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SCIENCE MEDICINES HEALTH

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Committee for Human Medicinal Products (CHMP)

## European Medicines Agency procedural advice for users of the centralised procedure for similar biological medicinal products 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 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 Meetings with Applicants. Pre-Submission Meetings (which should take place approximately ~~6~~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 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.

### [Instructions for users:-](#)

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 Meeting.

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~~So, if you would desire further clarification on any of the included topics and apply for a Pre-Submission Meeting, please use the "The Pre-Submission Meeting Request Form" and mark which topics you would like to be addressed by the Agency. Along with the "Pre-Submission Meeting Request Form", you should also submit the "Pre-Submission request form (Eligibility)".~~

~~When you have completed the request form for a Pre-Submission Meeting at the EMA return it by mail or electronic mail. If you need further information on the content of this document or on the conduct of Pre-Submission Meetings, please do not hesitate to contact:~~

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**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".

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 similar biological medicinal products applications. For general requirements, please refer to the "[European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure](#)".

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# 1. Eligibility and reference product

## 1.1. What is a similar biological medicinal product?

A similar biological medicinal product, also known as “Biosimilar”, is a product which is similar to a biological medicine that has already been authorised, the so-called “reference medicinal product”.

The active substance of a similar biological medicinal product is a **known biological** active substance and similar to the one of the reference medicinal product.

A similar biological medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions. (Please refer to Question 43. “Will my similar biological medicinal product be considered interchangeable with the reference medicinal product?”).

In principle, the concept of similar biological medicinal product is applicable to any biological product. However, in practice, the success of such a development approach will depend on the ability to characterise the product and therefore to demonstrate the similar nature of the concerned products.

### Definition of biological medicinal product

According to Part I of Annex I of Directive 2001/83/EC, it is a product that contains a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing together with the production process and its control.

For example, recombinant proteins, monoclonal antibodies, medicinal products derived from human blood and human plasma, immunological medicinal products and advanced therapy medicinal products should be considered biological medicinal products.

### References

- [Directive 2001/83/EC](#)
- The Rules governing Medicinal Products in the European Union, [Notice to Applicants, Volume 2A, Chapter 1](#)
- [Guideline on Similar Biological Medicinal Products CHMP/437/04\\_Rev1](#)
- [Questions and Answers on Biosimilar medicines \(similar biological medicinal products\)](#)
- [Biosimilar Scientific Guidelines](#)

## 1.2. Is my similar biological medicinal product eligible for evaluation under the Centralised Procedure? **Rev. Feb 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 similar biological medicinal products, also known as “Biosimilars”, eligibility can be granted to the Centralised Procedure as follows:

### **1.2.1. Mandatory scope of the Centralised Procedure**

The mandatory scope of the Centralised Procedure is set up in Article 3(1) of Regulation (EC) No 726/2004. According to this Article, medicinal products developed by means of biotechnological processes as described in the Annex (point 1) of Regulation (EC) No 726/2004 should be authorised by the Union.

The reference medicinal product could be a product authorised via a National/MRP or Centralised Procedure.

### **1.2.2. Optional scope of the Centralised Procedure**

The optional scope for a similar biological medicinal product is applicable when the product does not fall under the mandatory scope of the Centralised Procedure, as explained above. Two situations can be found:

#### **Similar biological medicinal product of a centrally authorised product**

Similar biological 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.

#### **Similar biological medicinal product of a National/MRP/DCP product**

Similar biological medicinal products that do not fall under the mandatory scope could, at the request of the Applicant, be accepted for consideration under the Centralised Procedure Article 3(2)(b), 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 further guidance, reference is made to the [‘Guideline on Article 3\(2\) of Regulation \(EC\) No 726/2004 – Optional scope of the Centralised procedure’](#)

Regardless of whether the product falls into the mandatory or optional scope, an ‘eligibility request’ should always be submitted using the specific form and accompanied by a justification of eligibility for evaluation under the Centralised Procedure.

