6 December 2018
EMA/821278/2015
Human Medicines Evaluation Division

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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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.

Table of Content

1. Types of applications and applicants

1.1. Where can I find the relevant documents regarding the pharmaceutical legislation? Rev. Mar 2013

The **Treaties** on which the European Union and the European Communities are founded can be found on the European Union website: http://eur-lex.europa.eu/en/treaties/index.htm

To exercise the Union's competences, the institutions may adopt **regulations, directives, decisions, recommendations and opinions**.

Information about the hierarchy of the European Union 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 "**Rules governing medicinal products in the European Union**" concerning medicinal products for human use is published on the European Commission website:

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm
  - 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 5 – Variations

    Chapter 6 – Community Marketing Authorisation

    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 e.g. renewal procedures, variation procedures, summary of product characteristics (SPC), package information and classification for the supply, readability of the label and package leaflet requirements.
  - Volume 3 – Scientific guidelines
  - Volume 4 – Good Manufacturing Practices
  - Volume 9 – Pharmacovigilance

    With the application of the new pharmacovigilance legislation as from July 2012 Volume 9A is replaced by the good pharmacovigilance practice guidelines (GVP)

released by the European Medicines Agency. However, until the availability of the respective GVP modules Volume 9A remains the reference.

- The GVP modules refer to the Commission implementing regulation No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities. This is a legally binding act published by the European Commission in June 2012 which provides details on the operational aspects for the new legislation: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF Volumes 5, 6, 7 and 8 apply only to veterinary medicinal products
- Volume 10 – Clinical trials

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 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:

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb&jsenabled=true

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, in particular:

- EMA pre-submission guidance for users of the centralised procedure
- EMA Procedural advice for users of the centralised procedure for generic/hybrid applications
- EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications
- EMA post-authorisation guidance for users of the centralised procedure
- Product information templates

References

- "Procedures for marketing authorisation", The Rules governing Medicinal Products in the European Community, Volume 2A, Notice to Applicants, Chapter 1
- Commission implementing regulation No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council
- Good pharmacovigilance practice guidelines (GVP)

1.2. How can I tell if I am duly established in the EEA as an applicant? Rev. Feb 2012

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 will 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 Agency in order for an application to be validated (e.g. in the United Kingdom, a certificate of incorporation issued by the Registrar of Companies, and in France, an extrait du registre du commerce et des sociétés). This proof of establishment should be included in annex 5.3 of the application form.

It should be emphasised that while the MAH may delegate certain activities to third parties, the MAH remains responsible for assuring all the obligations imposed on MAHs 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

1.3. What special support is available for SMEs? Rev. Feb 2017

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 EudraVigilance[1].

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.

1.3.1. 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.

1.3.2. 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. For more information on fees, please refer to Fees payable to the European Medicines Agency.

1.3.3. 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

[1] The MedDRA fee waiver applies to micro and small enterprises only, not to medium-sized companies.

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 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
- Fees payable to the European Medicines Agency

1.4. How can I get support regarding emerging therapies and technologies? Jul 2007

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)
- Innovative drug development approaches – Final report from the EMEA/CHMP-think-tank group on innovative drug development (EMEA/127318/2007)

1.5. What do I have to consider regarding my centrally authorised medicinal product in Norway, Iceland and Liechtenstein? Rev. Mar 2017

Norway, Iceland and Liechtenstein have, through the European Economic Area agreement, adopted the complete Union acquis on medicinal products, and are consequently parties to the centralised procedure. However, legally binding acts from the Union, e.g. Commission Decisions, do not directly confer rights and obligations in Norway, Iceland and Liechtenstein, but first have to be transposed into legally binding acts in these states. 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 6 – Procedures for MA
- 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

1.6. What will be the legal basis for my application? Rev. Feb 2008

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.

1.6.1. 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.

1.6.1.1. '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.

1.6.1.2. 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 fulfil 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 welfare[2] and ethical considerations[3] 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);
- Request for granting of a conditional marketing authorisation in accordance with Article 14(7) of Regulation (EC) No 276/2004 and Regulation (EC) No 507/2006.

1.6.2. Article 10 - Generic, hybrid or similar biological applications

1.6.2.1. 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.

2 Council Directive on Animal Welfare 86/609/EEC and Council Decision on the European Convention of the Protection of Vertebrae Animals

3 Declaration of Helsinki

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.

1.6.2.2. 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.

1.6.2.3. 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.

1.6.3. 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.

1.6.4. 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.

1.6.5. 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 Q&A "If I intend to submit multiple applications for a specific medicinal product?", 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
- Annex I to Directive 2001/83/EC, as amended by Directive 2003/63/EC
- 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)

1.7. What is an application for a paediatric use marketing authorisation (PUMA)? Rev. Dec 2015

1.7.1. 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.

1.7.2. 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.

1.7.3. 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&A "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.

1.7.4. 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.

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”
- Fees payable to the European Medicines Agency.
- EMA website, section “Special Topics - Medicines for children - PUMA”

1.8. What is the period of protection for my medicinal product? Jul 2006

1.8.1. Data exclusivity and market protection 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?”).

1.8.1.1. 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.

1.8.1.2. 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 beneficiate from an independent period of protection.

1.8.1.3. 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.

1.8.2. 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.

1.8.3. 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.

1.8.4. 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

1.9. Could my application qualify for a conditional marketing authorisation? Rev. Mar 2016

1.9.1. 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 at least 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 No. 1082/2013/EU (repealing 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 of 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 legal basis for a conditional marketing authorisation is Article 14 (7) of Regulation (EC) No 726/2004. The provisions for the granting of such an authorisation are laid down in Regulation (EC) No 507/2006.

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 (specific obligations) 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 and will ensure that additional data on a product are generated, submitted, assessed and acted upon.

1.9.2. Prior to submission

Applicants for a potential conditional marketing authorisation are strongly encouraged to engage in early dialogue with EMA and other stakeholders (e.g. health technology assessment bodies) and discuss their development plan. For instance, the applicants 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. It is recommended to discuss in advance the development plan and design of the intended studies (both the pre-authorisation studies and studies to be proposed as specific obligations for collection of remaining data after authorisation).

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. The applicants are also encouraged to consider requesting accelerated assessment for products deemed suitable for a conditional marketing authorisation (i.e. inter alia deemed to fulfil an unmet medical need).

1.9.3. Timing of the submission and documentation to be supplied

Six to 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 indicate that in the application form and include the corresponding justification in the section 1.5.5 of Module 1 if the dossier. Such justification should show that the medicinal product falls within the scope of Regulation (EC) No 507/2006 (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 also inform the European Commission.

For further guidance on the criteria for conditional marketing authorisations, justifications to be provided and the procedure to be followed please refer to the CHMP 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.

1.9.4. 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 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 together with the marketing authorisation application, or proposed by the CHMP (after having consulted with the applicant) during the assessment of the application. Nevertheless, in order to discuss properly the suitability of a conditional marketing authorisation and proposed specific obligations, and in order not to delay assessment, the discussions on possible conditional marketing authorisation should start as early as possible. Therefore, the applicants are strongly encouraged to engage in an early dialogue, plan conditional marketing authorisations timely and make the requests in the initial submission of application, when appropriate.

Upon granting of a conditional marketing authorisation, the specific obligations and the timeframe for their completion will be clearly specified in the conditions to the marketing authorisation (Annex II.C to the Commission Decision), and will be made publicly available by the Agency as part of the EPAR.

1.9.5. 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.

1.9.6. Differences between conditional marketing authorisation and marketing authorisation under exceptional circumstances Mar 2016

Conditional Marketing Authorisations are distinct from marketing authorisations granted under 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. Instead, once the missing data are provided, it should be possible to replace it with a standard marketing authorisation, 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 under exceptional circumstances.

Conditional Marketing Authorisation	Marketing Authorisation under Exceptional Circumstances
Authorisation before the availability of comprehensive data in order to address unmet medical needs. Comprehensive data are still being generated post authorisation in agreed timelines.	Authorisation when comprehensive data on the efficacy and safety cannot be obtained, but it is still appropriate to grant the authorisation due to exceptional circumstances.
Medicinal products without comprehensive data belonging to at least one of the following categories:	Medicinal products without comprehensive data on the efficacy and safety under normal conditions of use, because:

• Seriously debilitating diseases or life-threatening diseases, • Emergency situations, • Orphan medicinal products • and fulfilling all of the following criteria: • Positive risk-benefit balance • Applicant likely to be able to provide comprehensive data • Fulfilment of unmet medical need. • Benefits of immediate availability outweigh the risks that additional data are still required	• Indications 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
Authorisation valid for one year, to be renewed annually based on reconfirmation of the benefit-risk balance	Authorisation initially valid for 5 years (renewable), but the status of fulfilment of the specific obligations and the impact of the specific obligations' data on the benefit / risk balance is to be reassessed annually
Once the comprehensive data are provided, it can become a "standard" marketing authorisation	Will normally not lead to the completion of a full dossier and become a "standard" marketing authorisation

References

- Regulation (EC) No 726/2004
- Regulation (EC) No 507/2006
- CHMP 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
- "Can a new indication based on less comprehensive data be added to an already authorised medicinal product?" in the questions and answer on Type II variations of the EMA post-authorisation procedural advice for users of the centralised procedure

1.10. Is my medicinal product eligible for approval under exceptional circumstances? Jan 2006

1.10.1. 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.

1.10.2. 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 pre-submission meeting.

1.10.3. 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”.

1.10.4. 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.

1.10.5. Differences between Exceptional circumstances and conditional marketing authorisation

Conditional Marketing Authorisation	Marketing Authorisation under Exceptional Circumstances
Demonstrate positive benefit-risk balance, based on scientific data, pending confirmation	Comprehensive data cannot be provided (specific reasons foreseen in the legislation)
Authorisation valid for one year, on a renewable basis	Reviewed annually to reassess the risk-benefit balance, in an annual re-assessment procedure-
Once the pending studies are provided, it can become a “normal” marketing authorisation	Will normally not lead to the completion of a full dossier and become a “normal” marketing authorisation

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.

1.10.6. 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
- Annex I, Part II of Directive 2001/83/EC, as amended
- 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)

- "Can a new indication based on less comprehensive data be added to an already authorised medicinal product?" in the questions and answer on Type II variations of the EMA post-authorisation procedural advice for users of the centralised procedure

1.11. What should I do if I want to submit multiple/duplicate applications for the same medicinal product? Rev. Dec 2018

The EMA is regularly approached by applicants wishing to obtain, either simultaneously or successively, more than one Marketing Authorisation for a specific medicinal product (i.e. with the same qualitative and quantitative composition in active substance and the same pharmaceutical form) 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/duplicate 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
DG Health and Consumers
Unit B5: Medicines: policy, authorisation and monitoring
B232 06/094
B-1049 Brussels
Belgium

Alternatively it can be sent to the following e-mail address:
SANTE-PHARMACEUTICALS-B5@ec.europa.eu.

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.

Where the need for a separate marketing authorisation application follows from Article 7(3) of Regulation (EC) No 141/2000, which provides that orphan and non-orphan indications cannot be covered by the same marketing authorisation, no prior authorisation by the Commission under Article 82 (1) of Regulation (EC) 726/2004 is required for the submission of such application. This includes cases where (i) sponsors of an orphan medicinal product apply for a non-orphan indication of the same product and (ii) holders of a marketing authorisation of a non-orphan medicinal product have received, for the same product, an orphan designation for a new orphan indication.

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 Q&A "How and when should the eligibility request be sent to the EMA?". 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[4]

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
- Regulation (EC) No 141/2000
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2A, Chapter 1

4 Later submission of the dossier is not recommended due to difficulties with its alignment with the original application.

- EC communication on ‘Handling of Duplicate Marketing Authorisation Applications’
- EMA procedural timetables

1.12. In which exceptional cases would combination packs be acceptable in the centralised procedure, and where can I submit my request for consideration? NEW Aug 2017

Combination packs are to be understood as a combination of active substances, where the active substances are included in separate pharmaceutical forms which are included in the same package and are covered by a single marketing authorisation. Fixed combinations and combinations packs are not synonymous concepts.

As specified by the Notice to Applicants Chapter 1 Volume 2A – Section 5.5, these cases would be very exceptional and strictly related to public health, and should not be for convenience or commercial purposes. They will be considered on a case-by-case basis.

The applicant will have to justify that the marketing of such a combination of active substances in the same package is needed for indispensable public health reasons.

Applicants are advised to consult the EMA on the acceptability of the proposed combination pack at an early stage of the development in view of their acceptability only in very exceptional circumstances.

In any case, the acceptability of the combination pack should be confirmed before the request for eligibility to the centralised procedure and the submission of the Marketing Authorisation Application.

Combination pack requests can be submitted to the EMA using the following email address: CombinationPacks@ema.europa.eu. The EMA will endeavour to issue an outcome on the acceptability of the combination pack within 60 days.

When the acceptability of the combination pack is accompanied by additional questions on the overall development of the product, these can be submitted together with the Scientific Advice questions. The EMA will endeavour to provide a reply on the acceptability of the combination pack within the Scientific Advice outcome letter. For scientific advice requests, please consult the scientific advice and protocol assistance section on the EMA webpage.

References

- Notice to Applicants, Volume 2A, Chapter 1 – Section 5.5

2. Steps prior to submitting the application

2.1. Is my medicinal product eligible for evaluation under the centralised procedure? Rev. Feb 2010

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.

2.1.1. 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.

2.1.1.1. 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.

2.1.1.2. 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.

2.1.1.3. 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).

2.1.1.4. 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.

2.1.2. 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)

2.1.2.1. 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).

2.1.2.2. 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.

2.1.2.3. 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 1901/2006
- 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"

2.2. How and when should the eligibility request be sent to EMA? Rev. Feb 2010

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 Q&A "Is my medicinal product eligible for evaluation under the Centralised Procedure?").

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
- Regulation (EC) No 1901/2006
- "Scientific Aspects and Working definitions for the mandatory scope of the centralised procedure" (EMEA/CHMP/121944/2007)

2.3. What are the dates for submission of eligibility requests?

Please see the submission dates in the Q&A "What are the dates for submission of eligibility requests?" on the EMA website.

2.4. What is the procedure for appointment of Rapporteurs/Co-Rapporteurs and their assessment teams? Rev. Mar 2013

2.4.1. General principles

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 Committee for Medicinal Products for Human Use (CHMP) and alternate members. In addition for activities covering all aspects of the risk management of the use of human medicinal products a Rapporteur and if relevant a Co-Rapporteur shall be appointed from amongst the members of the Pharmacovigilance Risk Assessment Committee (PRAC) and alternate members. For Advanced Therapy Medicinal Products (ATMP) 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 two CHMP Co-ordinators will be appointed (one supporting the CAT Rapporteur assessment team and another supporting the CAT Co-Rapporteur assessment team).

The appointment of any 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.

2.4.1.1. Requesting the appointment of CHMP/PRAC/CAT Rapporteurs/Co-Rapporteurs and their assessment teams

Applicants shall request the appointment of CHMP/PRAC/CAT Rapporteurs/Co-Rapporteurs (in the following only described as (Co-) Rapporteurs) by sending a completed Pre-submission request form (selecting the indent "Intent to submit MA") to pa-bus@ema.europa.eu. The pre-submission request form can be accompanied by a cover letter. This notification is also called the "letter of intent".

We advise applicants to notify the EMA of their intent to submit and request assignment of (Co-) Rapporteurs 7 months prior to the intended submission date. Although applicants may submit the letter of intent earlier than 7 months prior to the intended submission date the (Co-) Rapporteurs appointment procedure will not be initiated prior to that date.

Intended MAA submission dates must be as realistic and accurate as possible as such information is crucial to the EMA and to the future appointed (Co-) Rapporteurs and their assessment teams for planning purposes.

The (Co-) Rapporteurs appointment procedure takes one month and applicants are notified about the outcome. It is the responsibility of the applicant to liaise with the EMA in due course to confirm its intended submission date and request (Co-) Rapporteurs appointment.

For submission deadlines for letters of intent see Q&A "What are the submission dates for Rapporteur appointment requests?".

Please be aware that separate pre-submission forms have to be submitted for requesting eligibility and the appointment of (Co-) Rapporteurs (selecting the corresponding indents on the first page of the pre-submission form), even if an applicant submits both requests in parallel.

Please note that the Applicant's proposals/preferences are not considered for the appointment of (Co-) Rapporteurs.

2.4.2. Appointment of (Co-) Rapporteurs and their assessment teams for different application types / procedures

2.4.2.1. Full applications

In the pre-authorisation phase of a full Marketing Authorisation Application (MAA), two Rapporteurs (i.e. a Rapporteur and a Co-Rapporteur) are appointed. The two Rapporteurs are usually members/alternate members of the CHMP, except for ATMPs, where the Rapporteur and Co-Rapporteur are appointed amongst the CAT members/alternate members with two Co-ordinators appointed from the CHMP.

Furthermore a PRAC Rapporteur and a Co-Rapporteur will be appointed.

