable and feasible, should be indicated with dots on the mock-ups (Module 1 – section 1.3.2).

### 34.2. Package leaflet for blind and partially sighted

On request the package leaflet should be provided for partially sighted people in a suitable print, taking into consideration all aspects determining the readability. For blind people the text has to be provided in an appropriate format, e.g. perceptible by hearing (CD-ROM, audiocassette, etc...) or in Braille.
Choice of the appropriate medium should be made by the MAH in consultation with representatives of organisations for the blind and partially sighted.

Further guidance on the implementation of the requirements for Braille and the requirements for the package leaflet for the blind and partially sighted is provided in the European Commission "Guidance concerning the Braille requirements for labelling and the package leaflet (Article 56a of Directive 2001/83/EC, as amended)". Please note that this guidance will be included in the Commission ‘Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use’, after finalisation of the revision of the guideline.

References

- Article 56a of Directive 2001/83/EC, as amended
- “Guidance concerning the Braille requirements for labelling and the package leaflet (Article 56a of Directive 2001/83/EC, as amended)”
- “Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
35. What is the period of protection for my medicinal product? *New July 06*

35.1. Data exclusivity and market exclusivity period for reference medicinal products

A reference medicinal product is a medicinal product, which has been granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC, as amended, and to which the marketing authorisation application for a generic, hybrid or similar biological medicinal product (i.e. application under Articles 10(1), 10(3) or 10(4) of the same Directive) refers (see also "What is the legal basis for my application?").

35.1.1. Submission of the Marketing Authorisation Application (MAA) before 20 November 2005: previous periods of protection

Reference medicinal products authorised through the centralised procedure for which the initial submission was made before 20 November 2005, continue to benefit from the previous periods of protection which are 10 years, (and 10 years for all medicinal products authorised following an opinion of the CHMP in accordance with Article 4 of Directive 87/22/EEC (ex-concertation procedure)).

According to Article 89 of Regulation (EC) No 726/2004, the new periods of protection do not apply to those reference medicinal products for which the initial application for authorisation (date of submission of the application and not validation) was submitted before 20 November 2005.

35.1.2. Notion of global marketing authorisation / Particular case of “Fixed combinations”

The *global marketing authorisation* contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation.

In accordance with Article 6(1) of Directive 2001/83/EC, as amended, all these presentations of a given product shall be considered as part of the same marketing authorisation for the purposes of applying the rules on data and marketing protection.

This means that for a reference medicinal product, the start of the data and market exclusivity periods is the date when the first marketing authorisation was granted in the Community. New additional strengths, pharmaceutical form, administration routes, presentations as well as any variation and extensions do not restart or prolong this period. This will apply even if the new presentation has been authorised to the same marketing authorisation holder through a separate procedure and under a different name.

The “fixed combinations” are not considered part of the global marketing authorisation and will benefit from an independent period of protection.
35.1.3. Submission of the MAA after 20 November 2005: new periods of protection

Directive 2001/83/EC, as amended, and Regulation (EC) No 726/2004 have introduced new rules concerning the periods, from the initial marketing authorisation of the reference product, during which generic, hybrid or similar biological medicinal products’ applicants cannot rely on the dossier of the reference product for the purposes of submitting an application, obtaining a marketing authorisation or placing the product on the market.

Applications for generic, hybrid or similar biological medicinal products can be submitted after a so-called “data exclusivity” period of 8 years from initial authorisation of the reference medicinal product. Generic, hybrid or similar biological medicinal products authorised in this way can be placed on the market after a so-called “market exclusivity” period of 10 years from initial authorisation of the reference medicinal product.

35.2. One year period of protection for new indications of well-established substances

According to Article 10(5) of Directive 2001/83/EC as amended, “where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.”

The data exclusivity period refers exclusively to the data concerning the new indications.

Commission Decisions authorising new therapeutic indications for well-established substances will contain a clear statement of whether the new indication is based on significant pre-clinical or clinical studies.

A well-established substance is an active substance included in the relevant medicinal product which can be shown to have a well-established use in accordance with the requirements of indent (a) in section 1 (“Well established medicinal use”) of Part II of the Annex to Directive 2001/83/EC as amended. This does not however mean that the medicinal product concerned must have been authorised under the legal basis of the well-established use procedure.

A new indication submitted after 20 November 2005 may benefit from this year of protection.

35.3. One-year period of protection for data supporting a change of classification

According to Article 74a of Directive 2001/83/EC as amended reads: “Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.”

The 1-year period of protection covers significant pre-clinical or clinical trials carried out for the purpose of substantiating an application for a change of classification. The interpretation by competent authorities of the notion of significant pre-clinical tests or clinical trials under Article 74a will be without prejudice to the interpretation of that phrase under Article 10(5) of the Directive.

When adopting a decision authorising a change of classification of a medicinal product, the competent authority must assess whether the change is based on significant pre-clinical tests or clinical trials. In the case of products authorised in accordance with Regulation (EC) No 726/2004, Commission
Decisions authorising a change of classification will contain a clear statement of whether the change is based on significant pre-clinical tests or clinical trials (see also "Guideline on changing the classification for the supply of a medicinal product for human use").

A change of classification authorised after 20 November 2005 may benefit from this year of protection.

35.4. Extension of the ten-year period of marketing protection in the case of new therapeutic indications (8 + 2 +1)

In accordance with Article 14(11) of Regulation (EC) No 726/2004, the ten-year period of marketing protection (8+2) may be extended by 1 year in the event of authorisation of new therapeutic indications but only if:

• The new application represents a significant clinical benefit in comparison with existing therapies,
• The new indication is granted during the first eight years since the initial marketing authorisation.

This additional year of marketing protection applies to the global marketing authorisation for the reference medicinal product. Generic, hybrid or similar biological medicinal products, with or without the new therapeutic indication, may not be placed on the market until expiry of the eleventh year.

The overall period of protection cannot exceed eleven years. Therefore, this provision can be used only once per ‘global marketing authorisation’ within the meaning of Article 6(1) of Directive 2001/83/EC as amended.

Commission Decisions authorising new therapeutic indications will contain a clear statement of whether the new indication represents a significant clinical benefit in comparison with existing therapies.

This year of protection shall apply only to those reference medicinal products for which the initial application for authorisation is submitted after 20 November 2005.

Detailed information on market exclusivity for orphan medicinal products is provided in the “Communication from the Commission on Regulation (EC) No 141/2000 on orphan medicinal products” (section D) and in the draft "Guideline on aspects of the application of Article 8 of Regulation (EC) No 141/2000".

References

• Regulation (EC) No 726/2004
• Directive 2001/83/EC, as amended
• The Rules Governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1
• “Guideline on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11 years) marketing protection period”
• “Guideline on changing the classification for the supply of a medicinal product for human use”, the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C
• Communication from the Commission on Regulation (EC) No 141/2000 on orphan medicinal products
- European Commission *Guideline on aspects of the application of Article 8 of Regulation (EC) No 141/2000*: Assessment of similarity and/or clinical superiority of orphan medicinal products when assessing marketing authorisation applications and variations
36. Do I have to submit an EU Risk Management Plan as part of my application? **New July 06**

36.1. **Legal basis and description of the risk management system**

Article 8(3) (ia) of Directive 2001/83/EC, as amended, requires that a marketing authorisation application (MAA) shall include, where appropriate, the detailed description of the risk management system that the applicant will introduce.

A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

The aim of a risk management system is to ensure that the benefits of a particular medicine (or a series of medicines) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

36.2. **EU Risk Management Plan (EU-RMP)**

The description of a risk management system should be submitted in the form of an EU-RMP. The EU-RMP contains 2 parts:

Part I
- A Safety Specification
- A Pharmacovigilance Plan, and

Part II
- An evaluation of the need for risk minimisation activities,
and if there is a need for additional (i.e. non-routine) risk minimisation activities:
  - A risk minimisation plan

36.3. **Situations when an EU-RMP is required**

An EU-RMP may need to be submitted at any time of a product’s life-cycle – i.e. during both the pre-authorisation and post-authorisation phases. In particular an EU-RMP should be submitted:

- With the application for a new marketing authorisation for:
  - any product containing a new active substance
  - a similar biological medicinal product
  - a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product

- With an application involving a significant change in a marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication) unless it has been agreed with the EMA that submission is not required.
  - On request from the EMA (both pre- and post-authorisation)
- On the initiative of a MAA/MAH when they identify a safety concern with a medicinal product at any stage of its life cycle

For situations where the submission of an EU-RMP is not mandatory, the need for it should be discussed with the EMA well in advance of the submission.

36.4. Liaise with the EMA: Scientific advice/pre-submission meeting

At any stage, but in particular during the pre-authorisation phase, a MAA/MAH may request advice on the need for, development or content of an EU-RMP through the scientific advice procedure.

Whether or not the scientific advice procedure has been used, discussion on the EU-RMP for a medicinal product seeking a new authorisation through the centralised procedure should take place at the pre-submission meeting.

