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Committee for Human Medicinal Products (CHMP)

European Medicines Agency procedural advice for users of the centralised procedure for generic/hybrid applications

This integrated version has been created for printing purposes only. Please refer to the individual Question & Answers as published under 'Pre-authorisation', 'Regulatory' section on the Agency's website for access to the hyperlinked information.

This document addresses a number of questions which users of the Centralised Procedure may have. It provides an overview of the EMA position on issues, which are typically addressed during the course of Pre-Submission interactions/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 Agency emphasises the importance of Pre-Submission interactions/meetings with applicants. Pre-Submission interactions/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 successful Pre-Submission interactions/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 interactions/meetings will also enable applicants to establish contact with the EMA staff closely involved with the application as it proceeds.

To obtain the information on a certain topic, simply click on the question. We trust that the information, linked to the question, answers most of your queries. However, since each application has its own particularities we strongly encourage applicants to ask for a Pre-Submission interactions/meeting.

Note:

It should be highlighted that this document has been produced for procedural advice only and should be read in conjunction with "The rules governing medicinal products in the European Union, Volume 2A, Notice to Applicants.

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Applicants must in all cases comply with all requirements of European Legislation. Provisions, which extend to European Economic Area (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.

The information provided in this document is specific for generic/hybrid applications. For general requirements, please refer to the "European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure".

Table of Content

1. Eligibility and reference product

1.1. *Is my generic or hybrid medicinal product eligible for evaluation under the Centralised Procedure? Rev. Aug 2019*

Regulation (EC) No 726/2004, creates a Centralised 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 European Union market. The types of products, which fall within the scope of the Regulation, are set out in Article 3 and the Annex to that Regulation.

For generic and hybrid medicinal products eligibility can be granted to the Centralised procedure as follows:

Generic/Hybrid medicinal product of a centrally authorised product:

Generic/hybrid medicinal product applications of medicinal products authorised via the Centralised procedure have automatic access to the Centralised procedure under Article 3(3) of Regulation (EC) No 726/2004

For generic/hybrid applications of a centrally authorised product, the applicant should state in their 'Letter of intention to submit' that they have automatic access to the Centralised procedure under Article 3(3).

Before submission of the dossier, applicants should notify the Agency of their intention to submit an application, preferably 6-18 months in advance (see Pre- Submission guidance on letter of intention and documentation) and indicate that the application is a generic/hybrid medicinal product application of a medicinal product authorised via the centralised procedure.

EMA will inform the applicant on the outcome of the eligibility request.

Generic/Hybrid medicinal product of a national/MRP/DCP product:

Generic/hybrid medicinal product applications of medicinal products authorised via the national/MRP/DCP procedure could, at the request of the applicant, be accepted for consideration under the centralised procedure, when the applicant shows that the medicinal product constitutes:

- a significant therapeutic, scientific or technical innovation, or
- the granting of a Union authorisation for the medicinal product is in the interest of patients at Union level.

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 Union level when

it addresses a specific health issue, allows access to medicines, or provides another type of contribution to patient care in the Union.

Before submission of the dossier, applicants should notify the Agency of their intention to submit an application, preferably 6-18 months in advance (see Pre- Submission guidance on letter of intention and documentation to submit and justify why the product should qualify for the eligibility for the centralised procedure, citing the relevant specific provision(s) of Regulation (EC) No 726/2004.

The Agency will inform the applicant on the outcome of the eligibility request.

Eligibility for duplicate marketing authorisations

The eligibility request should also be submitted for duplicate generic/hybrid marketing authorisations.

At the time of the request for eligibility, the name proposed by the applicant for the duplicate should be different from the name of the original generic/hybrid medicinal product.

References

- Regulation (EC) No 726/2004

1.2. *What is the so-called 'reference medicinal product' referred to in the application for a generic or hybrid medicinal product? Rev. Feb 2019*

The 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 and to which the application for marketing authorisation for a generic/hybrid medicinal product refers, by demonstration of bioequivalence, usually through the submission of the appropriate bioavailability studies.

Applicants will have to identify in the application form for the generic/hybrid medicinal product the reference medicinal product (product name, strength, pharmaceutical form, MAH, first authorisation, Member State/Union), as follows:

1. The medicinal product which is or has been authorised in the EEA, used as the basis for demonstrating that the **data protection period** defined in the European pharmaceutical legislation has expired (see Question 12). This reference medicinal product, identified for the purpose of calculating expiry of the period of data protection, may be for a different strength, pharmaceutical form, administration route or presentation than the generic/hybrid medicinal product.

2. The medicinal product, the dossier of which is **cross-referred** to in the generic/hybrid application (product name, strength, pharmaceutical form, MAH, marketing authorisation number). This reference medicinal product may have been authorised through separate procedures and under a different name than the reference medicinal product identified for the purpose of calculating expiry of the period of data protection. The product information of this reference medicinal product will, in principle, serve as the basis for the product information claimed for the generic/hybrid medicinal product.

3. The medicinal product (product name, strength, pharmaceutical form, MAH, Member State of source) used for the **bioequivalence study(ies)** (where applicable).

References

- Directive 2001/83/EC
- NtA, Volume 2A, Chapter 1
- NtA, Volume 2B, Module 1: Application form

1.3. *What should I consider if my reference medicinal product is an orphan medicinal product? Rev. Feb 2019*

If the reference medicinal product in support of your generic/hybrid application is an orphan authorised medicinal product, you will have to consider, in addition to the expiry of the data exclusivity (explained in Q&A "When can I submit my generic/hybrid application considering the protection period of the reference medicinal product?"), the expiry of the market exclusivity period for the reference medicinal product.