2.4.2.2. Generic/hybrid medicinal products

Due to the particularities of generic/hybrid applications (e.g. legal basis, data requirements), the following principles are considered for the appointment of CHMP/PRAC Rapporteurs/Co-Rapporteurs and their assessment teams:

- A CHMP Rapporteur is appointed for the scientific evaluation of a generic/hybrid medicinal product. For the scientific evaluation of a generic application there is usually no Co-Rapporteur required.
- 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 a generic/hybrid medicinal product, a CHMP pharmacovigilance (PhV) Rapporteur is appointed. The CHMP PhV Rapporteur is the same CHMP member/alternate as the CHMP Rapporteur of the reference medicinal product as applicable.
- Furthermore a PRAC Rapporteur will be appointed.

2.4.2.3. Similar biological medicinal products

For the scientific evaluation of a similar biological medicinal product CHMP and PRAC Rapporteurs and Co-Rapporteurs will be appointed.

2.4.2.4. Non-prescription medicinal products

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 CHMP/PRAC Rapporteurs/Co-Rapporteurs and their assessment teams:

- For the scientific evaluation of a non-prescription medicinal product CHMP and PRAC Rapporteurs and Co-Rapporteurs shall be appointed.
  - In the pre-authorisation phase the CHMP/PRAC Rapporteurs and Co-Rapporteurs shall be involved.
  - In the post-authorisation phase, when a change in legal status is foreseen (e.g. switch from prescription to non-prescription), a CHMP peer reviewer shall be appointed to work with the existing CHMP/PRAC Rapporteurs and Co-Rapporteurs already in place for the given medicinal product.

2.4.2.5. Re-examination of a CHMP opinion

In cases of re-examination of a CHMP opinion a CHMP/CAT Rapporteur and a Co-Rapporteur shall be appointed. In case a PRAC Rapporteur is deemed necessary, he/she will be appointed. For CHMP opinions where the CHMP/CAT Co-Rapporteur was not involved in the initial evaluation, no re-examination Co-Rapporteur needs to be appointed. A different CHMP/CAT Rapporteur and, where applicable, a different CHMP/CAT 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.

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.

2.4.2.6. Ancillary medicinal substances or ancillary human blood derivatives incorporated in medical devices

The notified body is requested to submit the letter of intent at least 6 months before the expected date of submission.

A CHMP Rapporteur and Co-Rapporteur, if appropriate, will be appointed.

References

- CHMP Rules of Procedure (EMEA/CHMP/89672/2009)
- PRAC Rules of Procedure (EMA/PRAC/567515/2012)
- CAT Rules of Procedure (EMEA/CAT/454446/2008)
- Procedural Advice on the CHMP/CAT Rapporteur/Co-Rapporteur Appointment Principles, Objective Criteria and Methodology in Accordance with Article 62(1) of Regulation (EC) No. 726/2004 (EMA/151751/2010)
- Regulation (EC) No 726/2004

2.5. What are the submission dates for Rapporteur appointment requests?

Please see the submission dates in the Q&A “What are the submission dates for Rapporteur appointment requests?” on the EMA website.

2.6. When should I submit my marketing authorisation application? Rev. Dec 2017

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, Committee 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, (Co-)Rapporteurs 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 and (Co-)Rapporteurs of a 'real' submission date. The HMA-EMA ‘Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines’ is to be observed.

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 (Co-)Rapporteurs 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 re-confirm the submission date 2-3 months prior to the initially communicated intended submission date, by sending an email to the appointed EMA procedure manager. Otherwise the applicant should notify the European Medicines Agency and (Co-)Rapporteurs as soon as possible when the previously notified submission date cannot be met, by re-sending an updated 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. Applicants should ensure that a technically valid eCTD submission is received by the EMA before the submission deadline. Any technically invalid sequence will result in non-acceptance that may cause a delay in the start of the procedure.

In order to accelerate and facilitate the procedure, one electronic copy should be submitted to the (Co-) Rapporteurs after the eSubmission Gateway/Web Client confirmation of a technically valid submission to the EMA if the relevant NCA is not using the Common Repository (refer tothe published “Dossier requirements for Centrally Authorised Products (CAPs)”). Please note that the EMA requires only one

eSubmission Gateway/ Web Client submission without any paper cover letter. After the notification of a valid application, the Agency will charge the appropriate fee 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?".

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

References

- Dossier requirements for Centrally Authorised Products (CAPs)
- HMA-EMA 'Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines

2.7. How should I notify a change in the intended submission date of my application? Rev. Dec 2017

In case the previously indicated submission date of an upcoming application for marketing authorisation is changed, the applicant shall inform the EMA by re-sending to pa-bus@ema.europa.eu the completed Pre-Submission request form (pre-submission request form), where the scope of request should be selected as "notification of change" and the new intended date of submission indicated in the corresponding field. The text of the e-mail should also describe the type of the change requested.

The change in intended MAA submission date must be notified as soon as possible. Since this information is crucial to the EMA and to the appointed (Co-) Rapporteurs and their assessment teams for planning purposes the intended submission date should be accurate and realistic. In some cases, a change in the planned submission data could lead to re-appointment of one or several Rapporteurs, if the previously appointed Rapporteur(s) will not be able to perform the assessment according to the new timings. In such case the applicants will be informed accordingly.

References

- Pre-submission request form
- HMA-EMA 'Best practice guide on measures improving predictability of submissions/respinses and adherence to communicated submission/responses deadlines'

2.8. Is my product eligible for an accelerated assessment? Rev. Mar 2016

2.8.1. 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.

Applicants are reminded that evidence requirements for applications to be assessed under accelerated assessment are the same as for other applications.

If the CHMP accepts the request, the timeframe for the evaluation will be reduced to **150 days**. This time frame will be split into 3 phases of 90+30+30 days of assessment. The applicants will be allowed to have one month clock-stop by default for preparation of responses to Day 90 List of Questions and no clock stop by default after Day 120 List of Outstanding Issues.

In case of advanced therapy medicinal products, due to the need to include more scientific committees in the review of the application, the 150-day timetable will be adapted differently and split into 2 phases of 120+30 days of assessment.

2.8.2. Request for an accelerated assessment: timing and justification

Before the submission of a potential request for accelerated assessment, applicants should seek guidance from the Procedure Manager to ensure timely submission of their request.

It is strongly recommended that applicants request a pre-submission meeting six to seven months before submission to prepare for evaluation under accelerated assessment. In this meeting, they can discuss their proposal for accelerated assessment with rapporteurs from the CHMP, the PRAC (and CAT in case of an advanced therapy medicinal product) and the EMA and present the data package and risk management plan they intend to include in their application.

Any request for accelerated assessment should be made as early as possible before the actual submission of the marketing authorisation application (and at least 2-3 months before the actual submission).

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).

For further guidance on aspects that could be considered in the justification please refer to section 4 of the CHMP “Guideline on the scientific application and the practical arrangements necessary to

implement the procedure for accelerated assessment pursuant to Article 14(9) of Regulation (EC) No 726/2004" (EMA/CHMP/697051/2014)

2.8.3. Early identification of a need for pre-authorisation inspection(s)

The EMA has a legal obligation to verify the Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP) compliance of studies and manufacturers for applications for marketing authorisation. In order to better anticipate and integrate routine GCP and pre-approval GMP inspections into the accelerated assessment procedure the applicants should provide with their request for an accelerated assessment also the following information (using the published templates) that should be accurate, complete and reflect the content of the application dossier that will be submitted:

Concerning GMP aspects (template to be used)

For all manufacturers to be included in the planned dossier:

- name and address of the manufacturer,
- short description of manufacturing activities performed by the manufacturer,
- past GMP compliance history of the manufacturing site and details of any inspections by other authorities anticipated during the marketing authorisation assessment,
- confirmation of GMP inspection readiness of the manufacturer.

If any of the third country manufacturing sites have never been inspected by a competent authority of an EU/EEA member state or a country with appropriate Mutual Recognition Agreement, the applicants intending to request accelerated assessment are advised to contact EMA inspection services at GMPINS@ema.europa.eu at least three months prior to the submission of the application for marketing authorisation. Applicants are also advised to include this as a topic for discussion in the pre-submission meeting with the EMA.

Concerning GCP aspects (template to be used)

The Applicant should provide the list of all the pivotal clinical studies (protocol number and title) and for each pivotal study:

- the study synopsis (or a mature draft with information at least on the design and conduct of the study),
- a short discussion of the GCP compliance status (listing any GCP non-compliance identified, any breach of GCP, providing information on any site excluded including the reasons etc.),
- list of investigators and their addresses,
- number of subjects enrolled at each site,
- information on study administrative structure,
- list of GCP inspections conducted/planned by any regulatory authority (indicating the site inspected/to be inspected, the date of inspection and the regulatory authority involved). Alternatively, a confirmation that no inspections had been requested nor taken place and that no inspections are planned.

In case a need for an inspection is identified, the inspection will be requested as early as possible in the evaluation procedure in order to accommodate the inspection within the accelerated timetable (*please refer also to questions "When can I expect a pre-approval GCP inspection and how are they*

conducted?" and "When can I expect a pre-authorisation GMP inspection and how are they conducted?"). It should also be noted that when a triggered GMP and/or GCP inspection cannot be accommodated within the agreed time frame, the procedure timetable may need to be amended as necessary.

2.8.4. Submission and assessment of the request

When submitting an accelerated assessment request, the applicant should use the templates for Pre-submission request (selecting scope for Accelerated Assessment), Applicant's justifications for accelerated assessment and information for early identification of a need for GMP and GCP pre-submission inspections, which should be sent, electronically, to: pa-bus@ema.europa.eu.

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 and the outcome of the request made public in the CHMP meeting highlights and minutes. 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" (EMA/CHMP/697051/2014)) and the detailed assessment timetables published on the EMA website.

References

- Regulation (EC) No 726/2004
- "Guideline on the procedure for accelerated assessment pursuant to article 14 (9) of Regulation (EC) No 726/2004" (EMA/CHMP/697051/2014)
- Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such inspections

2.9. How is a marketing authorisation application pre-submission meeting conducted at EMA? Rev. Oct 2018

Please note that in light of the Agency's relocation to Amsterdam due to the departure of the United Kingdom from the European Union (EU), pre-submission meetings, for which the requests have been received after 1 October 2018, will be held remotely (TC or virtual meeting facility) until the Agency is fully established in the permanent premises. Furthermore, no pre-submission meetings will be accepted during a limited period from 11 February 2019 to 15 March 2019, when the Agency's physical move to the temporary premises takes place.

2.9.1. 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 follow up of the advice given in 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.

2.9.1.1. 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 who 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 they wish to discuss at the 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 the time of the 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.

2.9.2. Timing of MAA pre-submission meetings

Pre-submission meetings for marketing authorisation applications (MAA) usually take place 6-7 months before the intended submission date. The MAA pre-submission meeting request form should be sent at least 6 weeks before the targeted meeting date. It is recommended to send the Letter of Intent ahead of the meeting request, in order to avoid any delay in the meeting date as a result of the time needed to appoint the Rapporteurs and the EMA product team.

Please also note that during the period when the Agency is relocating to the Netherlands until its establishment in the permanent premises, for logistic reasons pre-submission meetings will only be held remotely at designated specific dates. Applicants may indicate their preference for a date in the

pre-submission request form, which will be taken into account by EMA when allocating the exact date and time for the meeting.

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.

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

EMA participants at MAA pre-submission meetings are the Procedure Manager (PM) and the EMA Product Lead (EPL) together with the EMA Quality, Risk Management and Regulatory Affairs Product Team Members (PTM). Depending on the topics to be discussed, other EMA staff from the following services/offices and departments may attend parts of the meeting: Orphan Medicines, SME, Paediatric Medicines, Labelling Review and Standards, Scientific Advice, Manufacturing and Quality Compliance, Clinical and Non-clinical Compliance, Product and Application Business Support and Specialised Disciplines Department (Non-clinical, Biostatics, Clinical pharmacology). CHMP/PRAC Rapporteurs and/or assessment team members may also participate in the meeting.

Please note that the PM will be chairing the meeting and will remain the primary contact point between the applicant and the rapporteurs during the procedure.

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

- The MAA pre-submission meeting request form needs to be filled in electronically and sent to PA-BUS at pa-bus@ema.europa.eu. This form includes topics and questions to be addressed at the pre-submission meeting. The form also indicates relevant background information and documentation to be provided in support of the 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.
- In addition to the background information to be provided with the MAA pre-submission meeting request form depending on the topics to be discussed, the applicant should provide further 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 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 Procedure Manager 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.

2.9.5. How are MAA pre-submission meetings conducted?

For request received as of 1 October 2018, pre-submission meetings are being held remotely preferably via teleconference, or video-conference.

The applicant should provide the remote set-up in advance of the meeting to PA-BUS (e.g. provide toll-free dial in details in case of a teleconference) and coordinate the audio-visual for the presentation, if applicable.

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 medicinal product and its development

- 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 + paediatric + orphan
- Pharmacovigilance
- Regulatory + procedural
- Product information
- Transparency
- Administrative
- Other

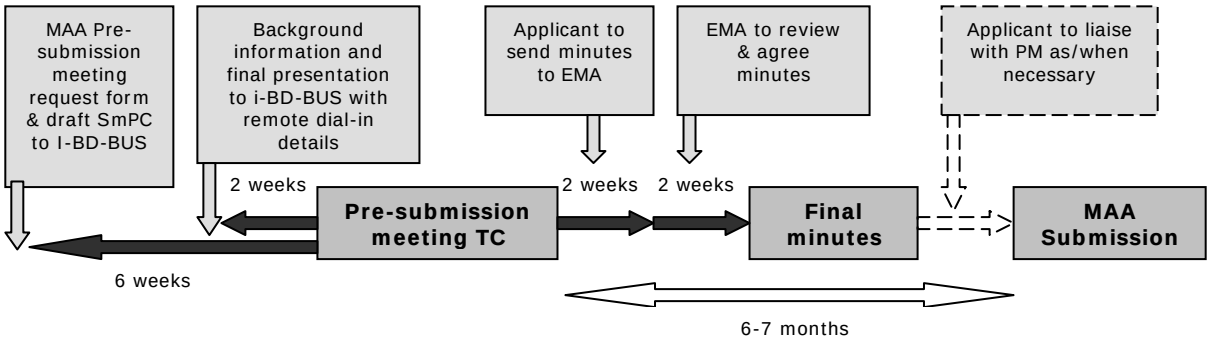
It is envisaged that the issues will be addressed in this order at the pre-submission meeting. This will allow a sequential discussion of all the applicant's questions on topics related to the same area, with involvement of relevant EMA staff with expertise in the area concerned (e.g. Labelling Review and Standards 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 Procedure Manager so that relevant EMA staff from the Product Team could participate in such a meeting via teleconference. In any case, minutes of such meetings should be provided to the EMA PM.

2.9.6. Follow up of MAA pre-submission meetings

Detailed meeting minutes should be prepared by the applicant and provided to the EMA PM 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.

2.9.7. Flow-chart summary



Timelines: Pre-submission meeting request, after submission of Letter of Intent, should be sent 6 weeks in advance of the targeted meeting date.
Meeting date should be targeted at 6-7 months in advance of the proposed intended submission date.
Consider to start the whole process, including submission of the Letter of Intent, around 7-8 months in advance of the intended submission date.

SmPC: Summary of Product Characteristics.
EMA: European Medicines Agency.
I-BD-BUS: Product and Application Business Support.
PM: Procedure Manager.

References

- MAA Pre-submission meeting request form
- Human pre-submission Q&A
- Pre-submission procedural advice for users of the centralised procedure

3. Preparing the dossier

3.1. Product name, product information and prescription status

3.1.1. How will I know if the proposed (invented) name of my medicinal product is acceptable from a public health point of view? Rev. Feb 2015

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" (EMA/CHMP/287710/2014).

It should be highlighted that when an applicant/MAH wishes to use instead of an invented name the common name or scientific name, together with a trademark or the name of the Marketing Authorisation Holder, this is also subject to NRG review.

3.1.1.1. 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" (EMA/CHMP/287710/2014), hereafter referred to as the 'Guideline'.

3.1.1.2. The EMA procedure for checking proposed (invented) names

3.1.1.2.1. 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 Q&A "How will I know if the proposed (invented) name of my medicinal product is acceptable from a public health point of view?". What are the dates for submission of invented name requests for the deadlines for submission of Proposed (Invented) Names.

Applicants may submit a name review request after eligibility has been confirmed by the CHMP or in parallel to the eligibility request. Applicants are advised to contact the NRG secretariat prior to submission of the name review request form for advice if eligibility is not yet confirmed at that time.

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 following 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.

Up to two (invented) names can be accepted per Marketing Authorisation Application from which the applicant should select the final name to be used. Up to two newly proposed (invented) names can be considered at each NRG meeting per Marketing Authorisation Application.

It should be noted that once two (invented) names have been deemed acceptable by the NRG for a Marketing Authorization Application, no further review of newly proposed names is allowed unless agreed with EMA on duly justified grounds (i.e. identification of safety issue/health concern after acceptance of (invented) names, conditional acceptability of previously reviewed (invented) names, constraints achieving a global (invented) name, issues relating to the application of the law on trademarks, etc.).

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).

3.1.1.2.2. Consultation with the Member States 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 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 Q&A "What are the dates for submission of invented name requests?" for the dates of NRG discussion/CHMP adoption.