When it is not mandatory that an EU-RMP is submitted and the MAA/MAH thinks it is unnecessary, the MAA/MAH should submit a brief justification with the application which will form part of the formal assessment by the Rapporteur. However, it is strongly recommended that this is discussed with the EMA before submission of the application.

For significant changes to an existing centralised marketing authorisation, the MAH should discuss the need for an EU-RMP with the EMA at least two months in advance of the submission.

36.5. Location in the dossier

An EU-RMP submitted at the time of an application for a Marketing Authorisation should be provided in Module 1.8.2 of the MAA in a stand-alone format allowing circulation to, and evaluation by pharmacovigilance and risk management experts. It should be accompanied by other relevant documents such as study protocols, where applicable.

36.6. Content of the EU-RMP

Part I of the EU-RMP incorporates the concepts of ICH-E2E regarding the Safety Specification, which summarises the safety profile of the medicinal product at the particular point in time of its life-cycle, and the Pharmacovigilance Plan which is based on the Safety Specification.

In part II, on the basis of the Safety Specification, MAA/MAH should consider carefully the need for risk minimisation activities to be introduced. Risk minimisation activities may be "routine" or "additional". Within the "evaluation of the need for risk minimisation activities," the MAA/MAH should discuss fully the use of routine risk minimisation activities and whether there is a need for additional risk minimisation activities. If only routine risk minimisation activities are required there is no need to submit a risk minimisation plan. If additional risk minimisation activities are thought necessary, the MAA/MAH should provide a risk minimisation plan within Part II of the EU-RMP. This risk minimisation plan should contain both the routine and additional activities for each safety concern.

Applicants are strongly advised to follow the "Guideline on Risk Management Systems For Medicinal Products For Human Use" (EMEA/CHMP/96268/2005) in order to meet the requirements for a detailed description of the risk management system.

36.7. Submission of updated EU-RMP documents

As additional information on the safety of a medicinal product becomes available, the Safety Specification and other sections of the EU-RMP should be updated accordingly.
The updated EU-RMP should be submitted at the same time as the next periodic safety update report (PSUR) unless other requirements have been laid down as a condition of the marketing authorisation.

In addition, an updated EU-RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities.
- Within 60 days of an important (Pharmacovigilance or risk minimisation) milestone being reached or the results of a study becoming available.
- At the request of the EMA.

A cover letter should be submitted with the updated EU-RMP briefly summarising the changes from the previous EU-RMP.

Where no changes to any part of the EU-RMP have occurred since the last submission, a letter stating this, and the date of the last EU-RMP submission should be sent. In this circumstance it is not necessary to re-submit the EU-RMP with the letter.

**References**

- [Directive 2001/83/EC](#), as amended
- "Guideline on Risk Management Systems For Medicinal Products For Human Use" (EMEA/CHMP/96268/2005)
37. How and when to submit a Pharmacovigilance system description? Rev. Feb 12

Companies are requested to provide a detailed description of the pharmacovigilance system, which the applicant will introduce, in accordance with Article 8(3)(ia) of Directive 2001/83/EC as amended. Companies are also required to provide proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country, in accordance with Article 8(3)(n) of Directive 2001/83/EC as amended.

These requirements are the same for any marketing authorisation application, independent of the legal basis for the application.

This section is required for all new applications (including Extension applications). It should be included in Module 1.8.1. of the application.

The description of the MAH’s pharmacovigilance system should follow the requirements as detailed in Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use. The information should be set out following the structure and headings provided in Part I, Section 2.2 of Volume 9A. Clarification is given in a number of places in the guidance on the level of detail expected in the DDPS. It is important that applicants take account of this in order to avoid providing an unnecessary level of detail, with the consequence this has for variations where this detail changes. The information below is an extract of Volume 9A, Part I, Section 2.2 highlighted in order to guide the applicant on the level of detail that is required (e.g. brief description of, summary of, etc).

37.1. Detailed Description of the Pharmacovigilance System

37.1.1. Location in the Marketing Authorisation Application and Update of the Detailed Description

The detailed description of the pharmacovigilance system, including the proof of the availability of the services of the QPPV and the proof that the Marketing Authorisation Holder has the necessary means for the collection and notification of any adverse reaction, should be provided in Module 1/section 1.8.1 of the application dossier.

The detailed description should comprise an overview of the pharmacovigilance system providing information on the key elements of that system. Where aspects of the system such as the organisational arrangements are particular to the product rather than the main system of the Marketing Authorisation Holder/company (Marketing Authorisation Holder or a group of Marketing Authorisation Holders sharing the same pharmacovigilance system) this should be indicated in a product-specific addendum.

The detailed description should be supported by documentation maintained by the company.

Updates to the information provided in the detailed description of the pharmacovigilance system should be submitted as a variation in accordance to the EC guideline on the details of the various categories of variations. Depending on the changes introduced to the existing DDPS they could fall under C.I.9 a) to i); however if none of the pre-specified options apply then it could be submitted as default type IB C.I.9 z) as listed in the Variation Application Form.
In case of the introduction of a new DDPS, such change will fall within the category C.I.8 and the variation, as appropriate, should be submitted.

37.1.2. Statement of the Marketing Authorisation Holder and the QPPV Regarding their Availability and the Means for the Notification of Adverse Reactions

The Applicant should provide a signed statement from the Marketing Authorisation Holder and the QPPV to the effect that the Applicant has their services available as QPPV and has the necessary means for the collection and notification of any adverse reaction occurring either in the Community or in a third country. This statement may make reference to the detailed description of the pharmacovigilance system (see Chapter I.2, Section 2.3), indicate what is already in place, and confirm which items will be put in place before the product is placed on the market in the Community.

37.1.3. Elements of the Detailed Description of the Pharmacovigilance System

All Marketing Authorisation Holders are required to have an appropriate system of pharmacovigilance in place. The detailed description of the pharmacovigilance system should include the following elements, as applicable, and be set out in a structured manner consistent with this list. Additional important elements pertinent to a specific situation should be added:

a) Qualified Person Responsible for Pharmacovigilance (QPPV)

- The name of the QPPV, located in the EEA (the EEA includes European Union Member States plus Iceland, Norway and Liechtenstein. Switzerland is not part of the EEA). The business address and contact details should be provided in the Marketing Authorisation Application form. Companies might, for example, use a 24-hour telephone number through which the QPPV or their back-up can be reached, diverting it to the appropriate person according to availability.

- A summary Curriculum Vitae of the QPPV with the key information relevant to their role (main qualifications, training and experience).

- A summary of the job description of the QPPV.

- A description of the back-up procedure to apply in the absence of the QPPV.

b) Organisation

- Identification and location of the company units or other organisations where the principal EEA and global pharmacovigilance activities are undertaken (in particular those sites where the main databases are located, where Individual Case Safety Reports (ICSRs) are collated and reported and where PSURs (Periodic Safety Update Reports) are prepared and processed for reporting to the Competent Authorities). Identification of affiliates may be made in a general sense, rather than affiliate-by-affiliate.

- Identification of the point(s) in the Community at which pharmacovigilance data are accessible (to include access to ICSRs, PSURs and the global pharmacovigilance data).

- High-level organisation chart(s) providing an overview of the global and EEA pharmacovigilance units and organisations (identified above) and, illustrating the relationships between them, with affiliate/parent companies and contractors. The chart(s) should show the main reporting relationships with management and clearly show the position of the EEA QPPV within the
organisation. Individual names of people should not be included. Licensing partnerships are usually product-specific and should be indicated in a product-specific addendum in the application for that product, unless a partnership is a consistent feature of the company’s organisation across most products.

- A brief summary of the pharmacovigilance activities undertaken by each of the organisations/units identified above.

Flow diagrams indicating the flow of safety reports of different sources and types. These should indicate how reports/information are processed and reported from the source, to the point of receipt by the Competent Authorities. These should be limited to the major processes identified in Volume 9A.

c) Documented Procedures

An essential element of any pharmacovigilance system is that there are clear, written procedures in place. The following list indicates topics that should usually be covered by these written procedures.

The detailed description should indicate for which of these topics there are written procedures in place, but should not list the procedure titles per se. A procedure may cover one or more of the topics or one topic may have one or more procedures depending on its complexity and the organisation of the company. Care should be taken to ensure that quality control and review are appropriately addressed in the various processes and reflected in the relevant procedures.