Article 8(1) of the Regulation (EC) No 141/2000 ("Orphan Regulation") provides for a 10 year period of market exclusivity for orphan medicinal products, during which Competent Authorities cannot accept applications for marketing authorisation for the same therapeutic indication in respect of a similar medicinal products. As explained in the Commission guideline on aspects of the application of Article 8(1) and 8(3) of Regulation (EC) No 141/2000, if the application concerns a generic medicinal product, similarity is assumed. Consequently, the application cannot be validated before the end of the period of market exclusivity unless justification is provided to support one of the derogations laid down in Article 8(3).

This 10-year period of market exclusivity can, however, be reduced to six years if, at the end of the fifth year, it is established that the criteria for orphan designation are no longer met (Article 8(2) of the Orphan Regulation) or extended to 12 years in case of compliance with a Paediatric Investigation Plan, in accordance with Article 37 of Regulation (EC) No 1901/2006 ("Paediatrics Regulation").

Therefore, irrespective of whether the reference medicinal product benefits from a period of data exclusivity of 10 or 8 years, it will not be possible to validate an application for a generic medicinal product before the end of the market exclusivity period for the reference medicinal product, unless justification is provided to support one of the derogations laid down in Article 8(3) of the Orphan Regulation.

The period of market exclusivity should be counted as starting from the date of notification of the marketing authorisation decision to the MAH, which can be found in the Official Journal of the European Union as well as in the Union register of medicinal products for human use on the European Commission website.

Applicants will also have to consider whether the reference medicinal product includes more than one designated orphan condition(s), as in such case a separate 10-year period of market exclusivity will apply for the orphan therapeutic indications granted for the separate orphan condition, starting on the date of the notification of the authorisation of the respective therapeutic indication(s). Therefore, these therapeutic indications can only be included in the proposed product information for the generic medicinal product after expiry of the respective period of market exclusivity, unless justification is provided to support one of the derogations laid down in Article 8(3) of the Orphan Regulation.

However, where the MAH of the reference medicinal product applies subsequently for another subset of the same designated orphan condition, the medicinal product will not benefit from any additional period of market exclusivity for that second authorised therapeutic indication.

References

- Regulation (EC) No 141/2000 on orphan medicinal products
- Regulation (EC) No 1901/2006
- Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products (2016/C 424/03)
- 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
- Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products
- Union register of medicinal products for human use

2. Steps prior to submitting the application

2.1. *What is the legal basis for my application? Rev. Jan 2021*

The legal requirements and the procedures for making an application for a marketing authorisation are set out in Directive 2001/83/EC and in Regulation (EC) No 726/2004.

For generic and hybrid applications the legal basis can be found in Article 6 of Regulation (EC) 726/2004 and Article 10 of Directive 2001/83/EC.

It should be noted that at the time of submission of the generic/hybrid application, the protection period of the reference medicinal product should have expired in order to allow the applicant to rely on the dossier of the reference medicinal product (see Q12)

Generic medicinal product

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 Union. The period of 8 years from initial authorisation of the reference medicinal product, providing a period of so-called "data exclusivity", applies only for reference medicinal products for which the marketing authorisation application has been submitted as of 30 October 2005 for MRP, DCP and national procedures and as of 20 November 2005 for centralised procedure according to the revised Union Legislation. (See question 'When can I submit my generic/hybrid application considering the protection period of the reference medicinal product?').

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

- the same qualitative and quantitative composition in active substance(s) 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.

Hybrid medicinal product

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 II of the Chapter 1 of the Notice to Applicants.

The type of applications mentioned above refer 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 Union on the basis of a complete dossier in accordance with article 8(3), 10a, 10b or 10c of Directive 2001/83/EC.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 1

2.2. *How will I know if the proposed (invented) name of my generic/hybrid medicinal product is acceptable from a public health point of view? Rev. Jan 2011*

For generic/hybrid medicinal products the same criteria apply as for any other medicinal products in respect to the acceptability of the proposed name by the name review group. Please see the EMA pre-submission guidance - "How will I know if the proposed invented name of my medicinal product is acceptable from a public health point of view?"

The use of a single name is also a requirement for generic/hybrid medicinal products regardless of whether the applicant/MAH wishes to use an invented name or a common name or scientific name, together with a trademark or the name of the Marketing Authorisation Holder.

It should be noted that the applicant/MAH will be required to identify the 'reference medicinal product' and the legal basis for submission of the application within the invented name notification.

The name review group should also be consulted where the applicant/MAH wishes to use the common or scientific name, together with a trademark or the name of the Marketing Authorisation Holder.

In such cases the Marketing Authorisation Holder should take into account the following rules:

- If an INN recommended by the World Health Organisation exists for the active moiety it should be used within the name of the medicinal product exactly as published without omissions or abbreviations. All the linguistic versions of the INN, including translations officially recognised at the national level, shall be considered to be the same name. If one does not exist, the usual common name should be used.
- If a Modified INN (INNM) recommended by the World Health Organisation exists for the active moiety, it should be used within the name of the medicinal product exactly as published without omissions or abbreviations.
- Where the active moiety is an unpublished INNM the name of the medicinal product should be that as agreed by users of INNs (pharmacopoeia, regulatory bodies, stakeholders), in accordance with the WHO INNM working document 05.167/3.
- The 'name of the MAH' within the name of the medicinal product should correspond to all or part of the official name of the MAH as presented in the proof of establishment of the applicant/MAH.