3.1.1.2.3. 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 the following possibilities:

- To submit up to two new (invented) names proposals, which are checked through the same procedure as described above. In the case that a name has already been accepted in a previous NRG meeting and two new names are submitted, the applicant is required to indicate in the 'Proposed (Invented) Name Request form' which two names should be finally retained in the NRG database.
- 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.

Applicants may submit justifications for rejected names in addition to the entitlement of 2 (invented) names reviewed per meeting. However, only two accepted names can be retained in the NRG database and therefore the applicant should indicate in advance which two names should be retained in case that they are accepted.

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).

3.1.1.2.4. 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 IA_{IN} (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 IA_{IN} 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 IA_{IN} 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 IA_{IN} variation notification.

References

- Regulation (EC) No 726/2004
- Directive 2001/83 EC as amended
- "Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure" (EMA/CHMP/287710/2014)
- Regulation (EC) No 1234/2008
- "Post-Authorisation Procedural Advice Human Medicinal Products" (EMEA-H-19984/03)

3.1.2. What are the dates for submission of (invented) name requests?

Please see the submission dates in the Q&A "What are the dates for submission of (invented) name requests?" on the EMA website.

3.1.3. How shall I compose the complete name of my medicinal product? Rev. May 2011

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:

{(invented) name strength pharmaceutical form}, whereby

- 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

3.1.4. Do I need to include Braille on the packaging of my medicinal product? Rev. Feb 2017

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.

3.1.4.1. 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).

3.1.4.2. Package leaflet for blind and partially sighted

On request from patient's organisations 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 'Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use'.

References

- Article 56a of Directive 2001/83/EC, as amended
- "Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use", the Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C

3.1.5. What additional information can I include on the outer packaging of my medicinal product? Rev. Dec 2017

Directive 2001/83/EC establishes the main principles for the information to be included on the outer packaging of medicinal products. The mandatory information to be included on the outer packaging of a medicinal product is defined in Article 54. In addition, information required for a particular Member State in accordance with Article 57 has to be included in the so called "blue box" (a boxed area included in the labelling, with a blue border, aimed at containing information specific to each Member State).

According to Article 62 of Directive 2001/83/EC, the outer packaging and the package leaflet of a medicinal product may contain also **additional symbols, pictograms** to clarify certain mandatory information **and other information**, but **only in case if it complies with all of the following requirements**:

- it is compatible with the Summary of Product Characteristics;
- it is useful to the patient;
- it does not contain any element of a promotional nature.

If the applicant proposes to include on the packaging of the medicinal product such additional information, a justification that the above requirements are met should be included in the submission (section 1.3.2 of Module 1).

Examples of additional elements on the outer packaging often proposed by the applicants include:

- Various **symbols and pictograms** used to explain the appropriate and safe use of the medicine. As an example, considerations on this aspect for non-prescription medicines are included in draft "QRD recommendations on pack design and labelling for centrally authorised non-prescription human medicinal products."
- **Quick response codes**. For further guidance please refer to guidance document "Quick Response (QR) codes in the labelling and package leaflet of centrally authorised medicinal products".
- **Company Logo**. It is acceptable to include the logo of the marketing authorisation holder, as this complements the name of the marketing authorisation holder already included on the outer packaging, and can help patients to identify the legal entity responsible for the product. Similarly, if the name of a local representative is mentioned in the "blue box" also the logo of the local representative can be included there (i.e. inside the "blue box" only, together with the name of the company).

  On the contrary, inclusion of an additional logo of a different company next to the logo of the marketing authorisation holder or elsewhere on the packaging could cause confusion among patients and could also be considered as an element of promotional nature therefore cannot be accepted. This applies also to co-promotion and co-marketing partners (unless the second company is also a local representative and its logo is placed inside the "blue box" together with the name of the company).
- **Trademark statements** cannot be considered as useful to the patient, and could be regarded as an element of promotional nature. Therefore, in principle, such statements should not be included on the packaging and the package leaflet, unless the non-inclusion of such trademark statement would constitute a breach of trademark law.
- Similarly, **statements on licencing relationships between companies,** and also **copyright statements,** cannot be considered as useful to the patient, and consequently are not accepted on the packaging and the package leaflet.

References

- Directive 2001/83/EC
- Notice to Applicants Guideline on the packaging information of medicinal products for human use authorised by the Union
- Quick Response (QR) codes in the labelling and package leaflet of centrally authorised medicinal products
- QRD recommendations on pack design and labelling for centrally authorised non-prescription human medicinal products

- See also questions “When should I submit mock-ups and/or specimens?”, “Where in the medicinal product information can I mention a local representative?”

3.1.6. When should I submit mock-ups and/or specimens? Rev. Feb 2015

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 is clear.

A "Specimen" is a sample of the actual printed outer and immediate packaging materials and package leaflet (i.e. the sales presentation).

The checking process of mock-ups and specimens in the Centralised Procedure is based on the following general principles:

- The European medicines Agency (EMA), through the 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 not 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).

Based on the above, EMA will not check the national requirements included in the blue box. However, 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 i.e. the blue outline of the ‘blue box’ should be displayed to show the location of the ‘blue box’ on the outer carton.

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 Union” as published by the European Commission in the Notice to Applicants, Volume 2C.

The inclusion of a national barcode on the labelling would normally be viewed as a Member State driven requirement located within the ‘blue box’ on the outer carton. However, EMA can also accept the inclusion of a national barcode on the immediate packaging (e. g. for traceability purposes), where space and readability permit.

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

3.1.6.1. Mock-ups

- At **the time** of **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 immediate 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,** revised mock-ups of the labelling and package leaflet should be submitted within Module 1.3.2 as part of the answers to the list of questions, in case of comments or in case the applicant changes the overall design.
- By **day 181**, further mock-ups may need to be submitted if there any outstanding comments made at Day 150 to be solved prior to the opinion.
- The applicant will liaise with the EMA by e-mail to muspecimens@ema.europa.eu to resolve any outstanding comment on the mock-ups of labelling and package leaflet prior to the adoption of the opinion.
- Submission of further mock-ups for review is not required after adoption of the Opinion. However, EMA would be willing to perform an additional review of updated mock-ups in the post-opinion phase, if requested by applicants prior to specimen printing.

3.1.6.2. Specimens

- **At the latest 15 working days before marketing**, one set of relevant specimens examples of the outer and immediate packaging and package leaflet for each strength or for each different total content per total volume (when the strength is expressed as concentration per unit volume (x mg/ml)) and each pharmaceutical form in each container type need to be provided to the EMA (using the "Specimen Submission Form" (see EMEA/305821/2006):
  - before first marketing in the EU,
  - before first marketing 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 on: muspecimens@ema.europa.eu.

References

- Directive 2001/83/EC, as amended
- 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
- The Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02)

3.1.7. How are ATC codes and international non-proprietary names (INN) applied within the centralised procedure? Rev. Nov 2015

3.1.7.1. 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 (MA) 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. 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.

3.1.7.2. 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 2009)’ 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”

3.1.8. Do I have to submit samples together with my application? Rev. May 2006

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

3.1.9. When and how should I submit information on user consultation? Jul 2006

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.

3.1.9.1. 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".

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).

3.1.9.2. 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)

3.1.10. Where in the medicinal product information can I mention a local representative? Rev. Jan 2006

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

3.1.11. What legal status can I obtain for my medicinal product? Rev. Jul 2006

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'.

3.1.11.1. 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.

3.1.11.2. 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.

3.1.11.3. 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

3.1.12. What is a multipack presentation and which information should I include in the product information for a multipack presentation? NEW Feb 2018

The 'Guideline on the packaging information of medicinal products for human use authorised by the Union' defines 'multipacks' as 'packs composed of several single packs of the same strength of a medicinal product.' The single packs should be understood as single authorised packs. Thus, it is acceptable to include the term 'multipack' only when it refers to a presentation composed of several single authorised packs of the same strength.

The multipack outer carton should display all legally required items (including blue box). The inner boxes should not contain the blue box and each individual inner box should contain a package leaflet. Information in Braille, when applicable, should be present on both the outer packaging and inner boxes. The inner boxes should include the mention 'can't be sold separately'.

All other relevant statements to include in the product information for a multi pack presentation are described in the QRD product information annotated template (i.e. in Section 6.5. of the SmPC, in the labelling and the package leaflet).

References

- Notice to Applicants Guideline on the packaging information of medicinal products for human use authorised by the Union
- QRD Product Information template with explanatory notes

3.2. Orphan and paediatric requirements

3.2.1. Do I need to address any paediatric requirements in my application? Rev. Feb 2012

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". 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. 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

- Regulation (EC) No 1901/2006
- 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”

3.2.2. What aspects should I consider if my medicinal product has been designated as an orphan medicinal product at the time of submission of my application? Feb 2013

If your medicinal product has been designated as an orphan medicinal product, you will have to consider the following points at the time of submission of your application for marketing authorisation:

- The applicant for the marketing authorisation application will have to be the same as the holder of the orphan designation; where necessary, the orphan designation will have to be transferred to the new sponsor in advance of the submission of the application for marketing authorisation. In case the sponsor remains the same person or legal entity but changes its name and/or address, a letter should be sent to the Agency indicating the new name and/or address details and confirming that the identity of the Sponsor remains the same.
- The therapeutic indication requested for your medicinal product will have to fall within the scope of the orphan designation, i.e. the therapeutic indication applied for cannot be broader than the orphan indication. Reference is made on this regard to Article 7(3) of Regulation (EC) No 141/2000 (“Orphan Regulation”), which provides that the marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfill the criteria for designation set out in Article 3.
- It is not possible to combine within the same application for marketing authorisation orphan and non-orphan indications. However, this is without prejudice to the possibility of applying for a separate marketing authorisation for other indications which have not been designated as orphan, as provided for in the Orphan Regulation.
- You will have to submit at the same time as the submission of the initial application for marketing authorisation, a report on the maintenance of the orphan designation criteria, which will be reviewed by the COMP. This report should be addressed to the Head of the Orphan Medicines Section.

References

- Regulation (EC) No 141/2000 on orphan medicinal products
- Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another
- Sponsor's report on the maintenance of the designation criteria at the time of marketing authorisation applications for a designated orphan medicinal product

3.2.3. What aspects should I consider if the designation for my orphan medicinal product is still pending at the time of submission of my application for marketing authorisation? Rev. Dec 2015

When an application for orphan designation is still pending at time of submission of the application for marketing authorisation, it is nevertheless possible for the medicinal product to be authorised as an orphan medicinal product, provided that the orphan designation is granted and confirmed by the COMP before the granting of the marketing authorisation.

However, in such cases, the eligibility to the centralised procedure (which precedes the submission of the application for marketing authorisation) cannot be based on Article 3(1), Annex 4 – Orphan designated medicinal product. Similarly, a fee reduction will not be applicable, as it can only be considered if orphan designation has already been granted at the time of submission of the application for marketing authorisation.

References

- Fees payable to the European Medicines Agency

3.2.4. What aspects should I consider if there are other orphan medicinal products for a condition related to my proposed therapeutic indication? Rev. Feb 2017

In advance of submission of your application for marketing authorisation, irrespective of whether your medicinal product has been designated as orphan or not, you are advised to check the Community register of orphan medicinal products, for information on medicinal products designated as orphan which are under market exclusivity protection.

You will have to indicate in the application form (section 1.2.2) if any medicinal product has been designated as an orphan medicinal product for a condition relating to the therapeutic indication proposed in your application and, if applicable, specify the respective orphan designation number.

If any of the designated orphan medicinal products has been granted a marketing authorisation in the Union, and a period of market exclusivity is in force, you will have to provide in Module 1.7.1 a similarity report addressing the possible similarity between your medicinal products and the orphan medicinal product(s) which have received a marketing authorisation.

This legal requirement arises from Article 8(1) of the Orphan Regulation which provides that where a marketing authorisation in respect of an orphan medicinal product is granted, the Agency and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Article 3 of Commission Regulation (EC) No 847/2000 defines **similar medicinal product** as a medicinal product containing a **similar active substance or substances** as contained in a currently authorised orphan medicinal product, and which is intended for the **same therapeutic indication**.

It also defines **similar active substance** as an identical active substance, or an active substance with the **same principal molecular structural features** (but not necessarily all of the same molecular features) and which acts via the **same mechanism**.

Based on the above mentioned definitions, the assessment of similarity between two medicinal products takes into consideration the following criteria

- Principal molecular structural features,
- Mechanism of action and
- Therapeutic indication.

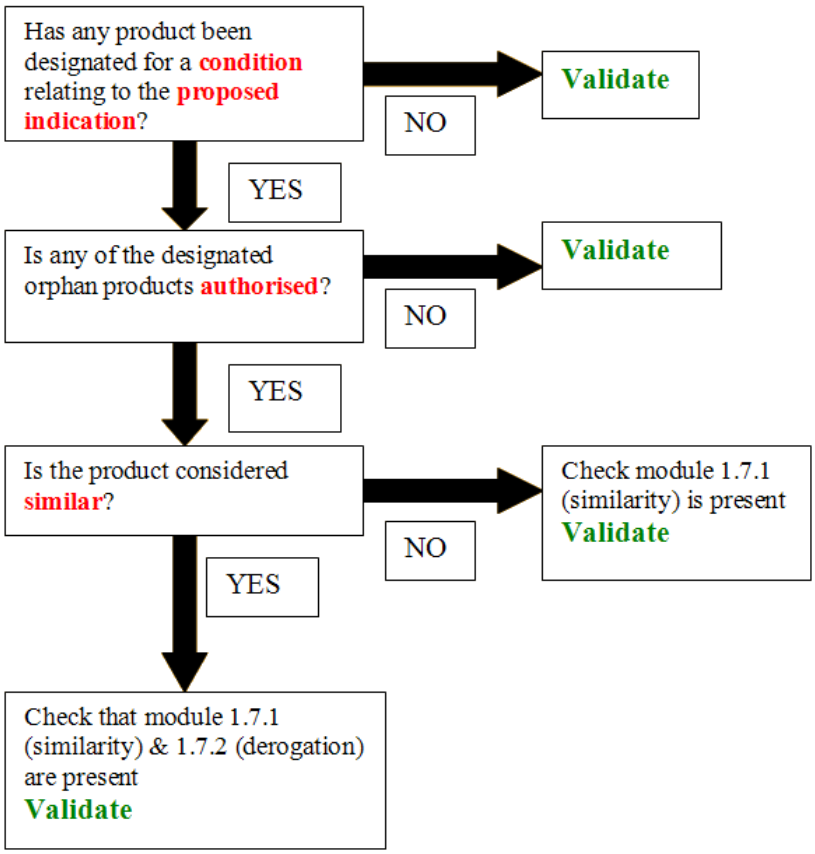
If significant differences exist within one or more of these criteria, the two products will not be considered as similar. These criteria are explained in the Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity.

For information on the procedure and timetable for assessment of similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products, please refer to Q&A “What is the procedure and timetable for assessment of similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products?”.

Please note that if the Agency identifies a possible similarity issue not addressed by the applicant before validation, the applicant will be asked to complete the application with information on similarity and, if applicable, on one of the derogations. Validation of the application will only proceed once the applicant has submitted a report justifying the lack of similarity or, if similar, additional information justifying one of the derogations in Article 8(3).

The flowchart below illustrates the Agency validation of marketing authorisation applications with respect to orphan similarity and derogation.

Orphan Validation Checklist



As considerable time may elapse between validation of an application and adoption of an opinion, if applicants become aware of medicinal products which have been authorised as orphans for a condition related to the therapeutic indication proposed in their application, this information should be communicated promptly to their Procedure Manager at the Agency in order to arrange for the submission of updated application form and modules 1.7.1 and 1.7.2, as applicable.

In any case, the Agency will check at certain milestones of the procedure, i.e. Day 120, Day 180 and prior to adoption of a CHMP opinion whether new orphan medicinal products have been authorised for the same condition.

References

- Regulation (EC) No 141/2000 on orphan medicinal products
- Regulation (EC) No 847/2000
- Community register of orphan medicinal products
- Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

3.2.5. What aspects should I consider if my medicinal product is considered similar to an orphan medicinal product? Rev. Feb 2015

If your product is considered to be similar to any authorised orphan medicinal product, you will have to provide in Module 1.7.2 justification that one of the following derogations, laid down in Article 8(3) of the Orphan Regulation applies, i.e.

- the holder of the marketing authorisation for the orphan medicinal product has given his consent for submission of your application, in which case a signed letter from the MAH of the orphan medicinal product should be provided confirming the consent for submission of an application for marketing authorisation;
- the holder of the marketing authorisation for the orphan medicinal product is unable to supply sufficient quantities of the medicinal product, in which case the applicant should provide a report including details of the supply shortage and justify that patients' needs in the orphan indication are not being met;
- the applicant can establish that their product, although similar to the orphan medicinal product already authorised, is more effective, safer or otherwise clinically superior, in which case a critical report justifying clinical superiority to the authorised product must be provided.

For information on the procedure and timetable for assessment of derogation report vis-à-vis authorised orphan medicinal products, please refer to Q&A "What is the procedure and timetable for assessment of similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products?"

Please note that if the Agency identifies a possible similarity issue not addressed by the applicant before validation, the applicant will be asked to complete the application with information on similarity and, if applicable, on one of the derogations. Validation of the application will only proceed once the applicant has submitted a report justifying the lack of similarity or, if similar, additional information justifying one of the derogations in Article 8(3).