- The activities of the QPPV and the back-up procedure to apply in their absence;
- The collection, processing (including data entry and data management), quality control, coding, classification, medical review and reporting of ICSRs;
- Reports of different types;
- Organised data collection schemes (solicited), unsolicited, clinical trials, literature;
- The process should ensure that reports from different sources are captured;
- EEA and third countries, healthcare professionals, sales and marketing personnel, other Marketing Authorisation Holder personnel, licensing partners, Competent Authorities, compassionate use, patients, others;
- The follow-up of reports for missing information and for information on the progress and outcome of the case(s);
- Detection of duplicate reports;
- Expedited reporting;
- Electronic reporting;
- Periodic Safety Update Reports (PSURs);
- The preparation, processing, quality control, review (including medical review) and reporting;
- Global pharmacovigilance activities applying to all products: Continuous monitoring of the safety profile of authorised medicinal products (product-specific risk management systems and pharmacovigilance planning are covered in Chapter 1.3.);
- Signal detection and review;
- Risk-benefit assessment;
• Reporting and communication notifying Competent Authorities and healthcare professionals of changes to the risk-benefit balance of products, etc;
• Interaction between safety issues and product defects;
• Responses to requests for information from regulatory authorities;
• Handling of urgent safety restrictions and safety variations;
• Meeting commitments to Competent Authorities in relation to a marketing authorisation;
• Global pharmacovigilance activities applying to all products (signal detection, evaluation, reporting, communication etc.). (Product-specific risk management systems and pharmacovigilance planning are covered in Chapter I.3.);
• Management and use of databases or other recording systems;
• Internal audit of the pharmacovigilance system;
• Training;
• Archiving.

The detailed description of the pharmacovigilance should indicate the processes for which written procedures are available. A list and copies of the global and EEA procedures should be available within two working days on request by the Competent Authorities. Any additional local procedures should be available to respond to specific requests.

d) Databases

A listing of the main databases used for pharmacovigilance purposes (e.g. compilation of safety reports, expedited/electronic reporting, signal detection, sharing and accessing global safety information) and brief functional descriptions of these should be provided including a statement regarding the validation status of the database systems.

A statement should be included regarding the compliance of the systems with the internationally agreed standards for electronic submission of adverse reaction reports as referred to in Part III.

A copy of the registration, of the QPPV, with the EudraVigilance system and identification of the process used for electronic reporting to the Competent Authorities.

There should be an indication of the responsibility for the operation of the databases and their location (with reference to the locations identified under Chapter I.2, Section 2.3.b above).

e) Contractual Arrangements with Other Persons or Organisations Involved in the Fulfilment of Pharmacovigilance Obligations

Links with other organisations such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. The company should identify the major subcontracting arrangements it has for the conduct of its pharmacovigilance activities and the main organisations to which it has subcontracted these (in particular where the role of the QPPV, the electronic reporting of ICSRs, the main databases, signal detection, or the compilation of PSURs is subcontracted).

A brief description of the nature of the agreements the company establishes with co-marketing partners and contractors for pharmacovigilance activities should be provided.
Co-licensing or co-marketing arrangements within the EEA should be identified and the distribution of the major responsibilities between the parties made clear.

Since co-licensing or co-marketing arrangements are mainly product-specific any information on these may be provided in a product-specific addendum, in the applicable Marketing Authorisation Application. Likewise if subcontracting is product-specific this should be indicated in a product specific addendum.

f) Training

Staff should be appropriately trained for performing pharmacovigilance related activities. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel or clinical research staff. Provide a brief description of the training system and indicate where the training records, Curricula Vitae (CVs) and job descriptions are filed.

g) Documentation

Provide a brief description of the locations of the different types of pharmacovigilance source documents, including archiving arrangements. Reference can be made to the organisation charts provided under Chapter I.2, Section 2.3.b.

h) Quality Management System

Provide a brief description of the quality management system, making cross-reference to the elements provided under the above Sections. Particular emphasis should be placed on organisational roles and responsibilities for the activities and documentation, quality control and review, and for ensuring corrective and preventive action.

A brief description of the responsibilities for quality assurance auditing of the pharmacovigilance system, including auditing of sub-contractors, should be provided.

i) Supporting Documentation

The Marketing Authorisation Holder should ensure that the pharmacovigilance system is in place and documented.

An essential feature of a pharmacovigilance system is that it is clearly documented to ensure that the system functions properly, that the roles and responsibilities and required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system.

Documentation supporting the pharmacovigilance system (and its detailed description) may be required during the pre-authorisation period, or post-authorisation, for purposes such as assessment or inspection.

References

- Directive 2001/83/EC as amended
- Volume 2C of the Rules Governing Medicinal Products in the European Union - Regulatory Guidelines: Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
38. What is the CHMP Peer Review? *New Oct 06*

Peer review is a process by which other members of the CHMP review the (Co) Rapporteurs’ scientific evaluation, as well as the validity of the scientific/regulatory conclusions reached. It applies during the initial phase of the assessment of a new Marketing Authorisation Application (MAA).

Peer review is part of a quality assurance system established at CHMP level. That is the review of the (Co) Rapporteurs’ assessment reports for the purpose of improving the quality of the day 120 List of Questions by those CHMP members that are assigned by the Committee as peer reviewers. It is also the particular task of those members assigned as peer reviewers to judge the quality of the assessment reports from (Co) Rapporteurs especially in relation to potential divergencies in scientific assessment made by (Co) Rapporteurs.

A strengthened peer review system that can improve the consistency of scientific assessments is one of the objectives set out in the EMA Road Map


On appointment of (Co) Rapporteurs during a CHMP meeting, the Committee also appoints Peer Reviewers. The Peer Reviewer’s are appointed from amongst the members of the CHMP (including co-opted members) or CHMP alternate members and are identified after having put their names forward on a nomination form (nomination form for Rapporteurs). The Committee also decides on the scope of the Peer Review (modules 3,4, and/or 5) and the number of Peer Reviewers to be assigned to this task.

On Day 112 of the procedure, a Dialogue (e.g. teleconference) is set up between (Co) Rapporteurs, Peer Reviewers and EMA staff to discuss and critically analyse the different objections and concerns raised in the (Co) Rapporteur’s "Overview and draft List of Questions".

Peer Reviewer’s comments are not made available to applicants. Moreover, it is not intended that applicants directly contact Peer Reviewers or other CHMP members in the context of an ongoing CHMP assessment of a MAA.

**References**

- Standard Operating Procedure “Peer Review / Quality assurance of the day 120 CHMP List of Questions and assessment reports (EMEA/SOP/H/3015)
- Notice to Applicants Volume 2A, Chapter 4 Centralised Procedure
39. Where can I find the relevant documents regarding the pharmaceutical legislation? New Mar 07

Information about the hierarchy of the community texts can be found in the Annex I to Chapter 1 of the Notice to Applicants (the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1)

The Treaties on which the European Union and the European Communities are founded can be found on the European Union website:


The "Rules governing medicinal products in the European Union" is published on the European Commission website:

  - Volume 1 – Pharmaceutical legislation, contains most of the relevant Directives, Regulations, Decisions and Communications
  - Volume 2 – Notice to Applicants (mentioned above)
    - Volume 2A - Procedures for marketing authorisation, is organised as follows:
      - Introduction
      - Chapter 1 – Marketing Authorisation
      - Chapter 2 – Mutual Recognition
      - Chapter 3 – Community Referral
      - Chapter 4 – Centralised Procedure
      - Chapter 5 – Variations
      - Chapter 6 – Community Marketing Authorisation
      - Chapter 7 - General Information
    - Volume 2B - Presentation and content of the dossier, provides guidance for the compilation of dossiers for applications for marketing authorisation, and is applicable for the centralised procedure and national procedures, including mutual recognition and decentralised procedures.
    - Volume 2C - Regulatory Guidelines, is related to procedural and regulatory requirements such as renewal procedures, dossier requirements for Type IA/IB variation notifications, summary of product characteristics (SPC), package information and classification for the supply, readability of the label and package leaflet requirements.
  - Volume 3 – Guidelines (scientific guidelines)
  - Volume 4 – Good Manufacturing Practices
  - Volume 9 – Pharmacovigilance
  - Volumes 5, 6, 7 and 8 apply only to veterinary medicinal products
The European Commission website offers the possibility to create a CD-Rom with the content of the "Rules governing medicinal products in the European Union" which can be used off-line with an integrated search engine.

The scientific guidelines related to quality, safety and efficacy have originally been published by the Commission in Volume 3 of “The Rules governing medicinal products in the European Union” (link provided above). Currently, all valid guidelines originally published in Volume 3 and all valid guidelines published by the EMA since 1995, plus their subsequent revisions and supplements can be found at the EMA website. It also includes concept papers, draft guidelines and overview of comments received during the consultation on draft versions:


The EMA also publishes on its website procedural and technical guidance and document templates which are intended to provide technical and procedural advice to applicants for marketing authorisations for medicinal products coming within the scope of the centralised procedure:

- ‘Application Procedures’ folder, in particular:
  - EMA pre-submission guidance for users of the centralised procedure
  - EMA post-authorisation guidance for users of the centralised procedure
  - Product information templates
- ‘General guidance’ folder

References

- "Procedures for marketing authorisation", The Rules governing Medicinal Products in the European Community, Volume 2A, Notice to Applicants, Chapter 1
40. Which European Directorate for the Quality of Medicines and HealthCare (EDQM) activities impact on the centralised procedure? *Rev. Jul 10*

40.1. Introduction

The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a Directorate of the Council of Europe. It was created in 1996.

The mission of the EDQM is to contribute to the basic human right of access to good quality medicines and healthcare, and to promote and protect human and animal health by:

- Establishing and providing official standards for the manufacture and quality control of medicines applicable in all the signatory states of the Convention for the Elaboration of a European Pharmacopoeia.