When submitting this request, the Applicant should use the [Pre-submission request form \(Eligibility\)](#) and send it electronically, to: [CPeligibility@ema.europa.eu](mailto:CPeligibility@ema.europa.eu), accompanied by the draft SmPC and a Justification for Eligibility, being the later especially required for medicinal products falling under the optional scope of Article 3(2)b.

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](#) ). The eligibility request can also be submitted as part of this “Letter of intent to submit”

For similar biological 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).

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

### 1.2.3. Eligibility for duplicate marketing authorisations

The eligibility request should also be submitted for duplicate similar biological 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 similar biological medicinal product.

#### References

- [Regulation \(EC\) No 726/2004](#)
- Centralised Procedure”, the Rules governing Medicinal Products in the European Union, [Notice to Applicants, Volume 2A, Chapter 4](#)
- [Guideline concerning the optional scope of the centralised procedure in accordance with Article 3\(2\)\(b\) of Regulation \(EC\) No 726/2004](#)

### 1.3. *What is the so-called ‘reference medicinal product’ referred to in the application for a similar biological medicinal product? Rev. Oct 2014*

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 and to which the application for marketing authorisation for a similar biological medicinal product refers to. Applicants will have to identify in the application form for the similar biological medicinal product the reference medicinal product (product name, strength, pharmaceutical form, MAH, first authorisation, Member State/Union), as follows:

- 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 (Please refer to Question 15. “When can I submit my similar biological medicinal product application considering the protection period of the reference medicinal product?”).

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 similar biological medicinal product.

- The medicinal product, the dossier of which is **cross-referred** to in the similar biological 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 similar biological medicinal product.

- The medicinal product (product name, strength, pharmaceutical form, MAH, Member State of source) used for the **comparability exercise**. In Module 1.5 of the dossier, Applicants will be requested to complete a table, indicating the chosen reference medicinal product used for the comparability exercise. (Please refer to Question 5. "What is the comparability exercise"?).

### 1.3.1. Source of the reference medicinal product and global development

With the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar medicinal product in certain clinical studies and in in vivo non-clinical studies (where needed) with a non-EEA authorised comparator (i.e. a non-EEA authorised version of the reference medicinal product) which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA (e.g. ICH countries).

Under this approach, it will be the applicant's responsibility to establish that the batches sourced outside the EEA is representative of the reference medicinal product authorised in the EEA through an extensive analytical comparison.

For demonstration of biosimilar comparability at the quality level, side-by-side analysis of the biosimilar product (from commercial scale and site) with EEA authorised reference product must be conducted. However, combined use of non-EEA authorised comparator and EEA authorised reference product is acceptable for the development of the Quality Target Product Profile of the biosimilar product.

If certain clinical and in vivo non-clinical studies of the development programme are performed with the non-EEA authorised comparator, the Applicant should provide adequate data or information to scientifically justify the relevance of these comparative data and establish an acceptable bridge to the EEA-authorised reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and may also include data from clinical PK and/or PD bridging studies for all three products. The overall acceptability of such an approach and the type of bridging data needed will be a case-by-case/product-type decision, and is recommended to be discussed upfront with the Regulatory Authorities. However, the final determination of the adequacy of the scientific justification and bridge will only be made during the assessment of the application.

This approach is reflected in the revised [Guideline on similar biological medicinal products \(CHMP/437/04 Rev 1\)](#). This global development approach may be applied by applicants as of adoption of the revised guideline by CHMP.

For further guidance on data requirements, please refer to the relevant general and product-specific guidelines.

## References



- [Directive 2001/83/EC](#)
- [Notice to applicants, volume 2A, chapter 1](#)
- [Notice to applicants, volume 2B, module 1: Application form](#)
- [Guideline on Similar Biological Medicinal Products CHMP/437/04 Rev1](#)
- [Biosimilar scientific guidelines](#)

## 2. Steps prior to submitting the application

### 2.1. What is the legal basis for my application?

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 similar biological applications the legal basis can be found in Article 6 of Regulation (EC) 726/2004 and Article 10(4) of Directive 2001/83/EC.