As considerable time may elapse between validation of an application and adoption of an opinion, if applicants become aware of medicinal products which have been authorised as orphans for a condition related to the therapeutic indication proposed in their application, this information should be communicated promptly to their Procedure Manager at the Agency in order to arrange for the submission of updated application form and modules 1.7.1 and 1.7.2, as applicable.

In any case, the Agency will check at certain milestones of the procedure, i.e. Day 120, Day 180 and prior to adoption of a CHMP opinion whether new orphan medicinal products have been authorised for the same condition.

References

- Regulation (EC) No 141/2000 on orphan medicinal products
- Regulation (EC) No 847/2000
- Community register of orphan medicinal products
- Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

3.3. Quality

3.3.1. What information relating to the manufacture and batch release should be provided as part of my application? Rev. Feb 2012

The EMA requires the applicant to provide background information in support of the application relating to the manufacture (including packaging), batch testing and batch certification (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.

3.3.1.1. 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.

3.3.1.2. 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 than 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).
- 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 the EEA listed 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.

3.3.1.3. 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

3.3.2. What batch release arrangements in the EEA are required for my medicinal product? Rev. Feb 2012

3.3.2.1. 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 Recognisition Agreement, a request for inspection will normally be triggered. The marketing authorisation procedure will require the inspection outcome before opinion.

3.3.2.2. 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).

3.3.2.3. 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

3.3.3. Is my product subject to batch release by an Official Medicines Control Laboratory? Rev. Nov 2016

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. It is advisable that this activity is also undertaken with a second OMCL and applicants seriously consider the nomination of two such OMCLs for batch release of the authorised product to the market, to secure the supply chain and minimise the risk of shortage.

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)

3.3.4. What information shall I provide if my medicinal product contains materials of animal and/or human origins or uses them in the manufacturing process? Rev. Jul 2006

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)

3.3.5. What should I submit if my medicinal product contains or consists of genetically modified organisms (GMOs)? Rev. Sep 2015

Potential applicants are advised to discuss their future applications which consist of or contain 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 with the designated GMO Competent Authorities (CAs) will be held in parallel.

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 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 (EC) No 726/2004 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.
- 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 (EC) 726/2004, it is recommended to complete Module 1.6.2 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.
- A summary following the Summary Information Format set out in the Annex to Council Decision 2002/812/EC.
- Bibliographical references.

The Module 1.6.2, presenting all these particulars, should stand alone 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.

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.

According to Article 12(2) of Directive 2001/18/EC, Articles 13 to 24 of Directive 2001/18/EC do not apply to any GMO as or in products as far as they are authorised by Regulation (EC) No 726/2004 provided that an environmental risk assessment is carried out in accordance with Annex II of Directive 2001/18/EC and the type of information in accordance with Annex III of Directive 2001/18/EC are provided.

Regulation (EC) No 726/2004 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 Module 1.6.2 assessor including any comments received from the bodies that the Community or Member States have set up in accordance with Directive 2001/18/EC, 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.

References

- Regulation (EC) No 726/2004 of the European Parliament and of the Council
- Council Directive 2001/18/EC
- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2B, Presentation and content of the dossier
- Guideline on Environmental Risk Assessments for Medicinal products containing or consisting of, Genetically Modified Organisms (GMOs) (EMEA/CHMP/BWP/473191/2006 – Corr.)
- Standard Operation Procedure “Consultation of environmental competent authorities on genetically-modified organisms with respect to environmental risk assessment in product evaluation (human use)” (SOP/H/3191)

3.3.6. How should I submit an Active Substance Master File (ASMF)? Rev. Aug 2016

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 and any post-authorisation changes as variations are to be submitted by the Marketing Authorisation Holder.

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.

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

Additional information can be found in the 'Practical Guidance on the use of the eCTD format for ASMF for Active Substance Master File Holders and Marketing Authorisation Holders'.

Applicants should note that the ASMF constitutes an integral part of the dossier and therefore should always be made available to the EMA and CHMP Members. The applicant is responsible for the submission of all necessary documents to the EMA.

The applicant or MAH should ensure that the submission of the ASMF dossier including all necessary documents is synchronized to arrive simultaneously with the planned MAA or variation. Therefore, a close communication between the MAH or applicant and the ASMF holder is highly recommended.

Marketing authorisation and subsequent variation applications cannot be validated until all the necessary documents (e.g. ASMF dossier) are received in a satisfactory form. Delays in the submission of ASMF-related responses to questions raised during a MAA (e.g. Day 120 LoQ and Day 180 LoOI) and to Requests for Supplementary Information for post-authorisation variation procedure may postpone the start of the procedure.

The ASMF is developed to keep intellectual property (IP) confidential. However, it should be noted that the introduction of an ASMF is also possible in cases where the applicant is also the IP holder of the active substance.

ASMF holders are reminded of their responsibility to inform the MAHs of any changes to their ASMFs. Similarly, MAHs are reminded of their legal obligation to submit the applicable variation to their MAs when changes are proposed to the ASMF, i.e. when an updated version of the ASMF is submitted, the MA(s) linked to that ASMF will only integrate the ASMF update once the applicable variation is submitted and positively concluded.

Additional information on the ASMF procedure can be found in the ASMF Working Group webpage. Technical information on how to submit ASMFs in the context of eCTD can be found on the esubmission website.

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)
- Procedural announcement CHMP Monthly report October 2004 (EMEA/CHMP/119155/2004)
- 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)

3.3.6.1. What data should be submitted by the ASMF holder? Rev. Aug 2016

In the first submission of an ASMF with an allocated EMEA ASMF reference number or for the introduction of an already submitted ASMF to the marketing authorisation of a different medicinal product (e.g. ASMF submitted to the Agency for medicinal product A is now being used for medicinal product B), the ASMF holder is required to submit:

- ASMF dossier (Applicant's part, Restricted part, Quality Overall Summary and Expert's *curriculum vitae*) only in the case of a first ASMF submission;
- Letter of Access (Annex 2 of the ASMF Guideline);
- Submission Letter and Administrative Details (Annex 3 of the ASMF Guideline) duly filled as detailed in the instructions provided in the additional guidance on documents relating to an active substance master file;
- A commitment to inform the applicant and the EMA of any change in the ASMF to be provided either as a separate letter or within the Letter of Access (Annex 2 of the ASMF Guideline).

For subsequent changes to an already approved ASMF, the ASMF holder is only required to submit:

- Submission Letter and Administrative Details (Annex 3 of the ASMF Guideline) dully filled as detailed in the instructions provided in the Additional guidance on documents relating to an active substance master file.
- The relevant revised sections of the ASMF dossier reflecting changes to the previously approved version. This includes Applicant's Part and/or Restricted Part, as applicable.

It is highly recommended that a table including the changes made to the Applicant's Part and/or Restricted Part of the ASMF compared with the currently approved version is provided. This information should be included in section "Table of changes" within Annex 3 or alternatively as a separate document.

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

The ASMF dossier and any subsequent updates should only be submitted once via the eSubmission Gateway or Webclient in eCTD format.

The ASMF holder may, at its discretion, contact the relevant Procedure Manager directly for pre-submission questions regarding classification of changes in the restricted part of the ASMF.

3.3.6.2. What data should be submitted by the applicant or MAH? Rev. Aug 2016

3.3.6.2.1. Initial marketing authorisation applications

In all cases, the applicant (in the context of a MAA) should submit:

- MAA application form stating, in section 2.5 "Manufacturers", the correct EMEA/ASMF or EU/ASMF reference number
- Copy of the Letter of Access (Annex 2 of the ASMF Guideline), included in Annex 5.10 of the dossier
- Copy of the complete current version of the Applicant's part of the ASMF in Module 3

- Copy of the commitment from the ASMF holder to inform the applicant and the EMA of any change in the ASMF to be provided either as a separate letter (Annex 5.11) or within the Letter of Access (Annex 5.10) (Annex 2 of the ASMF Guideline).

3.3.6.2.2. Variations to the terms of the marketing authorisation

In all cases, the MAH should submit:

- Variation application form stating the correct EMEA/ASMF or EU/ASMF reference number in section 3 “Types of change(s)”;
- If applicable, copy of the revised sections of the Applicant’s part of the ASMF which should be identical to the ones submitted by the ASMF holder.

In cases where a new ASMF is being introduced as part of a Type II variation (B.I.a.1.b – Introduction of a manufacturer supported by an ASMF), in addition to the documents mentioned above, the MAH should also submit:

- Copy of the Letter of Access (Annex 2 of the ASMF Guideline), included in Annex 5.10 of the dossier
- Copy of the complete current version of the Applicant’s part of the ASMF in Module 3
- Copy of the commitment from the ASMF holder to inform the applicant and the EMA of any change in the ASMF to be provided either as a separate letter (Annex 5.11) or within the Letter of Access (Annex 5.10) (Annex 2 of the ASMF Guideline).

The MAH or the applicant should ensure that the submission of the ASMF dossier is synchronized to arrive simultaneously with the planned variation or MAA. Therefore, a close communication between the MAH or applicant and the ASMF holder is highly recommended.

Effective liaison between the MAH and the ASMF holder will promote the appropriate classification of the changes in accordance with the Commission’s variations guidelines and for ensuring that the ASMF dossier or the relevant affect sections of the dossier have been submitted.

In the case of type IA and IB variation applications, the use of the IA and IB pre-notification checklist is recommended prior to the submission of the application. This is intended to help the MAH with the correctness of the submission and to avoid validation comments that may delay the finalisation of the procedure.

The latest version of the ASMF submitted in the context of a previous centralised procedure will be considered the current version of that ASMF. The current version of the ASMF should correspond to the version of the ASMF Applicant’s part declared in a new MAA or variation form and included in Module 3. This will be subject to compliance checks during validation of the MAA and MAV.

Example:

The version of EMEA/ASMF/12345 (EMA/ASMF/reference number) currently held at the Agency is: AP January 2012/RP April 2013.

If the version of the ASMF included in the Module 3 of the MAA and referenced in the application form is AP November 2011, the applicant will be requested to update Module 3 and the application form according to the current version of the EMEA/ASMF/12345.

Equally, if the version of the ASMF included in the Module 3 of the MAA and referenced in the application form is AP December 2012, the ASMF holder will be requested to submit the latest version of the ASMF together with the Annex 3 of the ASMF Guideline.

3.3.6.3. What is the EMEA/ASMF reference number? Rev. Dec 2013

From 1 September 2013, ASMF holders submitting their ASMF dossiers relating to a Centrally Authorised Product are asked to send it to the Agency and Committee Members only once.

According to the new ASMF submission rules the Agency will assign a reference number on request prior to submission of the ASMF that can cover multiple CAPs.

The EMEA/ASMF/XXXXX number is an internal reference number sequentially assigned by the EMA to enable an appropriate data lifecycle management of ASMFs used in one or more centralised Marketing Authorisation.

The EMEA ASMF reference number does not replace the responsibility of the ASMF holders to version control their ASMF (in accordance with GMP) nor replaces their own ASMF numbering system.

3.3.6.4. Who should request an EMEA ASMF reference number? Rev. Aug 2016

The EMEA ASMF reference number should be requested by the ASMF holder for:

- new ASMFs submitted for MAAs and MAVs as of 1 September 2013. From this date, reference to an EMEA ASMF number will be checked at validation,
- ASMFs submitted to the EMA before 1 September 2013. In cases when the ASMF is referenced in a new MAA or variation. The request for the EMEA ASMF reference number should be made before submission of a new MAA or variation to update the ASMF.
- ASMFs submitted in relation to a variation application.

For previously submitted ASMFs, in cases where the ASMF is used in more than one MA the ASMF Holder should only request a EMEA ASMF reference number, when applicable[5]. The allocated EMEA/ASMF reference number should be communicated to the applicant or MAH, so that reference to the EMEA/ASMF/XXXXX number is made in all future submissions.

3.3.6.5. When and how to request an EMEA ASMF reference number? Rev. Aug 2016

Up to two weeks before submitting a complete ASMF, or an update to an already submitted ASMF, the ASMF holder should request the EMEA/ASMF reference number. The request should be sent to PA-BUS@ema.europa.eu.

EMEA/ASMF reference numbers are allocated sequentially.

The EMEA ASMF reference number allocated by the Agency should be referenced in all subsequent communications (e.g. in response to a validation issue, List of Questions, List of Outstanding Issues, upcoming variation) both by the ASMF Holder and the applicant and should always be included in the following documents:

- MAA (in the field of the *National ASMF number*) or variation application form (in the Present and Proposed field);
- Letter of Access (Annex 2 of the ASMF Guideline);
- Submission Letter and Administrative Details (Annex 3 of the ASMF Guideline)

[5] Example: substantially different route of synthesis/manufacturing process which results in changes to important quality characteristics of the active substance, e.g. bioavailability of the active substance, may result in the allocation of two different EMEA/ASMF numbers.

It is the responsibility of the ASMF holder to inform the applicant of a MAA or the MAH in case of variations of the allocated EMEA ASMF reference number. Failure to state a valid EMEA ASMF reference number on the MAA or variation application form will trigger validation questions and may delay the start of procedure.

3.3.6.6. EMA ASMF or EU ASMF reference number? Rev. Aug 2016

The EU/ASMF reference number allows for the identification by all Competent Authorities (National Competent Authorities and EMA) of ASMFs used in centralised and national (Decentralised and Mutual Recognition) MAAs or variations, and therefore enabling the ASMF Assessment Report Work Sharing (ASMF AR WS) procedure.
For more information on the ASMF AR WS and the request template forms please consult the ASMF WG webpage.

ASMF holders should either have an EMEA/ASMF reference number or an EU/ASMF reference number before submitting an ASMF. Both numbering systems run in parallel. ASMF holders are encouraged to request an EU/ASMF reference number if the ASMF is expected to be used in centralised and national applications (decentralised and mutual recognition procedures) and have not been used in any of these procedures previously.

Please note that this number is NOT equivalent of EMEA/ASMF number and should never be inter-changed.

3.3.6.7. Which format and submission channel should be used for submitting ASMFs? Rev. Aug 2016

The use of eCTD format is mandatory for all centralised procedure human ASMF submissions from 1 July 2016. After this date, it will no longer be possible to submit ASMFs relating to human medicinal products using NeeS format to EMA. An eCTD baseline should be provided for ASMFs currently in NeeS format. More information on how to provide an eCTD baseline can be found in “Practical Guidance on the use of the eCTD format for ASMF for Active Substance Master File Holders and Marketing Authorisation Holders”.

Additional guidance can be found on the eSubmission website. Please also refer to the EMA’s statement of intent of mandatory use of XML delivery files.

Submission requirements for the different Committee (Co-) Rapporteurs

ASMF holders should no longer send their ASMF dossiers for human medicines to individual Member States on CDs/DVDs or via the Common European Submission Platform (CESP).

Instead, ASMF holders should send these applications to the EMA via eSubmission Gateway/Web Client only. The ASMF dossier will automatically be made available to all national competent authorities via a common online repository.

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

3.3.6.8. How to proceed if the ASMF was previously submitted in paper format? Rev. Aug 2016

The ASMF holder of ASMFs previously submitted in paper format should request an EMEA ASMF reference number as indicated above.

After the reference number is allocated the ASMF holder should submit the ASMF in Electronic Common Technical Document (eCTD) format.

Guidance can be found on the eSubmission website. Additionally, please refer to the EMA's statement of intent of mandatory use of XML delivery files.

3.3.6.9. How to proceed if there is an existing eCTD life-cycle for the ASMF? Rev. Aug 2016

ASMF holders need to request the EMEA/ASMF number by filling the request form. The EMA will provide the requestor with the number within 3 working days. Please note that this number is NOT equivalent of EU/ASMF number and should never be inter-changed.

If the ASMF holder already has more than one eCTD life-cycle filed for the given substance, they will need to select one of these (informing the EMA in the cover letter which one it will be) and follow the eCTD life-cycle of the selected 'product' only. This, selected life-cycle will, then receive a new EMEA/ASMF/01xxx number covering all listed CAPs.

Once the ASMF holder is submitting an update or new version to the ASMF, they have to include the new number. The ASMF holder will have to prepare a new sequence (increasing by one) in which (module 1, cover letter) they declare that the previously submitted ASMF version has not been modified since it was last submitted.

If there have been modifications (new version) since the last ASMF submission, the relevant modules within this new eCTD sequence will have to be additionally updated.

ASMF holders have to inform all MAH(s) about the new EMEA/ASMF/xxxxx number and if an update is submitted to an ASMF related to their Centrally Authorised Product the MAH should then submit the relevant variation application.

3.3.7. What is the Community Plasma Master File certification system? Mar 2009

The concept of 'Plasma Master File' (PMF) was introduced with the Commission Directive 2003/63/EC in June 2003 amending Directive 2001/83/EC.

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.

3.3.8. What is the Community Vaccine Antigen Master File certification system? Mar 2009

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.

3.3.9. Can I apply for Design Space or Process Analytical Technology (PAT) in my application? Mar 2007

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.

3.3.9.1. 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**.

3.3.9.2. 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.