- Performing the evaluation of applications for Certificates of Suitability of the Monographs of the European Pharmacopoeia (CEPs) and related coordination of related inspections.

- Establishing the list of Standard Terms, which cover pharmaceutical forms, routes of administration and containers used for medicinal products for human and veterinary use.

- Co-ordinating activities performed by Official Medicines Control Laboratories network including annual sampling and testing programme for Centrally Authorised Products (CAPs) within the setting of a network.

- Co-coordinating activities for the elaboration of programmes and policies linking the quality of medicines to the quality and safety of their use, in the fields of pharmaceutical practice and care, risk prevention and management as regards counterfeiting of medicines, and the classification of medicines as regards their supply.

- Publishing and distributing all EDQM publications, including the European Pharmacopoeia.

The EDQM representatives participate as observers to the Agency’s Quality Working Party (QWP) and Biologics Working Party (BWP) meetings, the GMP inspection services group meetings as well as HMPC meetings at the European Medicines Agency.

40.2. European Pharmacopoeia and its use for an application

Pharmacopoeias are collections of standardised specifications, so called monographs, which define the quality reference for pharmaceuticals.


The texts of the European Pharmacopoeia cover active substances, excipients, substances or preparations for pharmaceutical use of chemical, animal, human or herbal origin, homoeopathic preparations and homoeopathic stocks, antibiotics, as well as dosage forms and containers. The texts of the European Pharmacopoeia also apply to biologicals, blood and plasma derivatives, vaccines and radio-pharmaceutical preparations.

QWP and BWP are consulted during the preparation and the revision of monographs.
Additionally, chemical and biological reference material of the European Pharmacopoeia (Chemical Reference Substances and Biological Reference Preparations) to be used where relevant as reference standards for the quality control of medicinal products and their constituents are adopted by the European Pharmacopoeia and centrally supplied from the EDQM.

With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

When test procedures and methods used for manufacturing and controlling the raw materials and active substances or the starting materials, excipients or finished medicinal products are described in the European Pharmacopoeia, the required description to be included in Module 3 shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).

40.3. What is the scope of the Certification Procedure of the EDQM?

The Certification Procedure is intended for substances for which a monograph (general monograph and/or specific monograph) has been adopted by the European Pharmacopoeia Commission. The procedure does not apply for direct gene products (proteins), products obtained from human tissues, vaccines and blood products and preparations.

Under the official procedure described in Resolution AP-CSP (07) 1 (adopted by the Public Health Committee (Partial Agreement), Council of Europe) and Directive 2001/83/EC and 2003/63/EC as amended of the European Union, manufacturers or suppliers of active substances or excipients (organic or inorganic, obtained by synthesis, extraction or fermentation), any product with transmissible spongiform encephalopathy (TSE) risk, or herbal products used in the production or preparation of pharmaceutical products can apply for a certificate of suitability (CEP) concerning:

- The evaluation of the suitability of the monograph for the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph; or
- The evaluation of the reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph; or,
- Both of the above; or,
- The evaluation of the suitability of the monograph for the control of herbal drugs and herbal drugs preparations.

A CEP can be used by the manufacturers of pharmaceutical products in their marketing authorisation applications to demonstrate the compliance of the substance used with the monographs of the European Pharmacopoeia as referred in Directive 2001/83/EC, as amended. As a result, the applicants are exempted of providing the concerned data in the relevant parts of Module 3 of the MAA, as deemed to be replaced by the CEP, except for some parts needed for the assessment of the medicinal product. For instance, in case of sterile substances, the applicant has to resubmit the data on the sterilisation of the substance to National Competent Authorities/Agency. Additionally the manufacturer should provide the applicant with the written assurance that the manufacturing process has not been modified since the granting of the certificate of suitability by the EDQM.

In case a new or updated Certificate of Suitability has been issued, the applicant should submit it through the relevant variation procedure.
This procedure is aimed at facilitating and simplifying exchanges between the partners to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, by issuing a so-called Certificate of Suitability (CEP or CEP for TSE).

CEPs are recognised by all signatory states of the European Pharmacopoeia Convention and by the European Union. There are also other countries which have also chosen to recognise them.

**Note on CEPs for biological substances of non-recombinant origin**

Following EDQM decision to exclude from the scope of the certification procedure the products classified as "other biological substances" by the CMD (h). Applicants are requested to submit full data on the Module 3 for new applications for Marketing Authorisation through the centralised procedure for medicinal products containing these biological substances. Existing certificates of suitability (CEPs) for these substances can be included in the dossiers but should not be used as replacement of the relevant data in the corresponding sections of Module 3.

The reasoning behind this decision is that for biologicals the characterisation and determination of the quality of these products requires not only a combination of physico-chemical and biological testing, but also extensive knowledge over the production process and its control.

The EDQM will therefore not accept any new application for a CEP for these biological substances.

**40.4. List of Standard Terms and its use**

The list of the Standard Terms was drawn up by the European Pharmacopoeia Commission for use in the marketing authorisation application and the product information (SPC, labelling, package leaflet). It has the double purpose of bringing information to the patient/user/prescriber and distinguishing the various presentations of a medicinal product. It should convey essential information on the properties and use of the particular medicinal product presentation.

The Standard Term concerns either the pharmaceutical form, route of administration or container. The pharmaceutical form standard term consists of a combination of the form in which a medicinal product is presented (form of presentation) and the form in which it is administered, including the physical form (form of administration). In special cases (e.g. identical products which may be distinguished only by reference to the container), the information about the immediate container can be included in the pharmaceutical form, e.g. "solution for injection in pre-filled syringes.

Moreover, due to the specificity of a medicinal product the complete characterisation of a pharmaceutical form may be constructed by using a combination of existing Standard Terms, e.g. "powder for solution for injection or infusion".

The route of administration indicates the part of the body on which, through which, or into which the medicinal product is to be administered.

The container is the packaging immediately in contact with the medicinal product.

When the nature of the medicinal product is such that no existing Standard Term or combination of Standard Terms accurately describes the product presentation, a request for a new Standard Term will have to be made to the EDQM. The need for such a request should be identified by the applicant preferably during the EMA pre-submission meeting. The applicant should submit to the EMA the request for a new standard term, together with appropriate supportive documentation i.e. a detailed description of the pharmaceutical form and proposed new term, together with a justification for the new term including why any of the existing terms are not appropriate and a draft SPC. The request will be reviewed by the Quality Review of Documents and the Quality Working Party groups. The EMA will
subsequently forward the applicant’s request and the common EMA position to the EDQM for final decision.

For more information on Standard Terms please refer to: http://www.edqm.eu/site/page_590.php

References

- EMA website (Inspections section)
- EDQM & HealthCare website
- List of Standard terms
41. When do I have to submit an Environmental Risk Assessment (ERA)? New Mar 07

In accordance with Article 8(3) (ca) and (g) of Directive 2001/83/EC, as amended, the evaluation of the potential environmental risks posed by medicinal products should be submitted, their environmental impact should be assessed, and on case-by-case basis, specific arrangements to limit the impact should be considered. In any event this impact should not constitute a criterion for refusal of a marketing authorisation.

The Environmental Risk Assessment (ERA) concerns the risks to the environment arising from the use, storage, and disposal of the medicinal product not to risks arising from the synthesis or manufacture of the product. The assessment of the potential risks is a step-wise, two-phase procedure. The first phase (Phase I) estimates the exposure of the environment to the drug substance by calculating the Predicted Environmental Concentration (PEC). The PEC calculation is restricted to the aquatic compartment (PECSURFACEWATER). If the PECSURFACEWATER value is equal or above 0.01 μg/L, then a Phase II environmental fate and effect analysis should be performed. More details are provided in the guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

An ERA is required for all new marketing authorisation applications (MAA) for a medicinal product through a centralised, mutual recognition, decentralised and national procedure.

The ERA or the justification for not providing it should be provided in Module 1.6, together with a dated signature of the author, information on the author’s educational, training and occupational experience (CV) and a statement of his/her relationship with the applicant.

For paper submissions, if the ERA consists of extensive documentation it should be provided in a separate volume as part of Module 1.

In case of an existing marketing authorisation, the evaluation of the environmental impact should be submitted with the application for type II variations or for extension applications according to Annex II of Commission Regulation (EC) No 1085/2003, if there is an increase in the environmental exposure.

An ERA is not required for renewals or Type IA/IB variations.

References

- Directive 2001/83/EC as amended
- “Guideline on the Environmental Risk Assessment of the medicinal products for human use” (EMEA/CHMP/SWP/4447/00)
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2B, Module 1 CTD
42. How are the ATC codes/INN applied within the Centralised Procedure? *New Mar 07*

### 42.1. ATC codes

The Anatomical Therapeutic Chemical (ATC) classification is a system in which medicinal products are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. The medicinal products are classified in groups at five different levels.