It should be noted that at the time of submission of the similar biological 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.

The reference medicinal product should have been authorised under Article 6 of Directive 2001/83/EC for not less than 8 years in a Member State or in the Union. This 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 European Union legislation. (Please refer to Question 15. “When can I submit my similar biological medicinal product application considering the protection period of the reference medicinal product?”).

A similar biological 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 Union on the basis of a **complete dossier**.

#### **Similar biological medicinal product**

According to Article 10 (4) of Directive 2001/83/EC, where a biological medicinal product which is similar to a reference biological medicinal 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 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 and the related detailed guidelines.

#### **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](#)
- [Guideline on Similar Biological Medicinal Products CHMP/437/04 Rev1](#)

## **2.2. What is the comparability exercise?**

According to Article 10(4) of Directive 2001/83/EC, when a biological medicinal product which is similar to a reference biological medicinal product does not meet the conditions in the definition of generic medicinal products, the results of appropriate pre-clinical tests and clinical trials must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I of Directive 2001/83/EC and the related detailed guidelines.

Within the EU regulatory framework, the primary objective in evaluating an Article 10(4) application is to determine the similarity (or not) of a given biological medicinal product to a reference medicinal product.

The comparability exercise should be a robust head-to-head comparison between the similar biological medicinal product and the reference medicinal product performed at the levels of quality, safety and efficacy.

Due to the diversity of biological medicinal products, the assessment of Biosimilar products should be done on a case-by-case basis. The amount of data required will take into account the specific characteristic of each individual medicinal product. The relevant general and product-specific guidelines should be followed. (Please refer to Question 14. "How shall I present my similar biological medicinal product application (format)?").

### **References**

- [Guideline on Similar Biological Medicinal Products CHMP/437/04 Rev1](#)
- [Biosimilar Scientific Guidelines](#)

## **2.3. When and how 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 the similar biological medicinal product applications (e.g. legal basis, data requirements), the following principles shall be considered on the appointment of CHMP/PRAC Rapporteurs/Co-Rapporteurs and their assessment teams:

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

### **Methodology on the appointment of Rapporteur/Co- Rapporteur and their assessment teams for similar biological medicinal products**

*Normally, for similar biological medicinal product applications the appointment procedure of Rapporteur/Co-Rapporteur and her/his assessment team 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 PRAC (Co-) Rapporteurs 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 similar biological 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 Experts for meetings](#) (SOP/H/3021, EMEA/201528/2004)
- [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 similar biological medicinal product application (format)?**

Marketing authorisation applications for a similar biological 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 similar biological medicinal product – a so-called ‘Biosimilar’ (Art 10.4).

This summary should include details on the similar biological medicinal product, its active substance, raw materials and manufacturing process. Differences with relevant attributes of the reference medicinal product should be included. Any other changes introduced during development which could affect comparability should be highlighted.

The comparability exercise versus the reference medicinal product for quality, safety and efficacy should be described, and the reference medicinal product used throughout the quality, safety and efficacy development program (as appropriate) should be defined. Please note that the reference medicinal product used in the comparability exercise should have been authorised in the EEA.

Applicants should note that the chosen reference medicinal product used in the comparability exercise should have been authorised in the Union. (Please refer to Question 5. “What is the comparability exercise?”).

The table “OVERVIEW OF THE CHOSEN REFERENCE PRODUCT FOR COMPARABILITY” should be completed and included in Module 1.5.2

- An EU Risk Management Plan is required (Please refer to Question 39. “Should I submit an EU Risk Management Plan as part of my similar biological medicinal product application?”).

All the other requirements of Module 1 apply also to similar biological 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. Whenever new additional studies have been provided within the documentation, Non-clinical and Clinical Summaries should also be submitted.