3.3.9.3. 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
- Reflection Paper: Chemical, pharmaceutical and biological information to be included in dossiers when Process Analytical Technology (PAT) is employed (EMEA/INS/277260/2005)

3.3.10. Which activities of the European Directorate for the Quality of Medicines and HealthCare (EDQM) have impact on the centralised procedure? Rev. Jul 2010

3.3.10.1. 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.

3.3.10.2. European Pharmacopoeia and its use for an application

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

Directive 2001/83/EC on medicines for human use refer to the mandatory character of European Pharmacopoeia monographs in the preparation of dossiers for Marketing Authorisation Applications (MAA).

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).

3.3.10.3. 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.

3.3.10.4. 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

3.3.11. Medical devices NEW Aug 2017

Medical devices are currently governed by the Medical Device Directive 93/42/EEC (MDD) and the Active Implantable Medical Device Directive 90/385/EEC (AIMDD). A new medical device Regulation (EU) 2017/745), replacing these two directives, was adopted on 5 April 2017 and will apply as of 26 May 2020.

Medical devices are any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. A product is regulated either by the MDD or the AIMDD or by the medicinal products Directive (2001/83/EC). The conformity assessment procedure or the marketing authorization procedure to be followed prior to placing a given product on the market will therefore be governed either by the MDD/AIMDD or by the medicinal products Directive. The procedures of both Directives do not apply cumulatively. In deciding whether a product falls under the MDD/AIMDD or the medicinal products Directive, the principal mode of action of the product will be taken into account.

Medical devices, necessary to administer a medicinal product, may be supplied together with the medicinal product, i.e. as an integral component of the medicinal product (see question 1.1), as a separate drug-delivery device co-packaged with the medicinal product (see question 1.2), or independently of the medicinal product.

The European Commission provides a range of medical device guidance documents (MEDDEV) relating to questions of application of EC directives on medical devices. These documents provide useful guidance to assist stakeholders taking common positions throughout the European Union.

This Questions and Answers document (applicable to the current MDD and AIMDD) is intended to provide guidance on procedural aspects for the submission of a Marketing Authorisation Application (MAA) to the European Medicines Agency in cases where such applications also concerns medical devices. In cases of questions regarding the medical device component, it is recommended to consult the EMA before the submission of an MAA and clarify any requirements in a pre-submission meeting (see question 'How is a marketing authorisation application pre-submission meeting conducted at EMA?').

3.3.11.1. When is my medical device and medicinal product considered to form a single integral product?

If a medical device is placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single-integral product is governed by Directive 2001/83/EC.

The second paragraph of Article 1(3) of the MDD sets out three cumulative conditions that need to be satisfied at the moment of the placing on the market:

- the device and the medicinal product form a single integral product;
- intended exclusively for use in the given combination;
- which is not reusable.

This single integral product is governed by the medicinal products Directive and all aspects of this single integral product will be evaluated as part of the assessment of the MAA. A medical device and medicinal product forming a single integral product will not require a CE mark. The relevant essential requirements of Annex I to the MDD will apply as far as the safety and performance-related device features are concerned. All elements needed in the evaluation of the device need to be submitted in the relevant part of the dossier.

Examples of single integral products which are not reusable are pre-filled syringe or pre-filled pens, nebulizers pre-charged with a specific medicinal product; and patches for transdermal drug delivery (for additional examples refer to MEDDEV 2. 1/3 rev 3).

3.3.11.2. When is a drug-delivery product regulated as a medical device?

This category concerns devices that are intended to administer a medicinal product but do not form a single integral product at the time of placing on the market. In this case, the device is governed by the MDD, without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product. These types of medical devices can be supplied separately or co-packaged with the medicinal product. If the medical device will be supplied with the medicinal product, it is strongly recommended to submit evidence demonstrating that the device is CE marked as part of the initial marketing authorisation application for the medicinal product and in any case, a CE mark is required prior to the adoption of the CHMP opinion.

Examples of medical devices used in the administration of medicinal products are nebulisers, drug delivery pump, and reusable injection pens (for additional examples refer to MEDDEV 2. 1/3 rev 3).

3.3.11.3. What do I need to consider in the electronic application form if my application for a medicinal product contains a medical device?

Applications for a MA containing one or more medical devices should complete section 2.2.4 of the current electronic application form. The applicant should indicate in this section if a medical device will

be submitted within the MAA and complete the relevant sections as required (e.g. address of Notified Body for devices which are CE marked). This applies both to medicinal products forming a single integral product with the medical device and to medical devices which do not form such an integral product with the medicinal product and require a CE mark.

References

- Medical Device Directive 93/42/EEC (MDD)
- Active Implantable Medical Device Directive 90/385/EEC (AIMDD)
- EC guidance on medical devices
- Guidance document – Scope, field of application, definition - Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative - MEDDEV 2.1/3 rev. 3
- Directive 2001/83/EC
- Regulation (EC) 726/2004
- Concept paper on developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product

3.4. Compliance, Environmental Risk Assessment and Pharmacovigilance

3.4.1. Which information do I need to provide in my marketing authorisation application regarding GCP inspections and GLP compliance? Rev. Sep 2015

Applicants are requested to provide the following information **as annexes to the Cover Letter** in their marketing authorisation applications:

GCP Inspections

A list of GCP inspection(s) conducted or planned by any regulatory authority at clinical trial sites for all clinical trials included in the dossier. In case of BE trials a list of the inspections conducted at the clinical and analytical facility where the study was conducted.

Alternatively, a confirmation that no inspections had been requested nor taken place and that no inspection are planned.

Please also refer to Q&A “When can I expect a pre-approval GCP inspection and how are they conducted?” for more information on GCP Inspections and the information to include in the application regarding GCP compliance.

GLP Compliance

A summary table, listing the non-clinical studies claimed to be GLP compliant and indicating for each study:

- study title,

- study code (*Unique identifier assigned to the study*),

- date of completion of the Final Report ,

- test facility and test sites in which the study was conducted,

- complete address of the test facility (and test sites where applicable),

- period in which the test facility(ies) and/or test site(s) was(were) used indicating if in that period they were part of an European Union (EU) or an Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data (MAD) accepted GLP monitoring programme.

Regarding GLP compliance, as per Notice to Applicant, Volume 2B, there should be a comment in Module 2.4 Nonclinical Overview and Module 2.6 Nonclinical Summary on the GLP status of the studies submitted in the application.

References

- The Rules governing Medicinal Products in the European Community, Volume 2B, Notice to Applicants, Common Technical Document
- GCP inspections template
- GLP compliance

3.4.2. When do I have to submit an Environmental Risk Assessment (ERA)? Rev. Oct 2014

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 for medicinal products for human use.

The environmental risk assessment (ERA) concerns the risks to the environment arising from the use, storage, and disposal of the medicinal product. Risks arising from the synthesis or manufacture of the product are under the remits of the national competent authorities.

The ERA follows 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 applies to the aquatic compartment ($PEC_{SURFACEWATER}$). If the $PEC_{SURFACEWATER}$ 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 and in the related “Questions and Answers on Guideline on the environmental risk assessment of medicinal products for human use” document.

An ERA is required for all new MAAs for a medicinal product through a centralised, mutual recognition, decentralised and national procedure including applications submitted under Article 10 of the mentioned directive.

The ERA, including the relevant study reports, should be provided in module 1.6 of the MAA together with the dated signature of the author, information on the author’s educational, training and occupational experience (curriculum vitae) and a statement of his or her relationship with the applicant.

In the case of medicinal products containing natural substances e.g. vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids and of vaccines and herbal medicinal products, a justification for not submitting ERA studies should be provided in module 1.6.

In case of an existing marketing authorisation, a re-evaluation of the ERA should be submitted with the application for type II variations or for extension applications.

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

Studies in the context of an ERA are expected to be assessed during the initial marketing authorisation or relevant post-marketing procedures (e.g. extension of indication, extension applications). In the exceptional case that ERA study results are provided stand-alone, they should be submitted as a type IB C.1.z variation as described in the Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure.

References

- Directive 2001/83/EC as amended
- Guideline on the Environmental Risk Assessment of the medicinal products for human use
- EudraLex – Volume 2 – Pharmaceutical legislation: Notice to applicants and regulatory guidelines medicinal products for human use
- Questions and answers on the Guideline on the environmental risk assessment of medicinal products for human use
- Practical questions and answers to support the implementation of the variations guidelines in the centralised procedure

3.4.3. What are the requirements for my pharmacovigilance system? Rev. Jan 2016

3.4.3.1. Requirements regarding the summary of the pharmacovigilance system

Applicants for marketing authorisation are required to provide a summary of their pharmacovigilance system, in accordance with Article 8(3) (ia) of Directive 2001/83/EC, which they will introduce once the authorisation is granted.

The requirement for the summary of the pharmacovigilance system was introduced by the new pharmacovigilance legislation (Directive 2010/84/EU amending, as regards pharmacovigilance, Directive 2001/83/EC).

The summary of the pharmacovigilance system should be provided in Module 1.8.1 of the application for marketing authorisation and includes the following elements:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
- the Member States in which the qualified person resides and carries out his/her tasks,
- the contact details of the qualified person,
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC,
- a reference to the location where the pharmacovigilance system master file (PSMF) for the medicinal product is kept.

The applicant may combine this information in one single statement using the required statement as per Article 8(3)(ia) of Directive 2001/83/EC regarding the obligation to have the necessary means to fulfil the tasks and responsibilities listed in Title IX (Pharmacovigilance). Such statement should be signed by an individual who can act on behalf of the legal entity of the applicant/MAH and by the

qualified person responsible for pharmacovigilance (QPPV). The title, role and responsibility of each individual signing the statement should be clearly specified in the document.

The summary of the pharmacovigilance system is specific to each marketing authorisation application as per legislation and therefore should be signed by the relevant applicant/MAH.

Applicants are required to include a summary of the applicant's pharmacovigilance system at the time of submission of an initial marketing authorisation application (MAA).

The requirement for the summary of the pharmacovigilance system is the same for any marketing authorisation application, independent of the legal basis for the application.

3.4.3.2. Requirements regarding the pharmacovigilance system and pharmacovigilance system master file

The MAH has to operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks.

The pharmacovigilance system master file (PSMF) is a detailed description of the pharmacovigilance system used by the MAH with respect to one or more authorised medicinal products.

The PSMF is not part of the marketing authorisation (MA) dossier and is maintained independently from the MA. It should be permanently available for inspection and should be provided within 7 days to the Competent Authorities if requested. The PSMF must be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the QPPV operates. The QPPV has to both reside and operate in the Union.

Applicants are required, at the time of initial MA application, to have in place a description of the pharmacovigilance system that records the system that will be in place and functioning at the time of granting of the MA and placing of the product on the market. During the evaluation of a MA application the applicant may be requested to provide a copy of the PSM for review.

The PSM has to describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.

The pharmacovigilance system will have to be in place and functioning at the time of granting of the MA and placing of the product on the market.

3.4.3.3. Subcontracting pharmacovigilance activities

The MAH may subcontract certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file (PSMF).

The MAH will have to draw up a list of its existing subcontracts between himself and the third parties, specifying the product(s) and territory(ies) concerned.

When delegating any activities concerning the pharmacovigilance system and its master file, the MAH retains ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF and its provision to competent authorities upon request. Detailed written agreements describing the roles and responsibilities for PSMF content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.

For more guidance on the requirements for pharmacovigilance system and PSMF, please refer to the relevant Good Pharmacovigilance Practice (GVP) Modules.

3.4.3.4. Pharmacovigilance system master file number (PSMF)

Applicants are encouraged to request a PSMF number (MFL EVCODE) in advance of the marketing authorisation application.

If available, the PSMF number (MFL EVCODE) assigned by the extended EudraVigilance Medicinal Product Dictionary (XEVMPD) should be included in the statement in Module 1.8.1. However this information is not part of the compulsory elements as per Article 8(3)(ia) of Directive 2001/3/EC.

For more information on how to obtain a PSMF number, please refer to the Detailed Guidance on electronic submission of information on medicines.

3.4.3.5. Is it mandatory to enter and maintain the Location of the Pharmacovigilance System Master File in the XEVMPD? If so, how do we enter this information in the XEVMPD? Jan 2016

At the time of marketing authorisation application (MAA), the applicant should submit electronically the PSMF location information using the agreed format as referred to in chapter IV, Article 26, paragraph 1(a) of the Commission Implementing Regulation (EU) No 520/2012, and subsequently include in the MAA, the PSMF number (MFL EVCODE), which is the unique code assigned by the Eudravigilance (EV) system to the master file when the EudraVigilance Medicinal Product Report Message (XEVPRM) is processed.

Once the marketing authorisation is granted, the PSMF will be linked by the marketing authorisation holder to the EudraVigilance Medicinal Product Dictionary (XEVMPD) product code(s). Master File Location (MFL) EVCODE should be the same for all authorised medicinal products covered by the same pharmacovigilance system and described in the same pharmacovigilance system master file declared at the one location within the European Union.

Following the initial MAA submission, marketing authorisation holders shall electronically notify to the Agency any amendments to the QPPV and PSMF location information by updating the Art 57 database (please refer to Question “How to inform the authorities of a change in the summary of the pharmacovigilance system?” in the Pharmacovigilance system section of the post-authorisation guidance).

3.4.3.6. Is the information on the Deputy QPPV required as part of the summary of the pharmacovigilance system? Jan 2016

No, the information on the deputy QPPV is not within the required information to be included in the summary of the applicant’s pharmacovigilance system, as per Article 8(3)(ia) of Directive 2001/83/EC. According to the legislation and guidance in GVP Module I, as part of the pharmacovigilance system, the marketing authorisation holder shall have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU (QPPV). Therefore back-up procedures in case of absence of the QPPV shall be in place. The QPPV should ensure that the back-up person has all necessary information to fulfil the role. The information relating to the QPPV provided in the PSMF shall include details of back-up arrangements to apply in the absence of the QPPV.

3.4.3.7. Is there a PSMF template? Jan 2016

There is no specific “PSMF template”. The structure and content of the PSMF as well as its maintenance are prescribed in Commission Implementing Regulation (EU) No 520/2012 and in GVP Module II.

3.4.3.8. Pharmacovigilance System Master File location: can the server of the Pharmacovigilance System Master File be physically located and administered outside EU if it is validated and operational/accessible 24/7 for EU markets and EU QPPV? Jan 2016

According to Article 5(3) of Commission Implementing Regulation (EU) No 520/2012, the pharmacovigilance system master file may be stored in electronic form provided that the media used for storage remain readable over time and a clearly arranged printed copy can be made available for audits and inspections.

In addition, Article 7 of Commission Implementing Regulation (EU) No 520/2012 clarifies that:

1. The pharmacovigilance system master file shall be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the qualified person responsible for pharmacovigilance operates.

2. The marketing authorisation holder shall ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.

3. The pharmacovigilance system master file shall be permanently and immediately available for inspection at the site where it is kept.

4. Where the pharmacovigilance system master file is kept in electronic form in accordance with Article 5(3), it is sufficient for the purposes of this Article that the data stored in electronic form is directly available at the site where the pharmacovigilance system master file is kept.

3.4.3.9. What information will be made public on the EU web-portal regarding pharmacovigilance contact details and PSMF locations? Will details of the QPPV be made public? Jan 2016

Article 26(1)(e) of Regulation (EC) No 726/2004 places the responsibility on the EMA, in collaboration with Member States, to make public, at least, a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products for human use authorised in the Union. On this basis:

Pharmacovigilance enquiries

EMA will publish contact information for pharmacovigilance enquiries from the data submitted under Article 57(2) of Regulation (EC) No 726/2004, as follows:

- email address for pharmacovigilance enquiries (Art 57(2) data field AP.7 enquiryemail)
- phone number for pharmacovigilance enquiries (Art 57(2) data field AP.8 enquiryphone)

Location of PSMF

EMA will publish the locations in the Union where pharmacovigilance system master files are kept, from the data submitted under Article 57(2) of Regulation (EC) No 726/2004, as follows:

- Code assigned to the PSMF (Art 57(2) data field MF.2 ev_code)
- Company name (Art 57(2) data field MF.3 mflcompany)
- PSMF location country code (Art 57(2) data field MF.10 mflcountrycode)

No information on the QPPV will be published by the EMA unless it is the same as that listed above (Art 57(2) XEVMPD data fields AP.7, AP.8, MF.2, MF.3, or, MF.10).

References

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- Directive 2010/84/EU
- Commission implementing Regulation No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council
- European Commission Question on transitional arrangements concerning the entering into force of the new pharmacovigilance rules provided by Directive 2010/84/EU amending Directive 2001/83/EC and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (SANCO/D5/FS/(2012)1014848)
- HMA-EMA Questions and answers on practical transitional measures for the implementation of the pharmacovigilance legislation (EMA/228816/2012 – v.3)
- Guideline on good pharmacovigilance practices - Module I – Pharmacovigilance systems and their quality systems (EMA/541760/2011)
- Guideline on good pharmacovigilance practices - Module II – Pharmacovigilance system master file (EMA/816573/2011)
- EMA Post-Authorisation Guidance regarding the pharmacovigilance system
- Detailed Guidance on electronic submission of information on medicines

3.4.4. What is Eudravigilance? How will it apply to my marketing authorisation? Mar 2009

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.