The Applicant for a Marketing Authorisation should apply for an ATC Code using the application form on the WHO website. For information on data to be submitted together with the application form please refer to the WHO website (www.whocc.no).

Within the Centralised Procedure, the ATC code is used in the application form for a Marketing Authorisation (MAA) and in the Summary of Products Characteristics (SPC). The Applicant should bear in mind that, if an ATC code is not yet assigned to the Medicinal Product, no temporary code should be mentioned in the SPC and "Not yet assigned", should appear in section 5.1 of the SPC. The proposed/temporary code should however be mentioned in the application form for a MAA, stating its status in brackets. If an ATC code has been assigned, it should be given in section 5.1 of the SPC without any spaces and without brackets (e.g. N02BE01).

When the Applicant receives the final ATC code from the WHO, if this happens before CHMP opinion, the EMA should be informed as soon as possible in writing with the appropriate proof of the change in status from WHO and the SPC should be amended accordingly. If the ATC code is obtained after opinion, the EMA should be informed and the SPC should be amended accordingly either as a Type IA Variation or at the occasion of another variation after the Commission Decision has been obtained. The same procedure applies, in case of a revision of a final ATC code by the WHO for medicinal products already authorised.

### 42.2. INN

An International Non-proprietary Name (INN) identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognised and is public property. The aim of the INN system has been to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance. To make INNs universally available they are formally placed by WHO in the public domain, hence their designation as "non-proprietary".

The names, which are given the status of an INN are selected by the WHO on the advice of experts from the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The process of INN selection follows three main steps:

- A request/application is made by the manufacturer or inventor, using an 'INN request form' from WHO website (http://www.who.int)
- After a review of the request a proposed INN is selected and published for comments in WHO Drug Information
- After a time period for objection has lapsed, the name will obtain the status of a recommended INN and is published as such by the WHO if no objection has been raised
If applicants for Marketing Authorisation (MA) wish to apply for an INN, it is strongly recommended to liaise with WHO well in advance of MA submission, in order to obtain a recommended INN for their pharmaceutical substance as soon as possible and preferably no later than the CHMP opinion is obtained. Within the Centralised Procedure, the INN is used throughout the MA dossier. If a recommended INN is not available at submission, the proposed INN can be used in the application form and in the Product Information (PI). When the applicant receives the recommended INN from the WHO, if this happens before CHMP opinion, the EMA should be informed as soon as possible in writing with the appropriate proof of the change in status from WHO and the PI should be amended accordingly. If the INN is obtained after opinion, the EMA should be informed and the PI should be amended accordingly either as a Type IA Variation or at the occasion of another variation after the Commission Decision has been obtained.

For certain biologicals, because of their complexity, general rules for INN are not easily formulated. Some of these substances may have descriptive names assigned by other institutions. These names may not be suitable as INNs. Some nomenclature schemes for groups of biological compounds are provided in the WHO guideline.

For vaccines the INN is not applicable and in these cases either the pharmacopoeial or common name of the antigens should be used.

In the absence of INN, the common name or scientific name of the pharmaceutical substance should be used.

References

- WHO Collaborative Centre for Drug Statistic Methodology website
- WHO “Guidelines on the Use of International Non-proprietary Names (INNs) for Pharmaceutical Substances” (WHO/PHARM S/NOM 1570);
- ‘Guideline on Summary of Product Characteristics (October 2005)’ the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C;
- WHO “International Non-proprietary Names (INN) For Biological and Biotechnological Substances”
43. Can I apply for Design Space or Process Analytical Technology (PAT) in my application? *New Mar 07*

The ICH Q8 (Pharmaceutical Development) introduces the notion of Design Space, defined as the multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. The Design Space is proposed by the applicant as part of the MAA and thus is subject to assessment.

Additionally the establishment of a robust Design Space is in line with new approaches on quality which focus on building quality into the medicinal product by design (the so-called QbD concept)

PAT is defined as a **system** for analysing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

PAT is a tool that allows enhanced control of the manufacturing process, can improve process understanding and so facilitates building quality into products and the development of a Design Space.

ICH Q9 (Quality Risk Management) provides an approach and a selection of tools which can be used to manage risks associated with these processes.

The main PAT tools are:
- multivariate data acquisition and analysis;
- modern process analysers or process analytical chemistry tools;

The introduction of the PAT system can bring a number of advantages:
- Possibilities to introduce “real time release”;
- Reduction of cycle times;
- Improved product quality;
- Possibilities for more efficient and effective control of some changes;

The introduction of PAT system can be applied to new or existing authorised medicinal products.

**43.1. When to inform the EMA of the introduction of PAT or Design Space approaches in my application**

- Where Design Space concepts or PAT approaches are used, Marketing Authorisation applicants should indicate this in their **letter of intent**. It is of interest for the Agency and CHMP to be aware of their use so it can be taken into account in the appointment of (Co)-Rapporteurship, as particular expertise from (Co)-Rapporteurs may be needed.
- In addition, when requesting a pre-submission meeting, the applicant should identify it in the relevant question of the **pre-submission request form**.

**43.2. The role of the EMA PAT team**

The EMA Process Analytical Technology Team is a forum for dialogue and understanding between Quality and Biologics Working Parties and Ad-Hoc Group of GMP Inspection Services to prepare a harmonised approach in Europe on assessment of applications and inspections of products/systems/facilities for Process Analytical Technology, including quality by design principles and
manufacturing science in the context of PAT. The PAT team may be consulted through QWP or BWP during the assessment of a centralised marketing authorisation application. Applicants using a PAT approach are encouraged to look at the PAT-related guidance and questions and answers document provided on the EMA website. If there are still questions or issues which are not addressed through those documents, applicants could take the opportunity to contact the EMA PAT team at early stage of pharmaceutical development. It should be noted that the PAT team only provides informal and non-binding advice which does not substitute for Scientific Advice/Protocol Assistance.

43.3. Presentation of PAT-related data in the application

When an application for, or variation to, a marketing authorisation is submitted, supporting documentation should be provided in accordance with CTD requirements (Module 3). In addition, the Expert Report provided in Module 2 (Quality Overall Summary) should include a critique highlighting the positive and negative aspects of the Design Space or PAT approach. For more information see: Reflection Paper - Chemical, pharmaceutical and biological information to be included in dossiers when Process Analytical Technology (PAT) is employed.

Applicants should note that submission of applications that include Design Space or PAT aspects could result in a specific product related inspection at the manufacturing site.

References

- EMEA website, Inspections section
- ICH (International Conference on Harmonization) Q8, Pharmaceutical Development
- ICH Q9, Quality Risk Management
- The Rules Governing Medicinal Products in the European Union, Volume 2A, Chapter 4 on "Centralised Procedure"
- Reflection Paper: Chemical, pharmaceutical and biological information to be included in dossiers when Process Analytical Technology (PAT) is employed (EMEA/INS/277260/2005)
44. Could my application qualify for a conditional marketing authorisation? New July 07

44.1. Criteria and general provisions

For certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally required. In such cases, it is possible for the CHMP to recommend the granting of a marketing authorisation subject to certain specific obligations to be reviewed annually ('conditional marketing authorisation').

This may apply to medicinal products for human use that fall under Article 3(1) and (2) of Regulation (EC) No 726/2004 and belong to one of the following categories:

- medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;
- medicinal products to be used in emergency situations, in response to public threats duly recognised either by the WHO or by the Community in the framework of Decision (EC) No 2119/98;
- medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

A conditional marketing authorisation may 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 the following requirements are met:

- the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/Ec, is positive;
- it is likely that the applicant will be in a position to provide the 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.


The granting of a conditional marketing authorisation should be restricted to situations where only the clinical part of the application dossier is not yet fully complete. Incomplete non-clinical and/or quality data should only be accepted if duly justified and only in the case of a product intended to be used in emergency situations, in response to public health threats.

Conditional marketing authorisations will be **valid for one year**, on a renewable basis. The holder will be required to complete ongoing studies or to conduct new studies with a view to confirming 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 will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and will ensure that additional data on a product are generated, submitted, assessed and acted upon.
44.2. Prior to submission

Applicants for a potential conditional marketing authorisation may request CHMP scientific advice or protocol assistance, as applicable, on whether a specific medicinal product being developed for a specific therapeutic indication falls within one of the categories set out in Article 2 and fulfils the requirement laid down in Article 4(1)(c) ("unmet medical needs will be fulfilled") of Regulation (EC) No 507/2006. In addition, the intention to request a conditional marketing authorisation and any practical or procedural issues with regards to a potential request for conditional marketing authorisation should be addressed at the pre-submission meeting.

44.3. Timing of the submission and documentation to be supplied

At least seven months before submission, applicants should notify the EMA of their intention to submit an application and include a statement on the intention to request a conditional marketing authorisation (in accordance with Article 14(7) of the Regulation).

The applicant may present a request for a conditional marketing authorisation at the time of the application for marketing authorisation.