The requirement for a single name for a generic medicinal product of a reference medicinal product authorised through the Centralised Procedure applies also in case the generic medicinal product is authorised by Member States via the Mutual Recognition or Decentralised Procedure.

References

- Regulation (EC) No 726/2004
- Directive 2001/83/EC
- "Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure" (CPMP/328/98)
- Regulation (EC) No 1085/2003

2.3. *When and how are Rapporteur and Co-Rapporteur appointed? Rev. Mar 2013*

The principles outlined in Section 2 of the paper "CHMP Rapporteur/Co-Rapporteur appointment: principles, objective criteria and methodology" shall apply.

However, due to the particularities of generic/hybrid applications (e.g. legal basis, data requirements), the following principles shall be considered as regards the appointment of CHMP/PRAC Rapporteur/Co-Rapporteur 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.

Methodology on the appointment of Rapporteur/Co- Rapporteur and their assessment teams for Generic/Hybrid medicinal products

Normally, for generic applications the appointment procedure of the Rapporteur and her/his assessment team will be initiated at a CHMP meeting preferably 3-7 months prior to the MAA submission date, to allow the actual Rapporteur /Co-Rapporteur appointment 2-6 months prior to the MAA intended submission date. At the same time the PhV Rapporteur and PRAC Rapporteur will be identified.

Normally, for hybrid applications the appointment procedure of Rapporteur/Co-Rapporteur and her/his assessment teams will be initiated as early as 7 months prior to the MAA submission date, to allow Rapporteur /Co-Rapporteur appointment 6 months prior to the MAA intended submission date. At the same time the PhV Rapporteur and PRAC Rapporteur will be identified.

The methodological steps for the appointment procedure of Rapporteur/Co-Rapporteur (where relevant) and their assessment teams as outlined in Section 4.2 of the paper "CHMP Rapporteur/Co-Rapporteur appointment: principles, objective criteria and methodology" shall apply.

Re-examination of a CHMP opinion of a Generic/hybrid medicinal product

Legal Framework

- Article 62(1) of Regulation (EC) No 726/2004 of 31 March 2004 (fourth subparagraph).

The principles and the methodology on the re-examination of a CHMP opinion as outlined in Section 5.1 of the paper "CHMP Rapporteur/Co-Rapporteur appointment: principles, objective criteria and methodology" shall apply.

See web-link: EMA PRE-SUBMISSION GUIDANCE FOR USERS OF THE CENTRALISED PROCEDURE - List of questions

References

- Procedural advice on 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 of the European Parliament and of the Council, of 31 March 2004
- Directive 2001/83/EC and its Annex I
- Notice To Applicants, Volume 2A
- CHMP Rules of Procedure (EMEA/CHMP/111481/2004, adopted by the CHMP in September 2004)
- EMA Pre-submission Guidance for users of the centralised procedure
- EMA Post authorisation Guidance –Human Medicinal Products (EMEA/H/19984/03)
- Check of Expert for product evaluation (SOP/H/3022, EMEA/127437/2005) (procedure for inclusion of experts in the Expert DataBase)
- EMA policy on the handling of conflict of Interests for EMA Scientific Committees Members and Experts
- The EMA code of conduct

2.4. *How shall I present my Generic/Hybrid application (format)? Rev. Mar 2013*

Marketing Authorisation Applications for a generic/hybrid medicinal product should follow the structure of the CTD format, as for any other Marketing Authorisation Application. Specific requirements that such applications should fulfil are listed below:

Module 1

- Applicants should provide in Module 1.5.2 a concise document (up to approximately 5 pages), summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted, is:
- A 'generic' of a reference medicinal product (Art 10.1). This summary should include details on the medicinal product, its qualitative and quantitative composition in active substance(s), its pharmaceutical form and its safety/efficacy profile of the active substance(s) in comparison to the active substance(s) of the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned.

- A so-called 'hybrid' of a reference medicinal product (Art 10.3). This summary should include details on the medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned.
- EU Risk Management Plan.

All the other requirements of Module 1 apply also to generic/hybrid medicinal products with the exception of the paediatric requirements set out in Articles 7 and 8 of the Paediatric Regulation.

When certain elements are not included, a justification for its absence should be provided in the respective section.

Module 2

Module 2 must include the Quality Overall Summary, Non-clinical Overview and Clinical Overview. Non-clinical and Clinical Summaries can be provided, but they are only mandatory if new additional studies have been provided within the documentation. The non-clinical and clinical overviews should particularly focus on the following elements:

- A summary of impurities present in batches of the active substance(s) (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed;
- An evaluation of the bioequivalence studies or a justification why studies were not performed with respect to the guideline on the investigation of bioequivalence
- An update of published literature relevant to the substance and the present application. It may be acceptable for articles in "peer review" journals to be annotated for this purpose.
- Every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.
- When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted

Module 3

A complete Module 3 should be submitted in accordance to the requirements set out in the Notice to applicants.

For all applications, the table A on 'Materials of animal origin covered by the Notice for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products should be completed and included in Module 3.2.R, stating not applicable, if relevant.

Module 4 and Module 5

- For a 'generic' of a reference medicinal product (Art 10.1) it is not required to provide the results of toxicological and pharmacological tests or the results of clinical trials. The results of the bioequivalence studies performed where appropriate should be included in section 5.3.1. When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that

their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted following the CTD structure.