3.5. Risk Management Plan (RMP)

3.5.1. When should I submit my RMP? Rev. Dec 2017

A RMP shall be submitted **for all initial marketing authorisations applications irrespective of its legal basis**. However, in certain circumstances, certain parts or modules of the RMP may be omitted, unless otherwise requested by the competent authority. Specific details can be found in Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems Rev 2, paragraph V.C.1.1. Applicants are generally encouraged to contact the EMA prior to submitting new applications to discuss RMP related questions.

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

Whether or not the scientific advice procedure has been used, discussion on any questions relating to the RMP (safety concerns or pharmacovigilance activities) for a medicinal product seeking a new/extension of an authorisation through the centralised procedure should take place at the pre-submission meeting.

3.5.2. What are the requirements for a RMP for a new application of an established generic product? Rev. Jun 2016

See the same question under EMA Procedural advice for users of the centralised procedure for generic/hybrid applications.

3.5.3. If there is no RMP in place for a reference medicinal product, how should module SVIII "summary of the safety concerns" be populated for a generic medicinal product? Rev. Jun 2016

See the same question under EMA Procedural advice for users of the centralised procedure for generic/hybrid applications.

3.5.4. Do I need to submit an RMP for my traditional herbal medicinal product?

The submission of a RMP is not required for an application for a traditional–use registration.

For other herbal medicinal products not falling within the scope of the traditional-use registration, an RMP will be required for any initial marketing authorisation applications.

3.5.5. How shall I present my RMP? Rev. Dec 2017

Guidance on the format and content of the RMP as outlined in GVP module V and RMP template is available in the Pharmacovigliance section of the Agency's website. The submitted RMP should follow the RMP template and guidance.

The RMP should be provided in CTD section 1.8.2.

RMP versions submitted for assessment should be version controlled and dated.

All parts and modules of the RMP should be submitted in one single PDF-file so that a complete RMP is provided to the Agency.

3.5.6. What template should I use for the RMP submission? NEW Dec 2017

Depending on the MA application submission date or procedural step, either the Revision 1[6] or the Revision 2 version[7] of the Guidance on format of the risk-management plan in the European Union should be used including for generics. The Rev. 2 version is also applicable to generics as it includes specific guidance to generics. The transitional arrangements for the RMP submission are presented in the table below:

RMP submission with:	01.10.2017 – 30.03.2018	On and after 31.03.2018
Initial submission of an initial marketing authorisation application (MAA)	Only Rev.2	Only Rev.2
Responses to D120 LOQ MAA	Only Rev.2	Only Rev.2
Responses to D180 LOI MAA	Rev.1 or Rev.2	Only Rev.2
Responses to D90 LOQ MAA – accelerated assessment	Rev.1 or Rev.2	Only Rev.2

[6] RMP Template EMA/465932/2013 Rev.1
[7] RMP Template EMA/PRAC/613102/2015 Rev.2

RMPs submitted using Rev. 1 of the template instead of Rev. 2 will not be rejected at validation of the application, but will automatically trigger an outstanding issue; applicants and MAHs will be required to update the RMP using the Rev.2 of the template and submit as part of the responses to the LOQ/LOI.

3.5.7. When and how will the RMP summary be published? Rev. Dec 2017

All RMPs using the *Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (Rev. 2)* will have the RMP Summary published after the adoption of the Commission Decision grating the MA.

The RMP Summary will be reviewed during the initial marketing authorisation application procedure under RMP Part VI, and will be approved as part of the agreed RMP.

Post-opinion, the MAH will be asked to add in the Summary the link to the EPAR summary landing page (provided by EMA in the Letter to Applicant), to extract the RMP summary as a stand-alone PDF document, and to send it via EudraLink to the EMA. The PDF document should not contain meta-data, headers or footers related to the overall RMP document, nor excessive formatting.

The extracted PDF RMP Summary will be published on the EMA website, on the product's page (EPAR summary landing page).

3.5.8. Should I provide documents with tracked changes highlighted to facilitate review? Rev. Sep 2015

Only clean versions of documents in PDF format should be managed within the eCTD lifecycle.
If additional formats are required by any authority to facilitate the assessment (e.g. tracked changes versions for SmPCs, Risk Management Plans or other documents as specified by the agency), these should be provided in Word formatin the separate folder 'XXXX-working documents'. Further details can be found in section 2.9.9 of the TIGes Harmonised Guidance for eCTD Submissions in the EU.

3.5.9. Should I include study progress reports in the Pharmacovigilance Plan summary tables of the RMP? Rev. Dec 2017

The purpose of specifying study milestones in the Pharmacovigilance Plan in the RMP is to track due dates when new information relevant to the benefit-risk balance of the product will be available. Study progress reports milestones should be included in the Pharmacovigilance Plan summary tables only in agreement with and at the request of the competent authorities, as part of the evaluation of the RMP.

3.5.10. Should I include all of my ongoing studies in the RMP? Rev. Dec 2017

Only studies related to proposed safety concerns in the RMP should be included in the Pharmacovigilance Plan (RMP Part III).

Studies in the PIP should not be routinely included in the pharmacovigilance plan. The aim here is to allow the safety concern to be investigated, not to provide studies reflecting the development plan for a paediatric indication. Where use in children results in a safety concern, it may be appropriate to include individual activities aimed at providing further safety information in the pharmacovigilance plan (e.g. follow up forms).

3.5.11. How is the assessment of an educational program as additional risk minimisation handled? Rev. Dec 2017

The description of the educational program is included in *RMP V.2. Additional Risk Minimisation Measures* and the key messages of the educational materials are included in *RMP Annex 6*, and will be assessed as part of the MA application and will be reflected in the Annex II.D of the marketing authorisation for centrally authorised medicinal products. Review of the educational materials incorporating these key elements is done at the Member State. Further guidance for the implementation of the educational material at national level can be found in GVP Module XVI addendum I – Educational materials.

3.5.12. Can the internet be used as additional risk minimisation measure (e.g. website with educational materials or videos)?

Use of websites should not be proposed in the RMP as a means of communicating information on additional risk minimisation measures. Mention of a specific medicinal product on a website is regarded as promotional in some Member States and may not be permissible. However, in some Member States it is possible that use of the internet may be permitted as part of the national communication plan agreed at Member State level.

3.5.13. How will my RMP be reviewed? Rev. Dec 2017

The CHMP and the PRAC will be involved in the RMP assessment performed during the initial MA procedure. The CHMP will focus its evaluation of the RMP on the safety specifications in light of the assessment made on the quality, safety and efficacy of the product while the PRAC will focus its evaluation on the prospective planning aspects i.e. the pharmacovigilance plan and risk minimisation measures.

The PRAC will issue a separate assessment before Day 120 and any comments and questions will be integrated in the CHMP AR and the Day 120 List of Questions. Thereafter the PRAC assessment will be integrated in a joint CHMP-PRAC assessment report..

See also question ”How shall my procedure be evaluated?”.

3.5.14. Can I submit after the opinion a version of the RMP to reflect the last minute changes made during the CHMP? Rev. Dec 2017

As a matter of principle the day of the CHMP Opinion is the last opportunity for the MAH to provide an updated version of the RMP (in word format) for agreement. The same RMP version with the same version number – without any additional changes - can thereafter be submitted as part of a formal eCTD closing sequence post-opinion. No additional changes can be introduced to the RMP post-opinion. Any update of the RMP to address issues identified post-opinion should be submitted, through the appropriate variation, once the Commission Decision granting the MA has been issued.

3.5.15. When should I submit the RMP Annex 1 to EudraVigilance? NEW Dec 2017

The RMP Annex 1 should always be submitted following the granting of a marketing authorisation. It should reflect the final version of the RMP as agreed at the time of the CHMP Opinion

The electronic submission to EMA is due within 30 calendar days after the publication of the European Commission Decision.

The RMP Annex I should be sent via Eudralink to h-eurmp-evinterface@ema.europa.eu.

Further detailed information is available on the EMA website.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Commission implementing Regulation No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities
- Guideline on good pharmacovigilance practices – Module V – Risk Management Systems
- RMP template
- GVP Module XVI addendum I – Educational materials

4. *Submission, validation and fees*

4.1. How and to whom should I submit my dossier? Rev. Aug 2017

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 of submission

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 an invalid Technical Validation the submission will not be accepted.

The latest version of the ICH M2 eCTD specification can be found at http://www.ich.org/products/electronic-standards.html, 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 or the eSubmission website with related documents.

Where applications are amended during the agency's review, such as responses to the lists of questions or a withdrawal, a new or consolidated eCTD sequence should be provided in order to maintain the eCTD life-cycle. Replacement sequences of a previously submitted eCTD application (e.g. following corrections) are not acceptable. Any modification of an eCTD application must be reflected in a new eCTD sequence.

For further information regarding the e-submission requirements in the context of the Centralised Procedure, please refer to the TIGes Harmonised Guidance for eCTD submissions.

From 1 July 2015, the use of the electronic Application Forms (eAFs) is mandatory for the Centralised Procedure. The EMA strongly recommends the use of a single electronic application form per submission, even if the submission concerns multiple strengths/pharmaceutical forms.

Information on the electronic Application Form electronic application form can be found on the eSubmission eAF webpage.

Cover letter

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).

Please refrain from sending additional and separate copies of cover letters as they will create delays in processing.

Product Information (PI)

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 eSubmission Gateway / eSubmission Web Client package within a folder called “xxxx_working documents”, where the number (xxxx) equals the sequence number.

Active Substance Master File (ASMF)

In cases where an Active Substance Master file (ASMF) exists, the applicant should ensure that the Active Substance Master File is or has been submitted by the ASMF holder to the Agency, (see also question "How should I submit an active-substance master file (ASMF)?), in order to proceed with the validation of the dossier. For submission requirements please refer to the “Dossier Requirements for referral, ASMF and NAP submissions (PASS107, Workshare, Signal Detection procedures) and ancillary medicinal substances in a medical device” document.

Submission to the EMA

From 1 March 2014 the use of the eSubmission Gateway or Web client is mandatory for all electronic Common Technical Document (eCTD) submissions through the centralised procedure. The European Medicines Agency (EMA) no longer accepts submissions on CD or DVD. This applies to all applications for human medicines.

More information on how to register and connect to the Gateway / Web Client can be found in the eSubmission website and detailed information on the required naming conventions and file formats can be found in the European Medicines Agency eSubmission Gateway: Questions and answers relating to practical and technical aspects of the implementation and the eSubmission Gateway web client: Guidance for applicants. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD or via CESP as this might lead to delays in the handling of applications.

An automated ‘acknowledgement’ e-mail is sent from the system confirming whether their submission has passed the relevant technical validation criteria and has been uploaded to the agency’s review tool and made available via the Common Repository. Applicants must not send any accompanying hard media or separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

Submission requirements for the different Committee (Co-) Rapporteurs

Submissions sent to EMA via eSubmission Gateway/Web Client will be considered delivered to all National Competent Authorities’ representatives and alternates. This will apply to all types of Human Centralised Procedure eCTD submissions, including PMF submissions and ASMF submissions related to centrally authorised products submitted in eCTD format.

For ASMF submission requirements refer to the document “Dossier Requirements for referral, ASMF and NAP submissions (PASS107, Workshare, Signal Detection procedures) and ancillary medicinal substances in a medical device”.

For a full overview of the submission requirements for the different Committee (Co-)Rapporteurs see: Dossier requirements for Centrally Authorised Products (CAPs).

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

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 to supply 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 (Co-)Rapporteurs, if necessary in accordance with the published

document “Dossier requirements for Centrally Authorised Products (CAPs)”. In this case, the validation can only be completed after receipt and verification of the information submitted. The submission of responses to validation supplementary information (VSI) should be sent in accordance with eCTD requirements including validation supplementary information (VSI) related to the ASMF part of the dossier, when applicable.

In order to start the procedure by the targeted start date, the applicant is required to provide the information requested within a given deadline. If the applicant is unable to respond within the deadline, the Agency is able to accept the responses up to 2 months from the VSI letter. The published submission timetable applies. If no response is received within 2 months the validation outcome will be considered negative and the application closed followed by a charge of the administrative fee.

If the (Co-)Rapporteurs have not received their copy of the dossier and/or supplementary validation information – for those procedures for which the Common Repository is not used for - on the day the dossier is validated by the Agency, the start of the procedure may be delayed until the procedural starting date of the next month. Please see “Dossier requirements for referral, ASMF and NAP submissions (PASS107, Workshare, Signal Detection procedures) and ancillary medicinal substances in a medical device”.

Submission requirements for the other Committee members

After validation of the application, the Agency will notify the applicant accordingly in writing. The same notification will also be sent to the (Co-)Rapporteurs.

All NCAs have access to centrally authorised product submissions directly via the Common Repository after submission to the Agency. Please refer to the “Dossier requirements for Centrally Authorised Products (CAPs)” document to see if an electronic copy should also be sent to other Committee members after the validation phase for evaluation, to maintain the life cycle of the eCTD dossier.

References

- The Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2B, Electronic Technical Document (eCTD)
- Official Website for ICH
- eSubmission Website
- eSubmission Gateway and the Web Client
- Electronic Application Form
- Common Repository website
- Dossier requirements for centrally authorised products
- Dossier Requirements for referral, ASMF and NAP submissions (PASS107, Workshare, Signal Detection procedures) and ancillary medicinal substances in a medical device
- The EU Harmonised Technical eCTD Guidance

4.2. What are the names and addresses of the Committee members?

Please see the names and addresses of the Committee members in the Q&A “What are the names and addresses of the CHMP members?” on the EMA website.

4.3. How are initial marketing authorisation applications validated at EMA?

Initial marketing authorisation (MA) applications submitted to the European Medicines Agency (EMA) as part of the centralised procedure are subject to a validation process. The objective is to make sure all essential regulatory elements required for scientific assessment are included in the MA application prior to the start of the procedure. Initial MA validation has been centralised and is now being performed by a dedicated service within the Agency.

There are two elements to validation:

- The first is technical validation which takes place once an electronic application has been received by the Agency. This ensures that the structure of the submission is compliant with the EU Module 1 Specification.
- The second element is regulatory and administrative content validation, which can only commence once the application has successfully passed technical validation.

4.3.1. What to expect once an Initial Marketing Authorisation Application has been submitted to the EMA?

Once submitted to the European Medicines Agency in the agreed standard format, the Agency performs a technical validation. The outcome of this technical validation is immediately notified to the applicant when the application is received via eSubmission / Web Client.

If the dossier is technically invalid and the replacement sequence is not delivered by the intended submission deadline, the start of the procedure is automatically postponed to the next month, as only technically valid and complete applications can be subject to the validation process. This also applies to the Active Substance Master File (ASMF) submissions (see “How to avoid most common quality validation issues – Active Substance Master File (ASMF)”).

The Agency will inform the applicant of the start of the regulatory and administrative content validation.

If any issues are found during validation then the Agency will issue a Validation Supplementary Information (VSI) request to the applicant. Applicants will have to respond to this request in order to resolve any validation issues before the procedure can start. Any response to this VSI request has to be sent as a new sequence.

The Agency will communicate to the applicant the outcome of the validation. A positive outcome means that the scientific evaluation will start on the next available starting date according to the Agency timetables and the applicant will be invoiced the relevant fee. A negative outcome means that the applicant will have to re-submit a new application and will be invoiced a negative validation administrative fee.

4.3.2. What are the potential scenarios when validating an Initial Marketing Authorisation Application?

There are four potential scenarios:

4.3.2.1. Scenario one (valid first time, no supplementary information requested)

- The applicant submits a complete application according to the Agency’s guidance (see below: *What are the main principles that my application should follow in order to pass validation successfully*?)

- The Agency does not require any additional information.
- The Agency will confirm the positive validation to the applicant via a positive validation letter.
- The scientific evaluation will start on the next available start date according to the EMA timetables.

4.3.2.2. Scenario two (validation supplementary information requested)

- The applicant submits an application that is not in accordance with the Agency's guidance (see below: *What are the main principles that my application should follow in order to pass validation successfully*?).
- The Agency will ask the applicant via a request for Validation Supplementary Information (VSI) to submit the additional information, clarifications or corrections.
- The applicant provides the above additional information within the validation timeline. If the additional information submitted is as requested, the Agency will confirm the positive validation to the applicant.
- The scientific evaluation will start on the next available start date according to the Agency timetables.

4.3.2.3. Scenario three (suspension of validation)

- The applicant submits an application that is not in accordance with the Agency's guidance. (see below: *What are the main principles that my application should follow in order to pass validation successfully*?).
- The Agency will ask the applicant via a request for Validation Supplementary Information (VSI) to submit the additional information, clarifications or corrections.
- However, if the additional information is not provided as requested and within the validation timeline, the validation will be suspended and the applicant informed accordingly. The applicant will have up to two months from the date of the initial Validation Supplementary Information (VSI) request to provide the additional information, clarifications or corrections.
- Within the two month period and according to the EMA timetables, the Agency will confirm the positive validation if all pending issues have been addressed otherwise a negative validation will be generated.

4.3.2.4. Scenario four (negative validation)

- In the case of non-compliance with applicable legal and regulatory requirements within the above mentioned 2 months, the Agency will issue a negative validation.
- In that case, the Agency will confirm the negative validation to the applicant via a negative validation letter and invoice the administrative fee.

