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Guideline on similar biological medicinal products

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* After adoption by CHMP applicants may apply some or all provisions of this guideline in advance of this date.

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*

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Guideline on similar biological medicinal products

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Executive summary

This Guideline outlines the general principles to be applied for similar biological medicinal products (also known as biosimilars) as referred to in 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 for establishing biosimilarity.

1. Introduction (background) and scope

1.1. Regulatory framework

A company may choose to develop a 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 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. Applying these principles will be indicated below as the "biosimilar approach".

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 European Union.

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

Evaluation of biosimilar medicines for authorisation purposes by the EMA do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. Substitution policies are within the remit of the EU member states.

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 dossier 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/CHMP/BMWP/42832/2005 Rev)

  Specific product related guidelines can be found on the EMA website under Home, Human Regulatory, Scientific guidelines, Multidisciplinary guidelines, 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) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.

In principle, the concept of biosimilarity is applicable to any biological medicinal product. However, in practice, the success of developing a biosimilar will depend on the ability to produce a medicinal product which is similar to the reference medicinal product, and to convincingly demonstrate the similar nature of the concerned products. This includes comprehensive physicochemical and biological characterisation and comparison 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 sufficient to demonstrate similarity of 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 methods, the manufacturing processes employed, as well as the availability of clinical models to evaluate comparability.
- The biosimilar approach is more likely to be successfully 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 active substance of a biosimilar must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. For example, for an active substance that is a protein, the amino acid sequence is expected to be the same.
- The posology and route of administration of the biosimilar must be the same as those of the reference medicinal product.
- Deviations from the reference product as regards strength, pharmaceutical form, formulation, excipients or presentation require justification. If needed, additional data should be provided. Any difference should not compromise safety.
- Intended changes to improve efficacy (e.g. glycooptimisation) are not compatible with the biosimilarity approach. However, differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be addressed, but may not preclude biosimilarity.
- The biosimilar shall, with regard to the quality data, fulfil 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.
- Comparable safety and efficacy of a biosimilar to its reference product has to be demonstrated or otherwise justified 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.
- If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.
- There is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product, e.g. in the context of a change in the manufacturing process, once the Marketing Authorisation has been granted.
- In order to support pharmacovigilance monitoring and in accordance with Article 102(e) of Directive 2001/83/EC, as amended, all appropriate measures should be taken to clearly identify any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to its brand name and batch number.

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 *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). In addition, it will be the Applicant's responsibility to demonstrate that the comparator authorised outside the EEA is representative of the reference product authorised in the EEA.

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.

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 differences have to be duly justified with regard to their potential impact on safety and efficacy.

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.

Generally, the aim of clinical data is to address slight differences shown at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product. Clinical data cannot be used to justify substantial differences in quality attributes

If the biosimilar comparability exercise indicates that there are relevant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full Marketing Authorisation Application should be considered instead.

The ultimate goal of the biosimilar 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, conduct, endpoints and/or population to detect such differences.

In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern.

It is recommended to discuss such simplified approaches with Regulatory Authorities.