If the applicant considers that the grounds for a conditional marketing authorisation apply, the applicant should tick the box 1.5.1 of the application form and include its justification in module 1.5.5. Such justification should show that the medicinal product falls within the scope of the conditional marketing authorisation Regulation (Article 2) and that the requirements for conditional marketing authorisation are fulfilled (Article 4), together with the applicant's proposal for completion of ongoing or new studies, or the collection of pharmacovigilance data. The request may cross-refer to specific parts of the application.

Upon receipt of a valid application containing a request for conditional marketing authorisation, the EMA will inform the Commission.

For further guidance on the criteria for conditional marketing authorisations, justifications to be provided and the procedure to be followed, reference is made to the draft guidance document published on the EMA website (Draft Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004).

44.4. CHMP assessment of a request for conditional marketing authorisation

The Rapporteur, Co-Rapporteur and the other CHMP members will assess the justification/data submitted for a Conditional Marketing Authorisation as part of the overall assessment of the benefit/risk of the application. The assessment of the justification will be reflected in the relevant assessment reports and in the final CHMP assessment report.

A conditional marketing authorisation may be requested by the applicant or proposed by the CHMP. Therefore, during the scientific assessment, after having consulted with the applicant, the CHMP may also propose a conditional marketing authorisation. Normally, the proposal and explanatory reasons will be given to the applicant in the day 120 list of questions, or exceptionally later, in the day 150 joint assessment report and day 180 list of outstanding issues. The reasons for proposing a conditional marketing authorisation will also be detailed in the relevant assessment reports and in the CHMP assessment report.
Upon granting of a conditional marketing authorisation, the specific obligations and the timeframe for their completion will be clearly specified in the conditional marketing authorisation (Annex II.C to the Commission Decision), and will be made publicly available by the Agency as part of the EPAR.

44.5. *Information included in the summary of product characteristics and package leaflet*

In order to provide clear information to patients and healthcare professionals on the conditional nature of the authorisations, the summary of product characteristics and package leaflet will mention that a conditional marketing authorisation has been granted subject to certain specific obligations to be reviewed annually.

*Differences between Conditional Marketing Authorisation and Marketing Authorisation under Exceptional Circumstances*

<table>
<thead>
<tr>
<th>Conditional Marketing Authorisation</th>
<th>Marketing Authorisation under Exceptional Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrate positive benefit-risk balance, based on scientific data, pending confirmation</td>
<td>Comprehensive data cannot be provided (specific reasons foreseen in the legislation)</td>
</tr>
<tr>
<td>Authorisation valid for one year, on a renewable basis</td>
<td>Reviewed annually to reassess the risk-benefit balance, in an annual re-assessment procedure</td>
</tr>
<tr>
<td>Once the pending studies are provided, it can become a “normal” marketing authorisation</td>
<td>Will normally not lead to the completion of a full dossier and become a “normal” marketing authorisation</td>
</tr>
</tbody>
</table>

Conditional Marketing Authorisations are distinct from marketing authorisations granted in exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004. In the case of the conditional marketing authorisation, an authorisation is granted before all data are available. The authorisation is not intended, however, to remain conditional indefinitely. Rather, once the missing data are provided, it should be possible to replace it with a marketing authorisation which is not conditional, that is to say, which is not subject to specific obligations. In contrast, it will normally never be possible to assemble a full dossier in respect of a marketing authorisation granted in exceptional circumstances.

**References**

- Regulation (EC) No 726/2004
- Notice To Applicants Volume 2A Chapter 4 (Centralised Procedure)
45. **What is PIM?** *Rev. May 11*

PIM (Product Information Management) is a system for managing and exchanging electronic product information (SmPC, Annex II, labelling and package leaflet) between applicants and competent authorities in the context of marketing authorisation applications in a structured way.

On 28 March 2011, the European Medicines Agency announced the closure of the PIM project.

The PIM project was established to increase the efficiency of the management and exchange of product information (SmPC, package leaflet and labelling) through the structuring of the information and its exchange by electronic means.

The Agency and its partners have demonstrated significant commitment to the PIM project over the years, however the Agency is currently undertaking a review of its business strategy and information-technology system requirements in the context of new legislation and a budgetary review. As a result, it has decided to halt the PIM project.

The Agency remains committed to the concept of structured product information and the efficient exchange of information. It will return to the issue once the review process has been completed.

For further details please consult the PIM Website: [http://pim.ema.europa.eu](http://pim.ema.europa.eu).
46. How can I get support from the EMA regarding emerging therapies and technologies? Role of the Innovation Task Force (ITF) New July 07

In order to provide support to medicines innovation in EU, the EMA has established an internal multidisciplinary group including scientific, regulatory and legal competences, creating a forum for early dialogue with applicants. ITF members are scientific and legal administrators appointed from different sectors of Human Units, Directorate and Inspection Services. To fulfil its task the ITF may consult as appropriate EMA scientific Committees and Working Parties or individual experts.

The scope of the ITF activities encompasses emerging therapies (i.e. gene therapy, cell therapy and engineered tissues), emerging technologies (i.e. new development strategies, new manufacturing approaches) and borderline therapeutics (i.e. combination of pharmaceuticals and devices) for which there is no established EMA scientific, legal and regulatory experience.

Support available to applicants include:

- General queries relating to Emerging Therapies and Technologies
- Briefing meetings aiming to provide an early guidance and information, in liaison when needed with relevant EMA scientific committees or Working Parties. Additionally briefing meetings complement and reinforce existing formal regulatory procedures e.g. scientific advice
- Requests for regulatory advice on the eligibility to EMA procedures e.g. marketing authorisation, scientific advice, consultation on ancillary medicinal and blood and plasma derivatives in medical devices

For more information on Innovation Task Force and on how to request a briefing meeting or Regulatory Advice refer to the EMA Emerging Therapies and Technologies website. The request forms for Briefing Meetings and Regulatory Advice should be submitted electronically to ITFsecretariat@ema.europa.eu taking into account the dates for submission.

References

- EMA Emerging Therapies and Technologies website
- Mandate of the EMEA Innovation Task Force (ITF)
47. Are there special incentives or assistance for applicants which are Small and Medium-Sized Enterprises (SMEs)?

Rev. May 11

Incentives and assistance are available from EMA for SMEs, which focus on reducing financial and administrative entry hurdles for SMEs in pre-marketing authorisation procedures such as scientific advice, the application for marketing authorisation and inspections.

These include:

- Administrative and procedural assistance from the SME Office at the Agency.
- Fee reductions for scientific advice, scientific services and inspections (90% fee reduction).
- Fee exemptions for certain administrative services (excluding parallel distribution).
- 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.
- Assistance with translations of the product information documents submitted in a centralised application for marketing authorisation.
- Waiver of the MedDRA licensing fee when registering with EudraVigilance⁵.

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.

Companies are classified according to their size (micro, small or medium):

- Micro enterprises employ less than 10 persons and have an annual turnover or balance sheet total not exceeding € 2 million;
- Small enterprises have fewer than 50 employees and an annual turnover or balance sheet total of not more than € 10 million;
- Medium enterprises have less than 250 employees and an annual turnover of not more than € 50 million or an annual balance sheet total of not more than € 43 million

and according to their category (autonomous, partner or linked).

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.

Further information on the definition of an SME is available in “The new SME definition - User guide and model declaration”, published by the European Commission.

A declaration of SME status (form available on EMA website on SMEs) should be submitted to the SME Office prior to requesting financial or administrative assistance from the agency.

⁵ The MedDRA fee waiver applies to micro and small enterprises only, not to medium-sized companies.
47.1. 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.

47.2. Fee Reductions/Deferrals

SME applicants wishing to request a fee reduction and/or deferral should address a letter of intent to the SME Office (see below) of the EMA. It should be noted that fee reductions and deferrals can only be considered once the applicant has been assigned SME status by the EMA and are subject to the SME status remaining valid at the time that their application or request is validated by the Agency. Fee reductions and fee deferrals will not be granted retrospectively. Further information on fee reductions/deferrals is available in the document “Fee reductions/deferrals for micro, small and medium-sized enterprises (SMEs)”.

47.3. Translation assistance

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 for translation of product information documents (summary of product characteristics, conditions of the marketing authorisation, label and package leaflet) required for the grant of an EU marketing authorisation. The applicant remains responsible for provision of the Norwegian and Icelandic translations according to the normal timelines and for the maintenance of all translations in the post-authorisation phase.

Due to the timelines required to translate the product information, the Agency will initiate translations through the Centre for Translation (CdT) in Luxembourg prior to CHMP/CVMP opinion (normally around day 180 of the procedure). These translations will then be checked through the national competent authorities in the Member States (see also "QRD product information - Tools used by the EMA to facilitate the streamlining of the European Decision Making process"). To be eligible for translation assistance the applicant’s SME status must be valid at the time the translations are initiated.

Companies wishing to benefit from SME incentives should visit the SME Office section of the EMA website first. This section provides useful information on how to request SME status, and provides a link to useful information sources (e.g. the User Guide for Micro, Small and Medium-sized Enterprises (SMEs) on the administrative and procedural aspects of the provisions, laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs).