4.3.3. What are the timelines of initial Marketing authorisation validation?

Validation takes place according to the Agency procedural timetable. Applications received on or before a quoted submission date will undergo validation by the Agency. The application must receive a positive validation outcome in order for a procedure to start on the next available start date.

4.3.4. What are the main principles that my application should follow in order to pass validation successfully?

The agreed standard format should be used. An eCTD structure according to the TIGes Harmonised Guidance for eCTD Submission should be sent and the format should strictly follow Volume 2B of the Notice to Applicants.

The use of the Electronic Application Form is mandatory as of 1 July 2015.

The application form and the different parts / modules of the dossier should be consistent (i.e. the composition is the same in the application form and in module 3 and SmPC).

4.3.5. How to avoid common validation issues? Rev. Dec 2017

Guidance on how to avoid common issues found during validation, can be found in the document 'Validation issues frequently seen with initial MAAs'.

4.4. What fee do I have to pay? Rev. Dec 2015

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.

The fee will become due on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 calendar days of the date of the said notification. After approximately 15 days an invoice will be sent to the applicants billing address held on the Agency's file.

The invoice will contain details of the product and type of procedure involved, the fee amount, the customer purchase order number associated with the procedures invoiced and financial information. Applicants requiring a purchase order number or similar references on the invoice are requested to clearly indicate it on the cover letter or application form accompanying the dossier. The Agency does not accept stand-alone notifications of purchase order numbers that are not associated with a dossier. Applicants not requiring a purchase order number on the invoice should also clearly state this in the cover letter. Applicants are requested to provide this information in the cover letter template.

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.

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

- Fees payable to the European Medicines Agency
- How to pay

4.5. What definition of strength is used for the calculation of fees? Rev. Dec 2015

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 "Fees payable to the EMA" and "Management of applications" – see question "How is an European Medicines Agency application number attributed?").

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 m^2, 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 m^2, 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
- Fees payable to the European Medicines Agency

4.6. When could a fee waiver/fee reduction be granted? Rev. Dec 2015

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.

Fees incentives for orphan medicinal products are automatically granted and sponsors of orphan medicinal products do not need to apply for such incentives. It should be noted that fee reductions can only be granted once a decision on orphan medicinal product designation has been adopted 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 the applicable fee reductions for an orphan medicinal product is provided in the Executive Director’s decision on fee reductions for designated orphan medicinal products (EMA/317270/2014).

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).

Deferral of the fee payable for the application for marketing authorisation or related inspections may also apply.

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 receive a written confirmation of fee incentive should address an e-mail to the EMA’s SME Office (sme@ema.europa.eu).

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. In such circumstances applicants should liaise with the Agency.

References

- Regulation (EC) No 141/2000
- Regulation (EC) No 2049/2005
- Commission Recommendation 2003/361/EC
- Fees payable to the European Medicines Agency
- Executive Director’s decision on fee reductions for designated orphan medicinal products (EMA/317270/2014)

4.7. How is an EMA application/procedure number attributed? Rev. May 2018

On receipt of a submission, details of the product/procedure are entered into a tracking database which attributes product and procedure numbers.

4.7.1. Procedures

The name and the active substance(s) of the product are the elements primarily used to identify marketing authorisation applications (MAA). 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. The EMA application number for CHMP Opinions under Article 58 of Regulation (EC) No 726/2007 are indicated by W for WHO e.g. EMEA/H/W/xxxxxx. EMA consultation procedures on an ancillary medicinal substance or an ancillary human blood derivative incorporated as an integral part in a medical device are sign marked with D for Devices e.g. EMEA/H/D/xxxxxx. This core number, which is provided after the submission of the initial application for Marketing Authorisation 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. A sequential number is also added for referral procedures affecting centrally authorised products (CAP). In addition, a unique four digit referral number will be assigned at the start of the procedure, in the order EMEA/H/A-xx(x)/xxxx/C/000xxx/00xx, where H stands for Human, A stands for the Article under which the referral procedure is initiated and the following four digits comprise the unique referral procedure number. The remaining identifiers are as defined above.

In the case of Periodic Safety Update Report Single Assessment procedures (PSUSA) the procedure number is the combination of the PSUSA acronym, the European Reference Data (EURD) unique ID and the applicable Data Lock Point (DLP) in YYYYMM format e.g. PSUSA/xxxxxxxx/YYYYMM. The PSUSA number is not sequential, the DLP being the only element that changes with each subsequent procedure. This procedure number will apply to both centrally and nationally authorised products in accordance with the EURD list, and does not include a reference to a specific product number as the procedure is substance specific.

The markers currently used are as follows:

Marker	Procedure	Example
/0000	First new application	EMEA/H/C/000789/0000
N/xxxx	Notification Art. 61(3)	EMEA/H/C/000789/N/0001
IA/xxxx	Type IA variation	EMEA/H/C/000789/IA/0002
IA_{IN}/xxxx	Type IA_{IN} variation	EMEA/H/C/000789/IA_{IN}/0003
IB/xxxx	Type IB variation	EMEA/H/C/000789/IB/0004
II/xxxx	Type II variation (regardless of procedural length)	EMEA/H/C/000789/II/0005

X/xxxx	Annex I application	EMEA/H/C/000789/X/0006
S/xxxx	Annual Re-assessment	EMEA/H/C/000789/S/0007
T/xxxx	Transfer of MA	EMEA/H/C/000789/T/0008
R/xxxx	Renewal of MA	EMEA/H/C/000789/R/0009
Z/xxxx	(Renewal of) Suspension of MA	EMEA/H/C/000789/Z/00010
IG/xxxx	Groups of Type IA/ IA_{IN} variations	EMEA/H/C/000789/IG/0011
/G	Grouping (The Agency's procedure number will reflect the highest type of variation in the group, with the addition of the suffix "/G").	EMEA/H/C/000789/II/0012/G (grouping of Type II + Type IB variations) EMEA/H/C/000789/IA_{IN}/0013/G (grouping of 2 or more Type IA and IA_{IN} variations) EMEA/H/C/000789/IB/0014/G (grouping of 2 or more Type IB variations) EMEA/H/C/000789/X/0015/G (grouping of Extension + Type II + Type IB variations)
WS	Worksharing	EMEA/H/C/000789/WS/0016
A-xx(x)/xxxx	Procedures under Articles 5(3), 20, 31, 107i of the Directive 2001/83/EC	EMEA/H/A-xx(x)/xxxx/C/000789/0017
PSUSA/xxxxxx/YYYYMM	PSUR Single Assessment procedure	EMEA/H/C/PSUSA/12345678/201509 (CAP) PSUSA/12345678/201509 (NAP)

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

The procedure numbers are allocated by the EMA upon submission. The procedure number will be assigned by the EMA only upon receipt of an eCTD application. Once this number has been assigned (e.g. EMEA/H/C/00xx/IB/xxxx), it must be quoted in all follow-up correspondence during and after the procedure (e.g. responses to EMEA/H/C/00xx/IB/variation number).

For PSUSA procedures the numbers are located in the EURD list and should already be included in the initial PSUR submission by the Applicant.

For referral procedures the referral and CAP sequential numbers are assigned at start of the procedure. Once the numbers are assigned (e.g. EMEA/H/A-xx(x)/referral_number/C/product_number/next_sequence_number), they must also be quoted in all correspondence.

For further information please also refer to the EMA Post authorisation Guidance: 'What procedure number will be given to grouped variation applications?' and 'What procedure number will be given to variation applications under worksharing?'.

4.7.2. 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:

Procedure	Example	Numbers in Annex A
First new application	EMEA/C/H/000789/0000	EMEA/H/C/000789/0000/00**1** EMEA/H/C/000789/0000/00**2** EMEA/H/C/000789/0000/00**3**
A grouping containing a Type II variation creating three new presentations	EMEA/C/H/000789/II/0004	EMEA/H/C/000789/II/0004/00**4** EMEA/H/C/000789/II/0004/00**5** EMEA/H/C/000789/II/0004/00**6**
Annex II application creating a further three new presentations	EMEA/C/H/000789/X/0005	EMEA/H/C/000789/X/0005/00**7** EMEA/H/C/000789/X/0005/00**8** EMEA/H/C/000789/X/0005/00**9**

NB: 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. After the initial authorisation, subsequent presentation EU numbers are allocated by the EMA and are included in the Annex A of the relevant CHMP Opinion to the procedure recommending the approval of the new presentations.

5. *Assessment of the application*

5.1. Procedure

5.1.1. How long does it take for my application to be evaluated? Rev. Dec 2018

Once the application is validated, the EMA starts the procedure at the monthly starting date published on the EMA website. The submission deadlines and full procedural detailed timetables are published on the EMA website (see: "submission deadlines and full procedural timetables").

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 below standard timetable, which can be shortened in exceptional cases (see Request for accelerated assessment). It is important that applicants adhere to agreed timelines for the submission of responses. The HMA-EMA 'Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines' should be observed.

DAY	ACTION
1*	Start of the procedure
80	Receipt of the Assessment Report(s) from Rapporteur and Co-Rapporteur(s) by CHMP members (which includes the peer reviewers) and EMA. The CHMP Rapporteur will focus his evaluation of the RMP on the safety specifications. EMA sends Rapporteur and Co-Rapporteur Assessment Report 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.
94	PRAC Rapporteur circulates the RMP assessment report, focusing on the prospective planning aspects: pharmacovigilance plan and risk minimisation measures and proposed RMP LoQ. EMA sends also the PRAC Rapporteur AR to the applicant.
100	(Co-)Rapporteurs, other PRAC and CHMP Committee members and EMA send comments (including peer reviewers).
101-104 (step exceptionally applicable)	PRAC adopts PRAC RMP Assessment Overview and Advice for D120 LoQ (PRAC discussion and adoption of advice during the 1st assessment phase is only envisaged for a minority of applications such as ATMP, PUMA or products assessed under accelerated assessment).
107	The updated PRAC RMP AR & LOQ is circulated to the CHMP (Co)-Rapporteurs, peer reviewer, PRAC and EMA.
115	Receipt of draft list of questions (including the CHMP recommendation and scientific discussions), from CHMP (Co-)Rapporteurs, as discussed with the peer reviewers, together with the PRAC RMP Assessment Overview and Advice by CHMP members and EMA
120	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.

DAY	ACTION
	At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).
121*	Submission of the responses, including revised SmPC, labelling and package leaflet texts in English. Restart of the clock.

* 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:

DAY	ACTION
157	Joint Response Assessment Report from CHMP (Co-) Rapporteurs and PRAC Rapporteur received by CHMP, PRAC members and the EMA. There is no standalone PRAC Rapporteur AR on the RMP circulated at this stage. 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.
160	PRAC and CHMP Committee members and EMA send comments on the RMP assessment.
166	The PRAC Rapporteur presents the assessment on the prospective planning aspects of the RMP and the members' comments received at the PRAC plenary. The PRAC Rapporteur will then liaise with the CHMP (Co)-Rapporteurs to reflect the members' comments and the PRAC plenary discussion in the joint Assessment Report. PRAC adopts PRAC RMP Assessment Overview and Advice for D180 LoOI.
170	Deadline for comments from CHMP Members to Rapporteur and Co-Rapporteur, EMA and other CHMP members. The CHMP Rapporteur will integrate the various contributions and views in the draft List of outstanding issues.
180	CHMP discussion and decision on the need for adoption of a list of outstanding issues (LoOI) and/or an oral explanation by the Applicant. Submission of final inspection report to the EMA, Rapporteur and Co-Rapporteur by the inspection team (at the latest by day 180). CHMP adopts the LoOI as well as the overall conclusions and review of the scientific data to be sent to the Applicant by the EMA. Clock stop. If an oral explanation is needed, the clock is stopped to allow the Applicant to prepare the oral explanation.
181	Restart of the clock with submission of responses or oral explanation (if needed).
194	The CHMP (Co-) Rapporteur/PRAC Rapporteur assess the applicant's responses including the RMP aspects in a joint assessment report.

DAY	ACTION
	A PRAC discussion is not foreseen at this stage.
200	PRAC and CHMP Committee members and EMA send comments on the assessment report.
204	The updated AR is circulated to the PRAC and CHMP Committee members and EMA.
By 210	Adoption of CHMP Opinion + CHMP Assessment Report. Adoption of a timetable for the provision of product information translations

Upon adoption of the CHMP opinion, the Agency will inform the MAH within 15 days as to whether the CHMP opinion is favourable or unfavourable (including the grounds for the unfavourable outcome).

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

DAY	ACTION
215 at the latest	Applicant provides to the EMA the product information and Annex A in the 25 languages (all EU languages including Icelandic and Norwegian) and the "QRD Form 1" by Eudralink*.
229	Member States will send linguistic comments on the product information by e-mail with a copy to the EMA together with QRD Form 1
235 at the latest	Applicant provides EMA with final translations of SmPC, Annex II, labelling and package leaflet and Annexes IV and 127a if applicable in the 25 languages (+ "QRD Form 2" and "PDF checklist") by Eudralink.
237	Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland.
239-261	Draft Commission Decision Standing Committee Consultation
By 277	Finalisation of EPAR in consultation with Rapporteur, Co-Rapporteur, CHMP and Applicant (the latter for confidentiality aspects)
277	Final Commission decision

*By e-mail: qrd@ema.europa.eu

Re-examination

In accordance with Article 9(2) of Regulation (EC) No 726/2004, applicants may give written notice to the Agency that he wishes to request a re-examination within 15 days of receipt of the opinion. The grounds for the re-examination request must be forwarded to the Agency within 60 days of receipt of the opinion. Of note, the re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee adopted the initial opinion.

In case the applicant requests that a Scientific Advisory Group (SAG) is consulted in connection with the re-examination, the applicant should inform the Agency as soon as possible of this request.

The CHMP will appoint different CHMP (Co-)Rapporteurs, to co-ordinate the re-examination procedure. For advanced therapy medicinal products, different CAT (Co-)Rapporteurs will be assigned and if PRAC involvement is required, a new PRAC Rapporteur is appointed.

Within 60 days from the receipt of the grounds for re-examination, the CHMP will consider whether its opinion is to be revised. If considered necessary, an oral explanation can be held within this 60 days timeframe.

References

- Regulation (EC) No 726/2004
- Centralised Procedure, the Rules governing Medicinal Products in the European Community, Volume 2A, Notice to Applicants, Chapter 6
- The linguistic review process of product information in the centralised procedure – human (EMEA/5542/02)
- HMA-EMA 'Best practice guide on measures improving predictability of submissions/responses and adherence to communicated submission/responses deadlines'
- Re-examination procedural advice

5.1.2. What is the procedure for assessment similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products? Feb 2013

The assessment of similarity and, where applicable, of the derogation report vis-à-vis authorised orphan medicinal products will be conducted by the CHMP Rapporteur and Co-Rapporteur in charge of assessing the quality, safety and efficacy of your medicinal product.

This assessment of similarity is conducted in parallel to the evaluation of the application for marketing authorisation or extension of the marketing authorisation, as applicable, and normally follows a 60 day timetable. This assessment includes the consultation of the Quality Working Party or the Biologicals Working Party, as appropriate, for the aspects concerning the similarity of the molecular structures of the products.

Where necessary, a list of questions will be adopted by the CHMP on Day 60 and a timetable of 30 days applies, normally, for assessment of the responses to the questions raised.

Where the outcome of the CHMP assessment is that the medicinal products are considered similar, the applicant will be requested to provide a justification that one of the derogations in Article 8(3) is fulfilled. This assessment will follow also a 60 day timetable with a possibility for raising questions to the applicant.

Where the CHMP concludes that the application for marketing authorisation is not similar to an authorised orphan medicinal product or, if similar, that one of the derogations claimed by the applicant applies, this will not prevent the granting of the marketing authorisation / extension to the marketing authorisation, provided that the quality, safety and efficacy of the medicinal product are demonstrated.

Should the CHMP conclude that the product which is the subject of the application for marketing authorisation is considered similar to an authorised orphan medicinal product and none of the

derogations provided for in Article 8(3) of the Orphan Regulation applies, the CHMP will adopt an opinion recommending the refusal of the granting of the marketing authorisation/extension to the marketing authorisation, irrespective of the demonstration of the quality, safety or efficacy of the medicinal product.

References

- Regulation (EC) No 141/2000 on orphan medicinal products
- Regulation (EC) No 847/2000
- Guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

5.1.3. What is the CHMP peer review? Rev. Feb 2015

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

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500067952.pdf

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.