- For a so-called 'hybrid' of a reference medicinal product (Art 10.3), the results of appropriate preclinical and clinical tests should be provided in accordance to the requirements set out in the notice to applicants.

As for any other application, it should be noted that the responsibility for the quality of the submitted documentation lies with the applicant and is crucial to the overall process.

For queries related to the presentation of the application, please contact the EMA. Alternatively, applicants may request a pre-submission meeting with the EMA to clarify any outstanding points.

References

- Notice to Applicants, Volume 2B, Presentation and content of the dossier

2.5. *When can I submit my generic/hybrid application considering the protection period of the reference medicinal product? Rev. Feb 2019*

At the time of submission of the generic/hybrid application, the protection period of the reference medicinal product should have expired in order to allow the applicant to rely on the dossier of the reference medicinal product (see Question 2 and Question 3).

For generic/hybrid application submitted through the centralised procedure, when referring to:

- a centrally authorised reference medicinal product, the 10-year or 8-year protection period, as applicable, should have expired and the eligibility should have been confirmed (see Question 1); the relevant protection period should be counted[1] as starting from the date of notification of the marketing authorisation decision to the MAH and can be found in the Official Journal of the European Union as well as in the Union register of medicinal products for human use on the European Commission website; as an example, a generic application of a reference medicinal product notified on Day A, could be submitted 10 or 8 years later than Day A+1, as applicable;
- a nationally authorised reference medicinal product, the 6/10-year protection period, depending on the Member State which has granted the marketing authorisation or 8-year protection period, as applicable, should have expired and the eligibility should have been confirmed (see Question 1). However, a generic application based on a nationally authorised reference medicinal product can only be processed via the centralised procedure after expiry of a 10-year period of protection if the reference product chosen by the applicant is also authorised in Member States where a ten-year period of protection applies.

Notion of 'global marketing authorisation'

The calculation of the protection period should take into account the notion of global marketing authorisation.

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

[1] The rules applicable to periods, dates and time limits can be found in Regulation no 1182/71

This means that for a reference medicinal product, the start of the data exclusivity and market protection periods is determined by the first MA in the Union which was granted in accordance with the relevant European pharmaceutical legislation (Acquis Communitaire).

In case of any doubt, the applicant can liaise with the EMA provided detailed information are given.

The new protection periods of '8+2+1' applies only to reference medicinal products for which the marketing authorisation application has been submitted as of 30 October 2005 for MRP, DCP and national procedures and as of 20 November 2005 for centralised procedure according to the revised European Legislation.

In line with the revised rules mentioned above, applications for generic/hybrid medicinal products can be submitted after expiry of the **data exclusivity period** for the reference medicinal product i.e. 8 years after the date of notification of the authorisation of the reference medicinal product to the MAH. However, the authorised generic/hybrid product can only be placed on the market 10 or 11 years after expiry of the **market exclusivity period** applicable for the reference medicinal product.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Chapter 1 (section 6), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A
- Union register of medicinal products for human use

2.6. *When will I have to submit a similarity and, where applicable, derogation report in the context of my generic/hybrid application? Feb 2013*

You will have to submit a similarity report in the context of your generic/hybrid application where there are authorised orphan medicinal products under market exclusivity for a condition related to the therapeutic indication proposed in your application.

In advance of submission of your application for marketing authorisation, you are advised to check the Community register of orphan medicinal products, for information on medicinal products designated as orphan.

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.

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.:

(a) 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;

(b) 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;

(c) 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 similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products, please refer to Q&A "What is the procedure for assessment similarity and, where applicable, derogation report vis-à-vis authorised orphan medicinal products?" of the EMA pre-submission procedural advice for users of the centralised procedure.

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 either 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 your application, this information should be

communicated promptly to their Product Team Leader 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.

Please note that Applicants are not expected to submit a similarity report against their reference medicinal product, since a generic/hybrid application can only be submitted once the period of market exclusivity of the reference medicinal product has expired, unless justification is provided to support one of the derogations laid down in Article 8(3) of the Orphan Regulation.

Generic medicinal products are, by definition, considered similar to the reference medicinal product and, therefore, the therapeutic indications for the reference medicinal product which benefit from a separate period of market exclusivity cannot be included in the proposed product information for the generic medicinal product, unless justification is provided to support one of the derogations laid down in Article 8(3) of the Orphan Regulation.

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

2.7. *Can I submit my generic/hybrid application even if some parts of the product information of the reference medicinal product are covered by usage patents? Jan 2011*

Companies use patent law to obtain further protection for an innovative medicine in some or all Member States. This protection applies e.g. to new uses of the medicine, such as new indications and pharmaceutical forms. While this 'usage patent' protection is in place, a generic/hybrid medicine cannot be marketed for the protected indication or pharmaceutical form, even if the period of data and market exclusivity of the reference medicine has expired.

Applications for marketing authorisation for generic/hybrid medicinal products can however be submitted and authorised even if some parts of the product information of the reference medicinal product are covered by patent law.

Article 11 of Directive 2001/83/EC and Article 3.3(b) of Regulation No 726/2004 allow applicants/Marketing Authorisation Holders to exclude from their proposed product information those parts of the SPC of the reference medicinal product referring to indications or dosage forms still covered by patent law.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004

2.8. *If the patent situation differs in the various Member States how will this be reflected in the product information of my generic/hybrid medicinal product?* ***Rev. Dec 2024***

It is not possible to have different product information for a particular medicinal product authorised via the centralised procedure, to take account of different patent situations in the various Member States.