It is recommended that the Non-clinical and the Clinical overall Summaries deal with comparability issues in separate sections in order to facilitate the regulatory review by cross referencing the appropriate separate sections of the dossier which contain the relevant data.

## **Module 3**

A complete Module 3 should be submitted in accordance to the requirements set out in the Notice to Applicants. In addition, Biosimilar applications should also provide a demonstration of comparability, as discussed in the “Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues”. Applicants should note that the comparability exercise for a similar biological medicinal product versus the reference medicinal product is an additional element to the normal requirements of the quality dossier and should be dealt separately when presenting the data. The detailed location of this data within the CTD structure can be discussed with the EMA prior to submission, but it is recommended to make use of section 3.2.R.

Section 3.2.A. should be provided as appropriate, giving information about Facilities and Equipment and Safety Evaluation of Adventitious Agents.

For all applications, the table A on 'Materials of animal origin covered by the *Note 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.

For materials of animal origin other than those covered by the *Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products*, Applicants are requested to complete the table B on '*Other materials of animal origin*'.

If an application relates to a medicinal product, which contains or uses in the manufacture materials of human origin, Applicants are request to complete the table C on albumin and other human tissue derived products.

#### **Module 4 and Module 5**

For a similar biological of a reference medicinal product, Art 10 (4), results of pre-clinical and clinical studies should be provided as appropriate following the CTD structure.

The requirements to demonstrate safety and efficacy of similar biological medicinal products have to comply with the data requirements laid down in Annex I to Directive 2001/83/EC.

General and product-class specific requirements are addressed in EMEA/CHMP guidelines. For situations where product-class specific guidance is not available, Applicants are encouraged to seek scientific advice from EU Regulatory Authorities.

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
- [Biosimilar Scientific Guidelines](#)

### ***2.5. When can I submit my similar biological medicinal product application considering the protection period of the reference medicinal product? Rev. Feb 2019***

At the time of submission of the similar biological 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 (Please refer to Question 3. "What is the legal basis for my application?" and Question 4. "What is the so-called 'reference medicinal product' referred to in the application for a similar biological medicinal product?").

For similar biological 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 (Please refer to Question 2. "Is my similar biological medicinal product eligible for evaluation under the Centralised

Procedure?”). The relevant protection period should be counted<sup>1</sup> 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 similar biological 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 (Please refer to Question 2. “Is my similar biological medicinal product eligible for evaluation under the Centralised Procedure?”). However, a similar biological 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 medicinal 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.

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 Communautaire*).

In case of any doubt, the Applicant can liaise with the EMA provided detailed information is 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 similar biological 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 similar biological product can only be placed on the market 10 or 11 years after expiry of the **market protection 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](#)

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

- [Union register of medicinal products for human use](#)

## **2.6. Can I submit my similar biological medicinal product application even if some parts of the product information of the reference medicinal product are covered by usage patents?**

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 similar biological medicine cannot be marketed for the protected indication or pharmaceutical form, even if the period of data and market exclusivity of the reference medicinal product has expired.

Applications for marketing authorisation for similar biological 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 SmPC 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](#)

## **2.7. If the patent situation differs in the various Member States how will this be reflected in the product information of my similar biological medicinal product? *Rev. Dec 2015***

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 the access to the Centralised Procedure for similar biological products, 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 similar biological medicinal products, justified on the basis of existing patent protection for the reference medicinal product, are eligible to fee incentives. Please, see "[Explanatory note on fees payable to the European Medicine Agency](#)".

## References

- [Fees payable to the European Medicines Agency](#)
- [Directive 2001/83/EC](#)
- [Regulation \(EC\) No 726/2004](#)
- [Handling of Duplicate Marketing Authorisation Applications](#)
- [Pre-submission Guidance – multiple applications](#)
- [Guideline on the procedure for accelerated assessment pursuant to article 14 \(9\) of Regulation \(EC\) No 726/2004](#)
- [The Rules governing Medicinal Products in the European Union, Notice to Applicants, Volume 2A, Chapter 1](#)

### ***2.8. If a therapeutic indication is covered by patent law which sections of the SmPC can be deleted in connection with the patented indication?***

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.