5.1.4. What is the QRD review of the product information? Rev. Jan 2006

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

5.1.5. What is the role of the EMA product team? Apr 2015

An EMA 'Product Team' is set up for each medicinal product submitted through the centralised procedure. The Product Team is responsible for providing support to the evaluation activities of the EMA scientific committees. In particular this includes:

- Provision of procedural guidance concerning all pre authorisation activities directly preceding the application and liaison with the (Co-)Rapporteurs in the conduct of such activities;
- Provision of advice to (Co-)Rapporteurs/committee members/applicant concerning all questions of a regulatory or procedural nature;
- Provision of advice to the applicant in the technical preparation of the marketing authorisation application and subsequent validation of such applications;
- In collaboration with the (Co-)Rapporteurs assessment teams production of the List of Questions, List of Outstanding Issues, draft summary of product characteristics to support committees discussion/adoption:
- Supporting the (Co-)Rapporteurs with regulatory, technical advice in briefing / debriefing / clarification meetings with applicants;
- To support planning and conduct of oral explanations, ad-hoc expert groups, referral to Working Parties, Scientific Advisory Groups etc;

- Managing the timeframe of the procedure to ensure it remains within legal timeframe;
- Co-ordinating the linguistic check of product information to ensure consistency and high quality;
- Informing the (Co-)Rapporteurs on elements of regulatory and scientific consistency of the application of quality, safety, efficacy and guidelines in the conduct of the evaluation procedure;
- To prepare the committee assessment report and subsequent Summary of Opinion (SMOP) and European Public Assessment Report (EPAR).

The Product Team is established during the pre-submission phase of the initial marketing authorisation application and is in place post-authorisation. It ensures oversight of all elements of product knowledge through the complementary contributions of the various team members. The composition of the team is adapted over time depending on the complexity of the product and procedure as well as the type of issues raised during the product's lifecycle. From an applicant's perspective the following team members are particularly relevant:

- the **procedure manager**, or **PM**, to oversee all aspects of the management of specific procedures. Procedure managers ensure regulatory consistency at EMA and are responsible for managing the regulatory process for each application. The PM is supported by the **procedure assistant (PA)** in terms of administrative and secretarial aspects.
- the **EMA product lead**, or **EPL**, to maintain oversight of a medicine as it moves through the different stages of its lifecycle.

The applicant will be notified of the appointed PM, including their contact details via the eligibility outcome letter and of the EPL in the CHMP Rapporteur appointment letter. Any subsequent change to the resource allocation for these functions will be communicated to the applicant/marketing authorisation holder.

Further team members assigned for each product are representing the functions of quality, risk management, labeling review and regulatory affairs. Specialised functions, like inspections and signal validation, will be involved as required.

Please see other relevant questions and answers in the EMA pre-authorisation guidance "Who is my contact at the European Medicines Agency during a marketing authorisation application (MAA) evaluation procedure?" and in the EMA post-authorisation guidance "Who is my contact at the European Medicines Agency during post-authorisation procedures?", "Who is my contact at the European Medicines Agency during an application procedure for extension of indication?" and "Who is my contact at the European Medicines Agency during the post-authorisation phase outside any evaluation procedures?".

5.1.6. Who is my contact at EMA during an application evaluation procedure? Apr 2015

In the context of an initial marketing authorisation application (MAA) evaluation in the centralised procedure, the procedure manager (PM) is the primary contact for the applicant prior to submission and throughout the procedure until the decision is granted by the European Commission.

The applicant will be notified of the allocated PM at time of confirmation of eligibility to the centralised procedure.

The PM will serve as the main liaison person between the EMA product team, the Rapporteurs and the applicant. The PM, in close co-operation with the EMA Product Lead (EPL) and the rapporteurs, will ensure that the applicant is kept informed of all aspects related to the MAA evaluation.

The applicant should contact the **PM** for all questions regarding the evaluation procedure, including

- Requests for guidance in the pre-submission phase, such as the pre-submission meeting;
- Any type of procedural questions during the evaluation, such as availability of assessment reports and Opinion documents;
- Discussion on timetables including requests for extension of clock-stops;
- Any question where guidance related to the evaluation procedure is needed; in such cases the PM will address or liaise and redirect as appropriate.

Questions concerning the validation of the MAA, once submitted, will be dealt with by an assigned Validation Officer.

At certain milestones during the evaluation procedure, the **EPL** will contact the applicant for a direct exchange to facilitate the discussion on the scientific evaluation. These include:

- Preparation and conduct of clarification meetings (where applicant requests such meeting);
- Immediate feedback regarding scientific aspects from committee plenary discussions, where required ;
- Expectations relating to the Oral Explanation, including topics to be addressed;
- Discussion of required post-authorisation measures;
- Late-stage revisions of the product information before adoption of the final Opinion.

These interactions occur in close co-operation with the Rapporteurs. Occasionally other members from the EMA Product team may contact the applicant directly to facilitate the discussion on specific aspects (e.g. quality, risk management, mock-up review).

Where the applicant is in direct contact with the EPL or another member of the EMA Product Team the PM should always be copied in the correspondence.

Please see other relevant questions and answers in the EMA pre-authorisation guidance “What is the role of the EMA product team?” and in the EMA post-authorisation guidance “Who is my contact at the European Medicines Agency during post-authorisation procedures?”, “Who is my contact at the European Medicines Agency during an application procedure for extension of indication?” and “Who is my contact at the European Medicines Agency during the post-authorisation phase outside any evaluation procedures?”.

5.1.7. How can I request a meeting with Rapporteurs to clarify the questions posed by the committee? May 2015

After the receipt of the adopted List of Questions or List of Outstanding Issues and prior to the formal submission of the responses, the applicant can request a clarification meeting with the (Co-) Rapporteurs (from CHMP, PRAC and/or CAT, as relevant) and the EMA (EMA Product Lead and other relevant team members as appropriate). The aim of these meetings is to provide clarifications and guidance to the applicant on the rationale for the Major Objections and/or other issues, and to discuss with the Applicants their response strategy and potential need to adjust the response timelines. Such meetings are intended to avoid the submission of inadequate, incomplete or premature responses potentially leading to prolongation of the procedure. It should be emphasised that these meetings are not intended to provide a pre-assessment of the intended responses. These meetings will usually take place via teleconference.

Applicants are advised to refer to “Guidance on meetings with applicants on the responses to questions received from EMA Scientific Committees during the evaluation within the centralised procedure” for further guidance.

References

- Guidance on meetings with applicants on the responses to questions received from European Medicines Agency Scientific Committees during the evaluation within the centralised procedure

5.1.8. What is an oral explanation and how is it conducted? Rev. May 2018

Oral explanations are intended to give opportunity to the applicant to explain their position and arguments. They are planned and organised by EMA when at Day 180 of the procedure there are still major objections preventing the EMA Committee from adopting a positive Opinion on the application. The need for an oral explanation is further discussed after the assessment of the responses to the Day 180 List of Outstanding Issues, confirmed by the relevant EMA committee and communicated to the applicant.

An oral explanation can also be requested by the applicant. It is important that applicants preparing for an oral explanation bear in mind that they are held to only allow clarification of the aspects relating to the outstanding issues.

When the applicant wishes to have the opportunity of an oral explanation, they should present a written request to the relevant committee. Such request should be sent to the EMA Procedure Manager.

Applicants are advised to refer to “Guidance to applicants / Marketing Authorisation holders on oral explanations at EMA” for practical guidance on preparation for and conduct of oral explanations. Applicants are also reminded that oral explanations are only held in English.

References

- Guidance to applicants /marketing authorisation holders on oral explanations at EMA

5.1.9. What type of post-authorisation measures can be requested at the time of the initial marketing authorisation? Nov 2015

At the time of opinion on an initial marketing authorisation application, the Agency’s Committee(s) may agree that the applicant/MAH should provide additional data post-authorisation, as it is necessary from a public health perspective to complement the available data with additional data about the safety and, in certain cases, the efficacy or quality of authorised medicinal products. Such post-authorisation measures (PAMs) are aimed at collecting or providing data to enable the assessment of the safety or efficacy of medicinal products in the post-approval setting.

The existence of such a system of PAMs does not aim at promoting premature approvals of marketing authorisations or post-authorisation procedures. The background and rationale for requesting PAMs will be described in the committee assessment report, which will present the context and nature of the PAM. PAMs are classified depending on their nature into the appropriate legal framework under which they will be enforced.

These measures may include, for example performing PASS (post-authorisation safety study) and PAES (post-authorisation efficacy study).

Such measures will be classified as follows:

- specific obligation
- annex II condition to the marketing authorisation
- additional pharmacovigilance activity in the risk-management plan (RMP)
- legally binding measure
- recommendation

Further details regarding PAMs, PASS, PAES can be found in the EMA post-authorisation procedural advice for users of the centralised procedure.

References

- EMA post-authorisation procedural advice for users of the centralised procedure

5.1.10. How are EU marketing authorisation numbers assigned? Feb 2013

The European Commission is responsible for assigning the EU main marketing authorisation number for new marketing authorisation (e.g. EU/1/04/276).

At the time of the adoption of a CHMP opinion for a new marketing authorisation, the Agency will liaise with the European Commission in order to include the EU sub-numbers for each presentation (e.g. EU/1/04/276/01, EU/1/04/276/02, etc.) in the Annex A of the medicinal product, which will be transmitted to the Marketing Authorisation Holder together with the CHMP Opinion and respective annexes.

The Marketing Authorisation Holder should include the assigned EU sub-numbers in all language versions of the Annex A and in all applicable sections of the product information, which are submitted following the CHMP opinion for linguistic review.

The inclusion of the EU sub-numbers in the Annex A transmitted to the Applicant is without presumption as to the outcome of the procedure, which requires the issuance of the Commission decision granting the marketing authorisation.

5.1.11. How and when can I withdraw my application? Rev. Dec 2015

If the applicant wishes to withdraw their application for marketing authorisation during assessment, it should inform the EMA Procedure Manager by providing a withdrawal letter stating that the applicant withdraws their application, specifying whether in full or partly (e.g. only a certain strength), and indicating reasons for the withdrawal.

The Letter should be signed by the authorised representative of the applicant. Applicants are advised that letters for withdrawal of marketing authorisation applications (in case of a full withdrawal) will be published on the EMA's website (after redaction of protected personal data).

Applicants can address the withdrawal request to the EMA at any point during the assessment (from validation of the application up until adoption of the final CHMP Opinion).

Of note, the Agency will charge the fee for the application at the start of the procedure, irrespective of its outcome (positive, negative or partial/full withdrawal) and publish information on withdrawn applications.

References

- Procedural advice on publication of information on withdrawals of applications related to the marketing authorisation of human medicinal products
- Fees payable to the European Medicines Agency

5.1.12. Can EMA assessment or inspection documents be shared with third parties?

Marketing Authorisation Holders (MAH) or applicants for centrally authorised products (CAPs) may share EMA assessment or inspection documents with third parties for their products.

This can be done, provided that the MAH/applicant assumes any and all liabilities for any disclosure, particularly with regard to the need to redact certain references in the documents where appropriate or legally needed (e.g. personal data of the assessor/inspector, quality and manufacturing commercial information). In all cases, including when the MAH/applicant redacts the Assessment Reports, they should ensure that the EMA is still recognised as the source of the original documents.

MAHs or applicants may request EMA to share directly assessment or inspection documents with regulators from authorities or organisations outside EU. In general EMA has no objections to share these documents. Confidentiality arrangements currently exist between EMA and the following international partners: US-FDA, Japan PMDA/MHLW, Health Canada, TGA Australia, Swissmedic and WHO. When MAHs/applicants request EMA to share assessment or inspection documents with non-EU regulators for which there is no Confidentiality Arrangement in place, they should consent to EMA sharing these documents.

EMA has developed a template to facilitate the MAH/applicant to give consent to EMA to share assessment and inspection documents, with non-EU authorities/organisations with whom there is no Confidentiality Arrangement in place. The template can be found here.

5.1.13. How can I change the applicant for an ongoing marketing authorization application? NEW Oct 2018

Changing the applicant for an ongoing MA application to a different entity is possible at certain procedural milestones in case the following requirements are met:

- For orphan medicinal products – the orphan designation has been transferred in advance of the change of applicant.
- The change of applicant will not create a 'duplicate application' to another pending application or authorised product, unless relevant authorisation from the European Commission is obtained (as per Article 82 of Regulation (EC) No 726/2004).

In order to request a change of the applicant, the following documents need to be submitted as part of responses to the Day 120 List of Questions or Day 180 List of Outstanding Issues:

- A letter requesting the change of applicant and signed by both the previous and the new applicant.
- Either a confirmation (as part of the cover letter) that this marketing authorisation application does not fall under the scope of a duplicate application as per Article 82 of the Regulation (EC) No 726/2004 or the relevant authorisation from the European Commission in case the application falls under the scope of a duplicate application as described above.
- A confirmation (as part of the cover letter) that the complete and up-to-date file concerning the medicinal product or a copy of this file (including any data/documents related to the paediatric obligations, if applicable) has been made available to or has been transferred to the new applicant.

- If applicable, a confirmation (as part of the cover letter) that the orphan designation has been transferred.
- An updated application form and its affected annexes (includes proof of establishment of the new applicant within the Union (EEA) issued in accordance with national provisions and which should be no older than 6 months).
- Updated product information.
- Updated mock-ups.
- Updated summary of the pharmacovigilance system master file (PSMF).
- Any other documents of the marketing authorisation dossier affected by the change of applicant, as relevant (e.g. an updated Letter of Access for an application that includes an Active Substance Master File).

In order to facilitate the process for the change of applicant, for the confirmations to be included in the cover letter the applicants are advised to use the standard statements in this template. In order to help ensuring that the requests to change the applicant are complete and correct, applicants are strongly recommended to use the published checklist and include the completed checklist in working documents of the respective submission.

The checkbox 'contains request for change of applicant' should be ticked in the eSubmission Gateway & eSubmission Web Client Delivery file user interface, as failure to do so may lead to significant delays in processing the change of applicant request.

As a consequence of a change of applicant, any fee invoiced since validation (i.e. fee for initial marketing authorisation and pre-authorisation inspection fee) will be credited to the original applicant and re-invoiced to the new applicant. This will include changes, if any, relating to micro, small or medium-sized enterprise applicants and orphan medicinal product designation.

Applicants are advised to liaise with the Procedure Manager as early as possible if a change of applicant is proposed.

5.2. Inspections

5.2.1. When can I expect a pre-authorisation GMP inspection and how are they conducted? Rev. Dec 2015

5.2.1.1. 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.

These guidelines are supplemented by a series of Annexes. Part III of the guide includes other related guidance.

Inspections will follow “The compilation of Community procedures on Inspections and exchange of information” which is published by EMA on behalf of the European Commission (http://www.ema.eu.int/Inspections/GMPhome.html).

5.2.1.2. Pre-submission notification

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

- The name 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, where this is applicable.
- Final manufacturing and batch release arrangements will have to be provided when submitting the application
- A description of the roles of all different sites involved. A flow chart is recommended for complex operations.

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 Union 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.

5.2.1.3. Submission

On receipt of the application, EMA reviews the information provided on the GMP status of the manufacturing sites involved and determines together with Rapporteur and co-Rapporteur whether to recommend that CHMP makes a request for inspection of the manufacturer of either the active substance or the medicinal product in order to complete the assessment. In addition an inspection request may be triggered by specific issues and questions raised during the assessment of the application.

The performance of these inspections by the EEA competent authorities will be co-ordinated by EMA.

5.2.1.4. Inspection Team

The inspection team will be drawn from the inspection services of the Supervisory and/or 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.

5.2.1.5. 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:

5.2.1.6. 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".

5.2.1.7. Manufacture of the Medicinal 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 by virtue of holding a manufacturing authorisation.

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, when 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.

5.2.1.8. Importing Site - Site located in the EEA

Importing sites in the EEA are required by the provisions of title IV 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.

5.2.1.9. 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 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 EMA will write 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.

5.2.1.10. 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.

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 EMA.

Inspectors will finalise the report and send it to EMA by Day 180 at the latest and the Rapporteur, Co-Rapporteur will receive a copy. In case of a non-satisfactory inspection outcome, a non-compliance statement may be issued and it will not be possible to have a positive opinion until the relevant issues have been resolved.

5.2.1.11. Documents for inspection

A site master file for use in preparing and carrying out the inspection will be necessary. The preferred format is given in Part III of the GMP guide and is the same as that recommended by the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The Applicant should supply this document directly to the Inspection Team when requested by it. The site master file is not required to be submitted to EMA.

5.2.1.12. Accelerated Assessment

In case a need for inspection is identified for an application under accelerated assessment, the inspection will be requested as early as possible. Please refer also to question “Is my product eligible for an Accelerated Assessment”.

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

5.2.2. When can I expect a pre-approval GCP inspection and how are they conducted? Rev. Dec 2015

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 Inspectors Working Group, composed of GCP 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 Procedure Manager, 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. In case a need for inspection is identified for an application under accelerated assessment, the inspection will be requested as early as possible. Please refer also to question "Is my product eligible for an Accelerated Assessment".

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.

Regarding the importance of GCP compliance for marketing authorisation applications, applicants/marketing authorisation holders are invited to refer to the EMA Position paper on the non-acceptability of replacement of pivotal clinical trials in cases of GCP non-compliance in the context of marketing authorisation applications in the centralised procedure.

References

- The Rules governing Medicinal Products in the European Community, Volume 2B, Notice to Applicants, Common Technical Document
- 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

5.2.3. What is the fee for a GMP/GCP/GLP pharmacovigilance inspection? Rev. Dec 2015

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.

For information on the level of fees applying, including cancellations please refer to the latest version of the Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures and the Explanatory note on fees payable to the European Medicines Agency (see references below).

The fee will become due on the date of the start of the on-site inspection and after approximately 15 days an invoice will be sent to the applicants billing address held on the Agency's file.

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.

References

- Fees payable to the European Medicines Agency
- How to pay