However, in order to facilitate generic/hybrid access to the centralised procedure, duplicate applications may be requested to the European Commission on grounds of the existence of patents protecting certain therapeutic indications or pharmaceutical forms.

The duplicate application may contain more or fewer indications or pharmaceutical forms than the original application/marketing authorisation when this is necessary to market the product in Member States where a specific indication or pharmaceutical form is protected by patent law.

However, in order to maintain the harmonisation of the SmPCs, the applicant should commit as part of the marketing authorisation application, to extend the indication(s)/pharmaceutical form(s) of the duplicate marketing authorisation as soon as the patent restrictions no longer exist or should commit to withdraw the marketing authorisation with restricted indications/pharmaceutical forms when the relevant patents are no longer in force.

Multiple marketing authorisation applications and post-authorisation activities for generic/hybrid medicinal products, justified on the basis of existing patent protection for the reference medicinal product, are eligible to fee incentives. Please, see 'New Fee Regulation (from 1 January 2025)'.

References

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- New Fee Regulation (from 1 January 2025)
- Handling of Duplicate Marketing Authorisation Applications

2.9. *If a therapeutic indication is covered by patent law which sections of the SPC can be deleted in connection with the patented indication?* ***Jan 2011***

Information directly related to the patented indication can be deleted from sections 4.1. therapeutic indications, 4.2. posology and method administration and 5.1. pharmacodynamic properties of the summary of product characteristics.

For public health reasons, safety related information in sections 4.3 to 4.8. of the SPC should be maintained.

If the applicant wishes to omit other information than the one mentioned above directly related to the patented indication, this must be properly justified.

2.10. *How can I update the product information of my generic/hybrid medicinal product after expiry of the patent of the reference medicinal product? Jan 2011*

The appropriate type IB variation should be submitted to align the product information of the generic/hybrid medicinal product with the product information of the reference medicinal product, following expiry of the patent.

References

- Regulation (EC) No 1234/2008

2.11. *Do I need to perform user consultation for a generic/hybrid medicinal product? When and how to submit information on user consultation? Jan 2011*

Articles 59(3) and 61(1) of Directive 2001/83/EC require that the package leaflet reflects the results of consultation with target patient groups ('user consultation') to ensure that it is legible, clear and easy to use and that the results of the assessment carried out in cooperation with target patient groups are provided to the competent authority. This legal requirement applies also to generic/hybrid medicinal products.

However, if the Package leaflet of the generic medicinal product has the same content and layout as that of the reference medicinal product or other generic medicinal product of the same active substance for which user consultation has been performed, reference to already approved package leaflets will generally be considered an acceptable justification for not performing user consultation. Such justification should be included in Module 1.3.4 of the dossier.

When changes have been made to the package leaflet of the generic medicinal product or in case of differences from the reference medicinal product for hybrid medicinal products (e.g. change in pharmaceutical form, change in route of administration, etc.), a bridging report might have to be submitted. The bridging report should be included in Module 1.3.4 of the dossier.

For further information on user consultation, including methods of user consultation and submission and assessment of information on user consultation, please refer to question 'When should I submit my marketing authorisation application?' 'of the general pre-submission guidance for users of the centralised procedure.

References

- Directive 2001/83/EC
- Guideline on the readability of the label and package leaflet of medicinal products for human use, the Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- Guidance concerning consultations with target patient groups for the package leaflet, the Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2C
- EMA Operational Procedure on Handling of "Consultation with target patient groups" on Package Leaflets (PL) for Centrally Authorised Products for Human Use

2.12. *Should I submit an EU Risk Management Plan as part of my generic medicinal product application? Rev. Jun 2016*

2.12.1. What are the requirements for an RMP for a new application of an established generic product?

Marketing authorisation applications for generic medicinal products under Article 10(1) of Directive 2011/83/EC should include an RMP in the application dossier. However as outlined in the Good Pharmacovigilance Practice (GVP) module V on risk management systems some parts or modules of the RMP for a generic may be omitted (see GVP V section V.C.3.1).

2.12.2. If there is no RMP in place for a reference medicinal product, how should module SVIII 'summary of the safety conserns' be populated for a generic medicinal product?

The applicant of the generic medicinal product should use the (European) public assessment and the summary of product characteristics of the reference medicinal product to obtain the safety concerns to be included in module SVIII of the RMP. Applicants may also discuss during the pre-submission phase what safety concerns should be included.

3. Assessment of the application

3.1. *How shall my generic/hybrid application be evaluated (timetable)? Rev. Mar 2013*

Upon receipt of the application, the Agency will start the validation on the next submission deadline stated on its website (see question 24). Validation has to be completed by the corresponding starting date of the procedure; applicants need to be ready to answer within few days to any issues raised at this stage.

At the end of the validation process and provided the Rapporteur and Co-Rapporteur have received the dossier, the EMA starts the procedure at the monthly starting date published on the EMA website. For generics of centrally authorised medicinal products, provided successful validation, the procedure starts the same month. Where the application concerns a generic/hybrid of a medicinal product authorised through a national/MRP/DCP procedure, the EMA will request from the Member state where the reference product received a marketing authorisation to transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the information on the full composition of the reference product and if necessary other relevant information. Therefore the evaluation process will only start once all relevant information has been received.

If, within a month from the start of the procedure, any other member of the CHMP has not received the requested parts of the dossier from the applicant, the EMA will stop the clock until the problem is resolved. A timetable is prepared by the Agency and presented to the CHMP for information.

Applicants are advised to submit the MAA according to the published EMA calendar (See Submission timelines).

