EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2013
CHMP/437/04 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Similar Biological Medicinal Products

Draft

Draft agreed by Biosimilar Medicinal Products Working Party and Biologics Working Party	March 2013
Adopted by CHMP for release for consultation	25 April 2013
Start of public consultation	30 April 2013
End of consultation (deadline for comments)	31 October 2013

This guideline replaces the Guideline on similar biological medicinal products (CHMP/437/04).

Comments should be provided using this template. The completed comments form should be sent to BMWP.Secretariat@ema.europa.eu

Keywords	similar biological medicinal product, biosimilar, biosimilarity exercise, comparability, reference medicinal product

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Guideline on Similar Biological Medicinal Products

Table of contents

Executive summary

This Guideline outlines the general principles to be applied for similar biological medicinal products (also known as biosimilars) as referred to in Section 4, Part II, Annex I to Directive 2001/83/EC, as amended, where it is stated that '*the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency*'.

This Guideline describes and addresses the application of the biosimilar approach, the choice of the reference product and the principles of establishing biosimilarity.

1. Introduction (background) and scope

1.1. Regulatory framework

A company may choose to develop a new biological medicinal product claimed to be "similar" to a reference medicinal product, which has been granted a marketing authorisation in the European Economic Area (EEA) on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. For this scenario, the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I to the said Directive lays down the requirements for the Marketing Authorisation Applications (MAAs) based on the demonstration of the similar nature of the two biological medicinal products. Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the similar biological medicinal product and the chosen reference medicinal product authorised in the EEA.

1.2. Scope

The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to substantiate the claim of similarity (or biosimilarity) used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product (as defined in Section 3.2.1.1, Part I, Annex I to Directive 2001/83/EC, as amended).

The scope of the guideline is to fulfil the requirement of section 4, Part II, Annex I to Directive 2001/83/EC, as amended, which states that *'the general principles to be applied [for similar biological medicinal products] are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency'*.

Therefore, the purpose of this guideline is to describe the concept of similar biological medicinal products (hereby designated as "biosimilars") and to outline the general principles to be applied. The CHMP guidelines addressing the planning and conduct of biosimilar comparability studies should always be read in conjunction with relevant scientific guidelines and legislative provisions in force in the Union.

Companies developing biosimilars are invited to contact Regulatory Authorities to obtain further advice on their development, whenever there is a need for more detailed information than provided in the guidelines already available.

The EMA evaluates biosimilar medicines for authorisation purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine.

2. Legal basis and relevant guidelines

The legal basis for similar biological applications can be found in Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC, as amended.

The data requirements for similar biological medicinal products are found in Part II, Section 4 of the Annex I of Directive 2001/83/EC, as amended.

In addition, the following guidelines should be taken into account:

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMA/CHMP/BWP/247713/2012)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/ EMEA/CHMP/BMWP/42832/2005)

Specific product related guidelines can be found in the EMA website under Home, Regulatory, Human medicines, Scientific guidelines, Multidisciplinary, Biosimilar.

3. General principles

3.1. Application of the "biosimilar" approach

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

In principle, the concept of a biosimilar is applicable to any biological medicinal product. However, in practice, the success of developing a biosimilar will depend on the ability to produce a close copy to the reference medicinal product and demonstrate the similar nature of the concerned products. This includes physicochemical and biological characterisation and requires knowledge on how to interpret any differences between a biosimilar and its reference medicinal product.

Therefore:

- The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) which is applicable to most chemically-derived medicinal products is in principle not appropriate to biological/biotechnology-derived products due to their complexity. The "biosimilar" approach, based on a comprehensive comparability exercise, will then have to be followed.
- The scientific principles of such a biosimilar comparability exercise are based on those applied for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (as outlined in ICH Q5E).
- Whether the 'biosimilar' approach would be applicable for a certain biological medicinal product depends on the state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences, e.g. as regards the possibility to identify comparability margins, availability of sensitive clinical endpoints and model conditions etc.
- Biosimilar comparability exercises are more likely to be applied to products that are highly purified and can be thoroughly characterised (such as many biotechnology-derived medicinal products). The 'biosimilar' approach is more difficult to apply to other types of biological medicinal products, which by their nature are more difficult to characterise, such as biological substances arising from

extraction from biological sources and/or those for which little clinical and regulatory experience has been gained.

- The posology and route of administration of the biosimilar should be the same as that of the reference medicinal product. Deviations from the reference product as regards formulation or excipients require justification or further studies.
- Intended changes to improve efficacy are not compatible with the biosimilarity approach.
- The biosimilar shall, with regard to the quality data, fulfill all requirements for Module 3 as defined in Annex I to Directive 2001/83/EC, as amended and satisfy the technical requirements of the European Pharmacopoeia and any additional requirements, such as defined in relevant CHMP and ICH guidelines.
- Safety and efficacy of biosimilars have to be demonstrated in accordance with the data requirements laid down in Directive 2001/83/EC, as amended. General technical and product-class specific provisions for biosimilars are addressed in EMA/CHMP guidelines (see section 2). For situations where product-class specific guidance is not available, applicants are encouraged to seek scientific advice from Regulatory Authorities.
- In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified in accordance with Article 102(e) of Directive 2001/83/EC, as amended. In particular, brand name and batch number should be recorded for any biological medicinal product.

3.2. Choice of Reference Product

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

A single reference medicinal product, defined on the basis of its marketing authorisation in the EEA, should be used as the comparator throughout the comparability programme for quality, safety and efficacy studies during the development of a biosimilar in order to allow the generation of coherent data and conclusions.

However, 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 in certain clinical studies and 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 (i.e. ICH countries). In addition, it will be the Applicant's responsibility to establish that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA.
If certain studies of the development programme are performed with only 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 typically 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 clinical PK and/or PD bridging studies data for all three products. All comparisons should meet the target acceptance criteria for analytical and PK/PD similarity which will be determined on a case-by-case/product-type basis. Moreover, the overall acceptability of such an approach and the type of acceptable bridging data will be a case-by-case/product-type decision, and should be discussed

upfront with the Regulatory Authorities. A final determination about the adequacy of the scientific justification and bridge will be made during the review of the application.

3.3. Principles of establishing biosimilarity

The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the reference product by the best possible means, ensuring that the previously proven safety and efficacy of the reference medicinal product also applies to the biosimilar.

A biosimilar should be highly similar to the reference medicinal product in physicochemical and biological terms. Any observed difference would have to be duly justified with regard to their potential impact on safety and efficacy and could contradict the biosimilar principle. Differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be explained, but may not preclude biosimilarity. If the biosimilar comparability exercise indicates early on that there are significant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development should be considered instead.

A stepwise approach is normally recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical *in vivo* studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical in vitro data.

The ultimate goal of the comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. Therefore, studies should be sensitive enough with regard to design, population, endpoints and conduct to detect such differences.

In specific circumstances, e.g. for structurally more simple biological medicinal products, a comparative clinical efficacy study may not be necessary if similarity of physicochemical characteristics and biological activity/potency of the biosimilar and the reference product can be convincingly shown and similar efficacy and safety can clearly be deduced from these data and comparative PK data. Such an approach may have to be supported by additional data, for example *in vitro* and/or clinical PD data from a comprehensive comparative PD fingerprint approach.

In general, such simplified approaches should always be discussed with Regulatory Authorities before commencement of such development.