For further information or requests please contact:

SME Office
Tel.: +44 (0)20 7418 8575
E-Mail: smeoffice@ema.europa.eu
References

- Commission Regulation (EC) No 2049/2005
- Commission Recommendation 2003/361/EC
- The new SME definition - User guide and model declaration
- ‘Declaration on the qualification of an enterprise as a micro, small or medium-sized enterprise (SME)’ (EMEA/366649/2005)
- User Guide for Micro, small and Medium-sized Enterprises (SMEs) on the administrative and procedural aspects of the provisions, laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs
- Fee reductions/deferrals for micro, small and medium-sized enterprises (SMEs) (EMEA/366526/2005)
48. Do I need to address any paediatric requirements in my application? Rev. Feb 12

Regulation (EC) No 1901/2006 (the ‘Paediatric Regulation’) lays down obligations, rewards and incentives for the development and placing on the market of medicines for use in children. The Paediatric Regulation places some obligations for the applicant when developing a new medicinal product, in order to ensure that medicines to treat children are subject to ethical research of high quality and are appropriately authorised for use in children, and to improve collection of information on the use of medicines in the various subsets of the paediatric population. The paediatric population is defined as the population between birth and the age of 18 years (meaning up to but not including 18-years).

As set out in Article 7 of the Paediatric Regulation, applications concerning a medicinal product “not authorised in the Community” on 26 July 2008 must include one of the following documents/data in order to be considered ‘valid’:

- The results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan (PIP).
  
  This means that the application will have to include the PIP decision but also the results in accordance with the agreed PIP.

- A decision of the EMA on a PIP including the granting of a deferral.
  
  This means that the application will have to include the PIP decision including the deferral granted and if applicable, any completed studies.

- A decision of the EMA granting a product-specific waiver.

- A decision of the EMA granting a class waiver together with the EMA confirmation letter of applicability if requested by the MAH.

Where results of paediatric studies are submitted, applicants should include in the clinical overview a rationale supporting the proposed changes to the Product Information. In particular, if the PIP is completed and the results of all studies are available, the applicant should explicitly discuss why the generated data support or do not support the intended paediatric indication(s) stated in the PIP.

Inclusion of the results of all studies performed in compliance with an agreed Paediatric Investigation Plan requirement in the Product Information is a prerequisite for benefiting from the paediatric reward (Article 36(1) of Regulation (EC) No 1901/2006).

The Global Marketing Authorisation (GMA) concept together with the notion of “same marketing authorisation holder” should be used to determine whether an application concerns a “medicinal product for human use which is authorised or not in the Community”. Further information can be found in the Procedural Advice document on “applications for PIPs, Waivers and Modifications” which is available on the EMA website under ‘Special Topics - Medicines for children’.

However, the following types of application are exempted from the application of the above requirements:

- Generic medicinal products (Art 10(1) of Directive 2001/83/EC)

- Hybrid medicinal products (Art 10(3) of Directive 2001/83/EC)

- Similar biological medicinal products (Art 10(4) of Directive 2001/83/EC)
Medicinal products containing active substance(s) of well-established medicinal use (Art 10a of Directive 2001/83/EC)

Furthermore, when planning submission of their marketing authorisation application, the applicant has to take into account also the need for a "PIP compliance check" to be done.

Such compliance check consists of verifying that the fulfilments of the measures as mentioned in the PIP decision including the timelines for the conduct of the studies or collection of the data are fulfilled. The compliance check procedure is explained in the document [Questions and answers on the procedure of paediatric-investigation-plan compliance verification at the European Medicines Agency](http://www.ema.europa.eu). Applicants are strongly recommended to apply for the compliance check before submission of the marketing authorisation application to not delay the validation phase.

Further details on the format timing and content of PIP or waiver applications as well as on the compliance check can be found in the [Commission guideline](http://www.ema.europa.eu). In addition, deadlines for submission of PIP or Waiver applications and application templates as well as “Procedural Advice documents respectively regarding applications for PIPs, Waivers and Modifications” and “validation of new MAA, Variation/Extension applications and compliance check with an agreed PIP” are available on the EMA website in section “Special Topics - Medicines for children”.

References

- Commission Guideline on “The format and content of applications for agreement or modification of a paediatric investigation plan and request for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies”
- Procedural Advice document related to “Paediatric investigation plans (PIPs), waivers and modifications”
- Questions and answers on the procedure of paediatric investigation plan compliance verification at the European Medicines Agency
- EMA website, section “Special Topics - Medicines for children”
49. Can I submit an application for a Paediatric Use Marketing Authorisation (PUMA)? Rev. Feb 12

49.1. Introduction

According to Article 30 of Regulation (EC) No 1901/2006 ("The Paediatric Regulation"), the paediatric use marketing authorisation (PUMA) is a dedicated marketing authorisation for medicinal products indicated exclusively for use in the paediatric population, or subsets thereof, with, if necessary, an age-appropriate formulation. It has been designed to promote paediatric development of already authorised products which are no longer covered by a supplementary protection certificate (SPC) or a patent qualifying for a SPC.

49.2. Eligibility to the centralised procedure

A PUMA application remaining outside the mandatory scope of Article 3(2)(a) of Regulation (EC) No 726/2004 has an ‘automatic access’ to the centralised procedure (Article 31 of the Paediatric Regulation) if the applicant chooses this route of registration.

Before a PUMA application is submitted for the centralised procedure, an eligibility confirmation must be requested by the applicant by submitting a Pre-submission request form (Eligibility) to CPeligibility@ema.europa.eu. For more information on the eligibility request, please refer to the European Medicines Agency pre-submission procedural advice for users of the centralised procedure.

49.3. Content of a PUMA application

The same range of supporting documentation should be provided as for other marketing authorisation applications through a combination of new data and/or existing data. Depending on the legal basis of the application, submission of literature and/or cross-reference to the dossier of another medicinal product may be used. In particular, cross-reference to the data contained in the dossier of an authorised medicinal product is possible if the relevant data protection has expired. For further information, please refer to the pre-submission Procedural advice for users of the centralised procedure for generic/hybrid applications.

A PUMA application has to contain the results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan (PIP). The corresponding EMA decision as well as the PDCO opinion on compliance or the applicant’s compliance report must be provided in Module 1.10 (please refer to the pre-submission procedural advice for users of the centralised procedure – Q. 48. Do I need to address any paediatric requirements in my application?).

Further details on the submission of a PIP are available on the EMA website in section “Special topics – Medicines for children”.

As per Article 34 of the Paediatric Regulation, applicants are required to detail in a risk-management plan submitted with their PUMA application the measures to ensure the follow-up of efficacy and of possible adverse reactions to the paediatric use of the medicinal product.

49.4. Incentives for PUMA

PUMA applications have an ‘automatic access’ to the centralised procedure (Article 31 of the Paediatric Regulation).
PUMA benefits from the 8+2 year period of data and market protection (Article 38 of the Paediatric Regulation).

A medicinal product for which a PUMA has been granted may retain the name of another medicinal product containing the same active substance for which the same holder has been granted an authorisation for use in adults (Article 30(4) of the Paediatric Regulation).

PUMA applications submitted under the centralised procedure benefit from a partial exemption from the payment of fees laid down in the Regulation (EC) No 297/95. This partial exemption applies to the submission of the PUMA application and some of the post-authorisation activities for 1 year as of the date of granting of the PUMA. Please refer to the Regulation (EC) No 297/95 and the Explanatory note on fees payable to the European Medicines Agency.

Further information on PUMA and paediatric requirements related to a PUMA application are available on the EMA website in section “Special topics – Medicines for children”.

References

- Articles 2 and 30 of Regulation (EC) No 1901/2006
- Procedural Advice document related to Paediatric investigation plans (PIPs), waivers and modifications
- Procedural advice for validation of new marketing authorisation application, extension/variation application and compliance check with an agreed PIP
- Commission Guideline on “The format and content of applications for agreement or modification of a paediatric investigation plan and request for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies”
- Explanatory note on fees payable to the European Medicines Agency.
- EMA website, section “Special Topics – Medicines for children – PUMA”
50. What is the Community Plasma Master File certification system? *New Mar 09*


The PMF is a compilation of all required scientific data on the quality and safety of human plasma relevant to medicines, medical devices and investigational products which use human plasma in their manufacture. These data cover all aspects of the use of plasma, from collection to plasma pool.

The PMF is a stand-alone document which is separate from the application dossier for a Marketing Authorisation for the medicinal product concerned.

The PMF certification is an optional procedure that follows a similar system to the Marketing Authorisation evaluation procedure (the ‘centralised procedure’) at the EMA.

Following the satisfactory outcome of an evaluation, the EMA issues a PMF Certificate of compliance with Community legislation, which is valid throughout the European Community.

A Marketing Authorisation (MA) or a Marketing Authorisation Application (MAA) may refer to one or more PMFs or respective certificates. Once the Applicant chooses to use the Community PMF certification system all variations to the corresponding plasma for all the linked MAs will have to be submitted through the same certification system.