Generic applications under Article 10(1) of Directive 2001/83/EC

The Agency shall ensure that the opinion of the CHMP is given in accordance with the standard Timetable for the evaluation of 'generic applications' under Article 10(1) of Directive 2001/83/EC.

DAY	ACTION
1*	Start of the procedure
80	Receipt of the Assessment Reports from CHMP Rapporteur by CHMP members and EMA. EMA sends CHMP Rapporteur Assessment Reports to the applicant making it clear that it only sets out their preliminary conclusions. The so-called Day-80 assessment reports in no ways bind the CHMP and are sent to the applicant for information only.
87	PRAC Rapporteur circulates the RMP assessment report and proposed RMP LoQ
90	Adoption of GxP Inspection Request
100	(Co-)Rapporteurs, other Committee members and EMA receive comments
101-104	PRAC adopts PRAC RMP Assessment Overview and Advice for D120 LOQ
115	Receipt of draft list of questions (LoQ) from CHMP Rapporteur, including the CHMP recommendation and scientific discussions, together with the PRAC RMP Assessment Overview and Advice by CHMP members and EMA (If applicable)

DAY	ACTION
120	Adoption CHMP Opinion + CHMP Assessment Report unless "major" objections, GxP Inspection issues or questions on the restricted part of the ASMF are identified. Adoption of a timetable for the provision of translations.

DAY	ACTION
121*	Submission of the responses, including revised SmPC, labelling and package leaflet texts in English.
	Restart of the clock
150	PRAC Rapporteur circulates the RMP assessment report and proposed LoOI
157	Circulation of the CHMP Rapporteur (Joint) Response Assessment Report (so-called Day-150 Assessment Report). 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
167	PRAC adopts PRAC RMP Assessment Overview and Advice for D180 LoOI
170	Comments from CHMP Members to Rapporteur, the EMA and other CHMP members
180	Adoption CHMP Opinion + CHMP Assessment Report unless "major" objections are identified to be addressed in writing or during an Oral explanation and/or outstanding GxP issues. Adoption of a timetable for the provision of translations
	Clock stop in case of Oral Explanation
181	Restart of the clock. Oral explanation and circulation of the final GxP Inspection Report
183	PRAC Rapporteur circulates the RMP assessment report
197	PRAC adopts the final PRAC RMP Assessment Overview and Advice
By day 210	Adoption of CHMP Opinion + CHMP Assessment Report Adoption of a timetable for the provision of translations

* According to the published EMA calendar (See Dates for CHMP meetings dates), after receipt of the responses, the EMA will prepare a timetable for the evaluation of the responses. In general the following timetable will apply:

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
+ 5 Days after adoption of Opinion	Applicant provides the EMA with SPC, Annex II, labelling, package leaflet and Annex A in all EU languages (including Icelandic and Norwegian). EMA circulates draft translations to Member States for review
+ 22 Days after adoption of Opinion	Applicant provides EMA with final translations of SPC, Annex II, labelling and package leaflet in all EU languages (including Icelandic and Norwegian), taking account comments received from Member States by +19 Days after adoption of the Opinion
+ 27 Days after adoption of Opinion	Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland

Further details on the post-opinion review of translations and forms to be used, are available in the "New linguistic review process of product information in the centralised procedure" guideline as published on the EMA website.

Mock-ups and specimens of the outer and immediate packaging together with the package leaflet must be submitted by the applicant to the EMA for review, before commercialisation of the medicinal product. Further details on the mock-ups and specimens requirements are available on the EMA website.

Hybrid applications under Article 10(3) of Directive 2001/83/EC

For hybrid applications under Article 10(3), the timetable for a new full application applies for the first evaluation phase. For the second evaluation phase, a shortened timetable could be agreed upon on a case-by-case basis.

References

- Regulation (EC) No 726/2004, (OJ L 136/1 of 30 April 2004)
- The New Linguistic Review Process of Product Information in the Centralised Procedure (EMEA/5542/02 Rev.4)
- Timetable for Generic Applications (EMEA/327896/2005)

3.2. *When can I expect a pre-authorisation GCP inspection and how are they conducted?* ***Rev. Aug 2019***

The GCP standards applied to clinical trials carried out for generic medicinal products are the same as those applied to any other medicinal product. In addition it should be noted that the Guideline on the investigation of bioequivalence states in the "Chemical analysis" section that the analytical part of bioequivalence trials should be conducted in accordance with the applicable principles of Good Laboratory Practice.

Timetable for GCP inspections for generic application

In accordance with the legislation, any pre-approval inspection in the centralised procedure is requested by CHMP. The Timetable for Generic Applications states that the inspection request is usually adopted by CHMP by day 90 of the centralised procedure. The inspection is announced to the applicant

within 10 days from the adoption of the inspection request and it is coordinated by the EMA Inspection Sector to take place as soon as possible thereafter.

If a GCP inspection is deemed necessary to complete the assessment of a centralised application for a generic medicinal product, a 120-day procedure may not be possible and a clock-stop during the procedure may be necessary. The inspection is carried out by the relevant inspectorate usually in parallel with the clock stop period and the inspection results are generally reported by day 150.

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

- Regulation (EC) No 726/2004
- Annex 1 Directive 2001/83/EC
- Directive 2001/20/EC
- Directive 2005/28/EC
- CPMP/EWP/QWP/1401/98 Guideline on the investigation of bioequivalence

3.3. *When can I expect a pre-authorisation GMP inspection and how are they conducted? Rev. Feb 2019*

The level of GMP supervision and the GMP standards applied to generic medicinal products are the same as any other medicinal product. The only difference relating to pre-authorisation GMP inspections between generics and other products assessed through the centralised procedure is that, for the former, a shorter timeline is possible (see Timetable for Generic Applications).