### ***2.9. How can I update the product information of my similar biological medicinal product after expiry of the patent of the reference medicinal product?***

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

## References

- [Regulation \(EC\) No 1234/2008](#)

## **2.10. Do I need to perform user consultation for a similar biological medicinal product? When and how to submit information on user consultation?**

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 similar biological medicinal products.

However, if the package leaflet of the similar biological medicinal product has the same content and layout as that of the reference medicinal product or other similar biological 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 similar biological medicinal product or in case of differences from the reference medicinal product, 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 the [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](#)

## **2.11. How shall I submit the information related to the biological active substance?**

Full information related to the active substance should be submitted within Module 3.2.S. (Please refer to Question 14. "How shall I present my similar biological medicinal product application (format)?").

It should be noted, that the CEP procedure (Certification of Suitability of the European Pharmacopoeia) does not apply for direct gene products (i.e. proteins), products obtained from human tissues, vaccines and blood products and preparations.

The EDQM has also decided to exclude from the scope of the certification procedure the products classified as "other biological substances" by the CMD(h). In this respect, the CMD(h) has published an [overview of biological active substances of non-recombinant origin](#).

The reasoning behind this decision is that the characterisation and determination of biological substances require not only a combination of physico-chemical and biological testing, but also an extensive knowledge of the production process and its control.

See web-link: [EMA PRE-SUBMISSION GUIDANCE FOR USERS OF THE CENTRALISED PROCEDURE - List of questions](#)

#### **References**

- [EDQM - Certification of Suitability to the Monographs of the European Pharmacopoeia](#)
- [CMD\(h\) – Overview of Biological Active Substances of non-recombinant origin](#)

### 3. Assessment of the application

#### 3.1. How shall my similar biological medicinal product 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. 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 Biosimilars of centrally authorised medicinal products, provided successful validation, the procedure starts the same month. Where the application concerns a Biosimilar of a medicinal product authorised through a National/MRP/DCP procedure, the EMA will request from the Member State where the reference medicinal 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 medicinal 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](#)).

The Agency shall ensure that the Opinion of the CHMP is given within 210 days (not counting clock-stops within the procedure) and in accordance with the standard timetable.

DAY	ACTION
1*	Start of the procedure
80	Receipt of the Assessment Reports from CHMP Rapporteur and (Co) Rapporteur by CHMP members and EMA. EMA sends CHMP Rapporteur and (Co) 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	Rapporteur, (Co) Rapporteur, other CHMP 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 and (Co) Rapporteur, including the CHMP recommendation and scientific discussions together with the PRAC RMP Assessment Overview and Advice, by CHMP members and EMA (If applicable). <b>Quality part of the dossier reviewed by BWP.</b>

DAY	ACTION
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.  <b>Clock stop.</b> At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary (inspection procedure starts).

DAY	ACTION
121*	Submission of the responses, including revised SmPC, labelling and package leaflet texts in English.
	Restart of the clock.  After receipt of responses, the CHMP will adopt a timetable for the evaluation of the responses. In general, the following timetable will apply:
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 and (Co) Rapporteur, the EMA and other CHMP members. <b>Responses to quality questions reviewed by BWP.</b>
180	CHMP discussion and decision on the need for adoption of a list of "Outstanding Issues" and/or an Oral Explanation by the Applicant. If an Oral Explanation is needed, the clock is stopped to allow the Applicant to prepare the Oral Explanation. Submission of final inspection report to the EMA, Rapporteur and Co-Rapporteur by the inspection team (at the latest by day 180).
181	Restart of the clock. Oral explanation (if needed) 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.