The competent authority that will grant or has granted a MA shall take into account the certification, re-certification or variation of the PMF on the concerned medicinal product(s).

For medicinal products that have been evaluated by the EMA through the Centralised Procedure and authorised by the European Commission, the public can find a summary of the quality and safety of the plasma in the product’s European Public Assessment Report (EPAR).

For detailed information related to the Plasma Master File certification, please consult the Plasma Master File webpage.
51. What is the Community Vaccine Antigen Master File certification system? New Mar 09

The concept of “Vaccine Antigen Master File” (VAMF) was introduced with the Commission Directive 2003/63/EC in June 2003 amending Directive 2001/83/EC.

A VAMF contains all relevant information of biological, pharmaceutical and chemical nature for one given vaccine antigen, which is common to several vaccines from the same marketing authorisation (MA) applicant or marketing authorisation holder (MAH).

The use of the VAMF certification system is optional and the VAMF is a stand-alone part of the marketing authorisation application dossier (MAA) for a vaccine.

The VAMF certification consists of a centralised assessment of the VAMF application dossier submitted by the MA Applicant/MAH, which results in a certificate of compliance to Community legislation, issued by the EMA. This certificate is valid throughout the European Community.

A Marketing Authorisation (MA) or a Marketing Authorisation Application (MAA) may contain one or more VAMF certificates and respective VAMF data. If, when submitting a new MAA, the MA Applicant decides to opt for vaccine antigen master files, the VAMFs must be submitted for all vaccine antigens in the respective MAA.

As a rule, one VAMF should be submitted per vaccine antigen. In the case of a group of antigens aimed at preventing a single infectious disease a VAMF should be submitted for each antigen in the group.

A VAMF application can only be submitted to the EMA for antigens that form part of at least one MA or MAA, which has been, or will be evaluated via a Community procedure (Mutual Recognition (MR), Decentralised Procedure (DCP) or Centralised Procedure (CP)).

Once the Applicant chooses to use the Community VAMF certification system, all variations to the corresponding MAs will have to be submitted through the same certification system.

The competent authority that will grant or has granted a MA shall take into account the certification, re-certification or variation of the VAMF on the concerned medicinal product(s).

For detailed information related to the Vaccine Antigen Master File certification, please consult the Vaccine Antigen Master File webpage.
52. What is Eudravigilance? How will it apply to my Marketing Authorisation? New Mar 09

The reporting of suspected serious adverse reactions is defined in the Community legislation. This process involves healthcare professionals, the EMA, national Competent Authorities (NCAs) and MAHs and is applicable to all medicinal products authorised in the EEA. The reporting includes suspected serious adverse reactions occurring both within and outside the EEA.

With effect from 20th November 2005, the electronic reporting of suspected serious adverse reactions, save in exceptional circumstances, has become mandatory.

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

EudraVigilance supports:

- Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between the European Medicines Agency (EMA), national Competent Authorities, marketing authorisation holders, and sponsors of clinical trials in the EEA.
- Early detection of possible safety signals associated with medicinal products for human use.
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions.

EudraVigilance is also one of the main pillars of the European Risk Management Strategy and facilitates the process of risk management at several levels including risk detection, risk assessment, risk minimisation and risk communication.

Practical and detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use can be found via this link: http://ec.europa.eu/health/documents/eudralex/index_en.htm.

A marketing authorisation holder should prepare for the electronic reporting of suspected adverse reactions to the EMA as follows:

- Provide the EMA with a written plan on how the company is going to implement the electronic transmission of ICSRs to the Agency and national Competent Authorities in the EEA. Please address your plan to the attention of Ms Sabine Brosch (sabine.brosch@ema.europa.eu).
- Follow the detailed instructions outlined in “10 Steps to Implementation”, where the procedure for the initiation of the electronic transmission of ICSRs is described.
- Register with EudraVigilance. Please note that a MedDRA license is required for electronic reporting of ICSRs. For further information on the EudraVigilance MedDRA licensing Policy, please refer to MedDRA licensing Policy in this website.
- Provide the required information for the EudraVigilance Medicinal Product Dictionary.

For detailed information related to EudraVigilance, please consult the EudraVigilance webpage http://eudravigilance.ema.europa.eu/highres.htm or contact eudravigilance@ema.europa.eu.
53. **What do I have to consider regarding the MA of my centrally authorised medicinal product in Norway, Iceland and Liechtenstein?** *Rev. Jan 13*

Norway, Iceland and Liechtenstein have, through the European Economic Area agreement, adopted the complete Community acquis on medicinal products, and are consequently parties to the centralised procedure. However, legally binding acts from the Community, e.g. Commission Decisions, do not directly confer rights and obligations in Norway and Iceland, but first have to be transposed into legally binding acts in these states, except for Liechtenstein, where they are directly applicable, according to national legislation. According to Decision No. 74/1999 of the EEA Joint Committee, when decisions on approval of medicinal products are taken by the Community, Norway, Iceland and Liechtenstein will take corresponding decisions on the basis of the relevant acts.

The EEA Joint Committee Decision No. 74/1999 on the extension of the Marketing Authorisation Procedures for medicinal products to Norway, Iceland and Liechtenstein entered into force on 1 January 2000.

**Specificities for Norway and Iceland**

Within the Linguistic Review Process of Product Information in the Centralised Procedure – Human EMEA/5542/02, applicants are required to electronically provide the EMA translations of the agreed product information in all EU languages, including Icelandic and Norwegian, after the adoption of the CHMP EN opinion for review. The Norwegian and Icelandic texts will be checked by the respective Agencies.

Once a Commission Decision is issued, the European Commission publishes the Commission Decision with Annexes in all EU languages on its website. Subsequently, the Norwegian and Icelandic PI texts are published on the EMA’s website.

**Norway**

The Norwegian authorities will grant a corresponding national authorisation within 30 days following the date of the Commission Decision after receiving final product information in Norwegian from the MAH. Provision of specimens and mock-ups to Norway is not required.

For information regarding the handling of variations in Norway for centralised medicinal products please consult the Norwegian Medicines Agency website:

http://www.legemiddelverket.no/English/regulatory-affairs/variations/Sider/Centralised-procedure---variations.aspx

Please contact:

Norwegian Medicines Agency
P.O. Box 63, Kalbakken
N-0901 Oslo
Norway
Tel.: +47 22 89 77 00
Fax: +47 22 89 77 99
E-mail: pi@noma.no.
**Iceland**

The Icelandic authorities will grant a corresponding national authorisation within 30 days following the date of the Commission Decision. Provision of specimens to Iceland is not required.

For information regarding the handling of variations in Iceland for centralised medicinal products please consult the Icelandic Medicines Agency website: http://www.imca.is/IMCA/News/nr/1120.

At least one month before marketing, the applicant has to provide the Icelandic authorities directly with mock-ups for all product presentations that are intended to be marketed in Iceland. Mock-ups should be sent by e-mail to mockups@ima.is. See also http://www.imca.is/imca/news/nr/1263

**References**

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 1 - Marketing Authorisation, Chapter 4 – Centralised Procedure, Chapter 6 – Procedures for MA , Chapter 7 – General Information
- Decision of the EEA Joint Committee No 74/1999
- The linguistic review process of product information in the centralised procedure – human
- The Revised Checking Process of Mock-Ups and Specimens of outer/immediate labelling and package leaflets of human medicinal products in the Centralised Procedure
54. Is my product subject to batch release by an Official Medicines Control Laboratory and if so, what should I consider? *New May 10*

Live vaccines, immunological medicinal products and medicinal products derived from human blood or plasma may be subject to batch release by a Member State laboratory or Official Medicines Control Laboratory (OMCL).

The OMCL supports the regulatory authorities and the national Inspection Services in ensuring the quality of medicinal products on the market by independent re-testing based on the legal requirements.

The European Medicines Agency and EDQM (European Directorate for the Quality of Medicines and Health Care) on behalf of the OCABR (Official Control Authority Batch Release) Network have been working on a common strategy with the aim of ensuring that the technical expertise of the OMCLs is taken into account in the development and assessment of testing methodologies for vaccines and plasma derived blood products that may be subject to OMCL batch release.

The input of the OMCLs is particularly important for products that include a novel quality control method or where there are known difficulties with a particular assay.

It is therefore strongly recommended for an applicant to enter into early collaboration with the OMCL. This collaboration should ideally begin at least one year before submission of the Marketing Authorisation Application, in order to allow for exchange of information between the OMCL and the Applicant which should be considered in the development of testing methodology.

For this purpose, Applicants are advised to consult the following site on the EDQM webpage for a contact list of OMCLs in the EU carrying out OCABR.

The information on the chosen OMCL by the Applicant will be recorded in the EMA pre-submission meeting and be passed onto the CHMP.

The European Medicines Agency will inform EDQM of any upcoming start of an authorisation procedure with official batch release.

**References**

- Directive 2001/83/EC, Article 114
- Guideline on submission of marketing authorisation application for Pandemic Influenza vaccines through the centralised procedure (EMEA/CPWP/VEG/4986/03)