This means that all the information included in the document: GMP inspections during the assessment of the application, published on the EMA website as part of the pre-submission guidance document, is applicable with the exception of the section: Timetable for Inspections.

Timetable for GMP inspections for generic applications

According to the legislation, any pre-authorisation inspection for medicinal products for human use in the centralised procedure is requested by the CHMP and, according to the Timetable for Generic Applications, the inspection request is adopted for generics by day 90 of the centralised procedure and the inspection results are reported by day 150.

As for any other centralised application, two types of pre-authorisation GMP inspections are possible: to verify compliance with European Union Good Manufacturing Practice Principles and Guidelines and/or to verify specific manufacturing and control activities related to the assessment of an application.

The first type of inspection is normally carried out when a manufacturing site located outside the European Economic Area (EEA) and in a country where no operational Mutual Recognition Agreement with the EU is in place, has not been inspected for GMP compliance in the last 3 years by an EEA competent authority.

The need for this type of inspection is identified in the early stages of the procedure and an early inspection request can be adopted by the committee (e.g. at day 30), so that unnecessary delays are avoided.

As assessment-related inspections cannot be foreseen until the Assessment Report is available, inspections are usually requested at day 90 of the centralised procedure. In this case a clock-stop might be necessary. The inspection is organised without delay by the EMA secretariat and is usually carried out by the responsible inspectorate within 3 months of the adoption of the inspection request by the committee.

References

- Regulation (EC) No. 726/2004
- Directive 2003/94/EC
- Directive 2001/83/EC
- EUDRALEX - The rules governing medicinal products in the European Union, Volume 4, Good manufacturing practice
- Timetable for Generic Applications (EMEA/327896/2005)

4. Post-authorisation

4.1. *What is a safety variation? Rev. Dec 2015*

Safety variations are variations that refer to safety issues, including those related to quality problems, requiring a change of the Summary of Product Characteristics (SmPC), Package Leaflet (PL) and/or Labelling, which does not need to be implemented via an Urgent Safety Restriction (see below), but should be implemented as soon as possible.

4.2. *When should a safety variation be submitted for a generic or hybrid medicinal product following changes to the reference medicinal product? Rev. Dec 2024*

For centrally authorised generics or hybrids of centrally authorised reference medicinal products, the EMA will publish the reference medicinal product tracked product information in all EU languages on the reference medicinal product EPAR page. MAHs of centrally authorised generics or hybrids of centrally authorised reference medicinal products are requested to download the EU tracked product information in all languages from the reference medicinal product EPAR page and submit a type IB variation as soon as possible or at the latest within 2 months to implement the changes in the Product Information (PI) as adopted for the reference medicinal product.

For centrally authorised generics or hybrids of nationally authorised reference medicinal products, the MAHs of centrally authorised generics or hybrids should submit a type IB variation as soon as possible or at the latest within 2 months, to align their product information with the nationally authorised reference medicinal product.

For more information on IB variations, please refer to the Q&A on post-authorisation procedural advice for users of the centralised procedure.

Simple reference to fees payable can be found on '[New Fee Regulation (from 1 January 2025)]'.

4.3. *How should the outcome of the safety variation be communicated to the outside world? Rev. Dec 2024*

The EPAR, the SPC and the PL will be updated on the EMA website.

In certain situations, the Agency/CHMP may decide that healthcare professionals should be informed quickly about the safety concern and the revised SPC and therefore request the MAHs of the reference medicinal product and generics to disseminate a Direct Healthcare Professional Communication (DHPC). MAHS are referred to the [Guideline on good pharmacovigilance practices (GVP) 3 Module XV – Safety communication] for details on the situations when DHPCSs are usually considered necessary and the procedures to follow.

This Guideline also contains the advice that MAHs for products with the same active substance should try to co-operate and propose a common DHPC as this will allow for dissemination of a single DHPC to the healthcare professionals.

In this Guideline, MAHs are also asked to propose to the EMA/CHMP, at the time of preparation of a DHPC, a plan for communication to patients and the general public for subsequent implementation.

4.4. *How soon after the safety variation for a generic/ hybrid medicinal product should the revised product information be implemented for batch release purposes?*

With the application for the safety variation, the MAH should indicate in the application form the time frame for implementation of the safety variation. The exact implementation date for batch release purposes is to be agreed with the EMA.

References

- Regulation (EC) No 1234/2008
- Notice to Applicants – Volume 2C, A Guideline on Summary of Product Characteristics.
- Notice to Applicants – Volume 2A, Chapter 5 – variations.
- EMA Post-authorisation guidance EMEA/H/19984/03

4.5. *How can I apply for the update of the product information after the outcome of a single PSUR procedure? Mar 2015*

See web-link: European Medicines Agency post-authorisation procedural advice for users of the centralised procedure – List of questions on PSURs

4.6. *What is an Urgent Safety Restriction (USR)? Rev. Dec 2015*

An USR is an urgent regulatory action, which is triggered by a MAH of a Centrally Authorised Product or the European Commission in the event of, or to prevent risk to public health associated with the use of this medicinal product.

The outcome of an USR is an interim change to the Product Information (PI), due to new non-clinical and/or clinical information having a bearing on the safe use of the medicinal product, concerning particularly one or more of the following items in the SPC: the indications, posology, contraindications and warnings. In rare cases the changes may also relate to quality problems requiring a change of the Product Information.