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 SmPC, 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 SmPC, 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.](#)

#### References

- [Regulation \(EC\) No 726/2004](#), (OJ L 136/1 of 30 April 2004)
- "Centralised Procedure", the Rules governing Medicinal Products in the European Union, [Notice to Applicants, Volume 2A, Chapter 4](#)
- [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. Is a product identified as a similar biological medicinal product?**

Similar biological medicinal products are approved under the same standards of quality, safety and efficacy as any other medicinal product. The SmPC structure does not have a section to indicate explicitly the legal basis under which a product has been approved. This information is publicly available in the EPAR (European Public Assessment Report) on the EMA website. However, for similar biological medicinal products, the following statement can be found under section 5.1 of the SmPC: "(Invented) Name is a Biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency <http://www.ema.europa.eu>".

#### References

- [European Public Assessment Reports: Biosimilars](#)

### ***3.3. Will my similar biological medicinal product be considered interchangeable with the reference medicinal product?***

The decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions.

#### **References**

- [Regulation \(EC\) No 726/2004](#)

## 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 similar biological medicinal product following changes to the innovator product? Rev. Dec 2015*

If a centrally authorised similar biological medicinal product refers to a centrally authorised innovator product, the EMA will provide the Marketing Authorisation Holder (MAH) of the similar biological medicinal product at the time of the CHMP Opinion on a safety variation for the reference medicinal product with the exact wording to be implemented and will request the MAH to 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 innovator.

In the case, the implementation of the change requires to be further substantiated by new additional data to be submitted by the MAH of the similar biological medicinal product (e.g. comparability); a type II variation will be requested.

For centrally authorised similar biological medicinal products of nationally authorised innovator products the EMA will provide the MAH of the similar biological medicinal product, upon notification by the respective competent authority, with the exact wording to be implemented and will request the MAH to submit a variation as soon as possible or at the latest within 2 months to implement the changes in the PI as adopted for the innovator.

The EMA Secretariat shall handle and finalise such “administrative” harmonisation between the reference and the similar biological medicinal product.

Simple reference to fees payable can be found in [the general pre-submission guidance for all products](#).

### 4.3. *How should the outcome of the safety variation be communicated to the outside world? Rev. Feb 2019*

The EPAR, the SmPC 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 SmPC and therefore request the MAHs of the innovator and Biosimilars to disseminate a Direct Healthcare Professional Communication (DHPC), commonly called “Dear Doctor-Letter”. 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 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 similar biological 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 timeframe 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. 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 SmPC: the indications, posology, contraindications and warnings. In rare cases the changes may also relate to quality problems requiring a change of the Product Information.

#### ***4.6. When should a USR be submitted for a similar biological medicinal product following a USR to the innovator product?***

If the centrally authorised similar biological medicinal product refers to a centrally authorised innovator product, the Agency will provide, once the USR has been finalised for the innovator product and the final wording of the PI has been agreed, the MAH of the similar biological medicinal 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 innovator.

For centrally authorised similar biological products of nationally authorised innovator products the Agency will provide, upon notification by the respective competent authority, the MAH of the similar

biological 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 innovator.

Once received, the CHMP assessment of the USR for the similar biological medicinal product will be finalised within 24 hours.

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

#### ***4.7. How should the outcome of the USR be communicated to the outside world? Rev. Feb 2019***

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 SmPC. MAHs are therefore requested to prepare and disseminate a Direct Healthcare Professional Communication (DHPC), commonly called "Dear Doctor-Letter". 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 as 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.

#### ***4.8. How soon after the USR for a similar biological medicinal product should the revised product information be implemented for batch release purposes?***

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 SmPC 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.](#)
- [SOP on Urgent Safety Restrictions SOP/H/3052](#)
- [EMA Post-authorisation guidance EMEA/H/19984/03](#)

#### **4.9. Do the provisions of the marketing /cessation notification and the sunset clause apply to my similar biological application?**

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 similar biological medicinal products.

For a similar biological 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 product 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 European 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 dates 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 \(section 2.4.2\) and Chapter 4 \(section 9\), 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 \(EMEA/180079/2005\)](#)