4.7. *When should a USR be submitted for a generic or hybrid medicinal product following a USR to the reference medicinal product? Rev. Dec 2024*

A USR is an urgent regulatory action to prevent risk to public health associated with the use of a medicinal product. In the case of a Centrally Authorised Product (CAP), it is triggered by the Marketing Authorisation Holder (MAH) or the European Commission.

The outcome of a USR is an interim change to the Product Information (PI), due to new non-clinical and/or clinical information having an impact on the safe use of the medicinal product. It usually concerns one or more of the following sections in the SPC: the indications, posology, contraindications

and warnings. In rare cases the changes may also relate to quality aspects requiring a change of the PI.

For centrally authorised generics or hybrids of centrally authorised reference medicinal products the Agency will provide, once the USR has been finalised for the reference medicinal product and the final wording of the PI has been agreed, the MAH of the generic/ hybrid with the exact wording to be implemented and request the MAH to submit a USR application to implement the exact PI wording of the reference medicinal product.

For centrally authorised generics or hybrids of nationally authorised reference medicinal products the Agency will provide, upon notification by the respective competent authority, the MAH of the generic/ hybrid product with the exact wording to be implemented and request the MAH to submit a USR application to implement the exact PI wording of the reference medicinal product.

Once received, the CHMP assessment of the USR for the generic or hybrid medicinal product will be finalised within 24 hours.

Immediately following the finalisation of the USR for the generic or hybrid medicinal product, the Agency will inform the MAH that the changes may be introduced and that a subsequent type IB safety variation should be submitted without any delay (no later than 15 days after the finalisation of the USR).

A similar procedure would apply when a safety concern is first identified for a generic/ hybrid medicinal product.

4.8. *How should the outcome of the USR be communicated to the outside world? Rev. Dec 2024*

Changes to the marketing authorisation introduced by means of an USR usually require that healthcare professionals are informed quickly about the safety concern and the revised SPC. MAHs are therefore requested to prepare and disseminate a Direct Healthcare Professional Communication (DHPC). MAHs are referred to the Guideline on good pharmacovigilance practices (GVP) 3 Module XV – Safety communication for details on the situations when DHPCs are usually considered necessary and the procedures to follow.

This Guideline also contains the advice that MAHs for products with the same active substance should try to co-operate and propose a common DHPC this will allow for dissemination of a single DHPC to the healthcare professionals.

In this Guideline, MAHs are also asked to propose, at the time of preparation of a DHPC, a plan for communication to patients and the general public.

4.9. *How soon after the USR for a generic/ hybrid medicinal product should the revised product information be implemented for batch release purposes? Rev. Dec 2015*

With the notification for a USR, the MAH should include a letter of undertaking proposing timeframes for distribution/recall if needed of the revised product information. This action plan, which should also include proposed timelines for the circulation of the DHPC, will need to be agreed by the CHMP.

The timelines will be determined on a case-by-case basis depending on the nature of the safety issue in question. The importance of the safety issue should always be considered in relation to the possible problem caused by a potential lack of supply to patients.

For safety issues, including those related to quality aspects, requiring only a change of the SPC and not the PL and/or labelling, the revised Product Information will be disseminated mainly by means of the DHPC.

References

- Commission Regulation (EC) No 1234/2008
- Regulation (EC) No 726/2004
- Human post-authorisation Q&A
- Notice to Applicants – Volume 2C, Guideline on Summary of Product Characteristics
- Notice to Applicants – Volume 2A, Chapter 5 – variations
- EMA Post-authorisation guidance EMEA/H/19984/03

4.10. *Do the provisions of the marketing /cessation notification and the sunset clause apply to my generic/hybrid application? Rev. Feb 2019*

The general principles described in the EMA Questions and Answers documents regarding marketing and cessation notification as well as the sunset clause monitoring apply similarly to generic and hybrid medicinal products.

For a generic or hybrid medicinal product, when the medicinal product is not placed on the market as of the granting of the marketing authorisation, the 3-year period without marketing will start counting, for the purpose of the sunset clause monitoring, from the date of notification of the marketing authorisation to the MAH. (i.e. after expiry of the data protection period of the reference medicinal according to the previous legislation (either 6 or 10 years)).

The new data protection rules (8+2+1) apply to those reference medicinal products for which the initial application for authorisation has been submitted after the entry into force of the revised Union Legislation, i.e. after 30 October 2005 for national, decentralised and mutual recognition procedures and as of 20 November 2005, for the centralised procedure.

However, the start of the three-year period should also take into account the date when the medicinal product can be placed on the market by the marketing authorisation holder, i.e. as of the end of the 10-(or 11) year period of market exclusivity of the reference medicinal product and at the end of other protection rules which must be respected.

MAHs are advised to inform the EMA, within 60 days from the granting of the marketing authorisation, of the existence and if known, the expiry date(s) of the other protection period(s) to be respected as appropriate. The need for an exemption request will be decided based on this information.

References

- Article 13(4) of Regulation (EC) No 726/2004
- Article 14(4-6) of Regulation (EC) No 726/2004

- Chapter 1 (section 2.4.2), The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A
- Questions and Answers on the notification to the EMA of actual marketing and cessation of placing on the market for centrally authorised medicinal products (EMEA/180078/2005)
- Questions and Answers on the application of the so-called "sunset clause" to centrally authorised medicinal products (EMEA/180079/2005)