



London, 22 February 2006
EMEA/CHMP/BWP/49348/2005

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING
BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES**

DRAFT AGREED BY BWP	February 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	16 March 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 June 2005
AGREED BY BWP	February 2006
ADOPTION BY CHMP	22 February 2006
DATE FOR COMING INTO EFFECT	01 June 2006

KEYWORDS	Similar biological medicinal product, recombinant proteins, quality, comparability exercise
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EXECUTIVE SUMMARY

The *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005)* lays down the quality requirements for a biological medicinal product claiming to be similar to another one already marketed.

The guideline addresses the requirements regarding manufacturing processes, the comparability exercise for quality, considering the choice of reference product, analytical methods, physicochemical characterisation, biological activity, purity and specifications of the similar biological medicinal product.

1. Introduction

1.1 Purpose

A company may choose to develop a new biological medicinal product claimed to be similar (Similar Biological Medicinal Product) in terms of Quality, Safety and Efficacy to an original, reference medicinal product, which has been granted a marketing authorisation in the Community (see Guideline on Similar Biological Medicinal Products, CHMP/437/2004).

Similar biological medicinal products are manufactured and controlled according to their own development, taking into account relevant and up-to-date information.

Comparison can be made against the official data, e.g. pharmacopoeial monographs or against other published scientific data. However, such comparisons at the level of both active substance and finished product are limited and not sufficient to establish all aspects pertinent to the evaluation. Consequently, an extensive comparability exercise will be required to demonstrate that the similar biological medicinal product has a similar profile in terms of quality, safety and efficacy to the reference medicinal product.

It is acknowledged that the manufacturer developing similar biological medicinal products would normally not have access to all necessary information that could allow an exhaustive comparison with the reference medicinal product. Nevertheless the level of detail must be such that firm conclusions can be made.

Based on the comparability approach and when supported by sufficiently sensitive analytical systems, the comparability exercise at the quality level may allow a reduction of the non-clinical and clinical data requirements compared to a full dossier. The similar biological medicinal product may refer to the non-clinical and clinical data previously generated with the reference product, however, non-clinical and clinical data will normally be required as identified in related non-clinical and clinical guidelines on similar biological medicinal products.

1.2. Regulatory framework

A full quality dossier (CTD Module 3) is required as detailed in current legislation and this should be supplemented by the demonstration of comparability, as discussed in this guideline. 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 with separately when presenting the data.

This guideline should be read in conjunction with all relevant existing guidelines pertaining to medicinal products containing biotechnology-derived proteins as active substance, and in conjunction with Part II of the Annex I of Directive 2001/83/EC, as amended.

2. Scope

This guideline addresses quality issues during demonstration of comparability for Similar Biological Medicinal Products containing recombinant DNA-derived proteins. As a consequence, the principles adopted and explained in this document apply to proteins and peptides, their derivatives and products of which they are components (e.g. conjugates). For other situations see Guideline on Similar Biological Medicinal Products, CHMP/437/04.

This guideline does not address the comparability exercise for changes introduced in the manufacturing process of a given product (i.e. changes during development and post-authorisation), as addressed by ICH Q5E.

3. Legal Basis

Directive 2001/83/EC, as amended and Part II of Annex I of Directive 2001/83/EC, as amended.

4. Manufacturing process of a similar biological medicinal product

The similar biological medicinal product, as for any other biological medicinal product is in part defined by its own specific manufacturing process for both active substance and medicinal product. These processes should be developed and optimised taking into account state-of-the-art information on manufacturing processes (i.e. expression system / cell substrate, culture, purification, viral safety, excipients, formulation, primary packaging interactions, etc.) and consequences on product characteristics. In addition, each medicinal product is defined by the molecular composition of the active substance resulting from its process, which may introduce its own process related impurities.

Consequently, the similar biological medicinal product is defined by the following two sets of characteristics: i) related to the characteristics of the molecule (including product related substances/impurities), and ii) related to its process (which may affect molecular characteristics and includes process related impurities). It is the duty of the Applicant to demonstrate the consistency and robustness of his own process according to existing guidelines.

Formulation studies should be considered in the course of the development of a suitable dosage form, even if excipients are qualitatively and quantitatively the same as the reference product. These studies should demonstrate the suitability of the proposed formulation with regards to stability, compatibility (i.e. with excipients, diluents and packaging materials), and integrity of the active substance (both biologically and physico-chemically) for its intended medicinal use.

As is the case for any biotechnology-derived medicinal product, a comparability exercise (as described in ICH Q5E) should be considered when a change is introduced into the manufacturing process (active substance and finished product) during development. For the purposes of clarity, any comparability exercise(s) for process changes introduced during development should be clearly identified and addressed separately from the comparability exercise versus the reference product. See also Section 1.2.

Although it is acknowledged that the manufacturing process will be optimized during development, it is advisable to generate the required clinical data for the comparability study with product manufactured with the final manufacturing process and therefore representing the quality profile of the batches to be commercialised.

5. Comparability exercise versus reference product, quality aspects

Although quality aspects of a similar biological medicinal product are a fundamental element in the comparability exercise versus the reference medicinal product, quality aspects should always be considered with regard to any implications for safety and efficacy. A stepwise approach should be undertaken to justify any differences in the quality attributes of the similar biological medicinal product versus the reference medicinal product in order to make a satisfactory justification of the potential implications with regard to the safety and efficacy of the product.

It is not expected that the quality attributes in the similar biological and reference medicinal products will be identical. For example, minor structural differences in the active substance, such as variability in post-translational modifications may be acceptable, however, must be justified. Likewise, differences between the impurity profiles of the similar biological medicinal product and the reference medicinal product should be justified and would be considered on a case-by-case basis, and supported by the comparability exercise for quality attributes in relation to safety and efficacy.

Therefore, differences in impurity profiles and significant differences in product related substances may have consequences with regard to the amount of non-clinical and clinical data which may be required in order to make satisfactory justification of the safety and efficacy of the similar biological medicinal product.

5.1. Reference product for similar biological medicinal products

Comparability of the similar biological medicinal product with the chosen reference product should be addressed for both the medicinal product and the active substance in the medicinal product.

The reference medicinal product must be authorised in the Community. Although the comparability exercise can be facilitated when the pharmaceutical form, formulation, strength, etc. of the similar biological medicinal product are the same as the reference medicinal product, other approaches may be considered by the applicant. In any case, a clear scientific justification of the criteria followed to select the reference medicinal product should be provided, with specific attention to its critical parameters and quality attributes. The same reference medicinal product must be used for all three parts of the dossier (i.e. Quality, Safety and Efficacy).

The brand name, pharmaceutical form, formulation and strength of the reference medicinal product used in the comparability exercise should be clearly identified. The shelf life of the reference product should be considered when performing a comparability exercise, and its effect on the quality profile should be discussed where appropriate.

In order to provide assurance that the molecular structure of the active substance present in the similar biological medicinal product can be considered comparable to that in the reference medicinal product, it is generally necessary to conduct appropriate comparative tests at the level of the active substance. This comparison and also with regard to impurity profiles is considered further, below. In cases where the required analyses of quality attributes of the active substance of the reference product can be made at the finished product stage, testing of the isolated active ingredient may not be needed.

The direct comparison of the active substance in the similar biological medicinal product to a publicly available standard as a reference (i.e. Ph. Eur., WHO, etc.) is not appropriate to demonstrate comparability of the active substance since this material may not have known and defined safety and efficacy profiles. However, the use of these standards plays an important role during development, as discussed further below. In addition, the manufacturer of the similar biological medicinal product generally does not have access to the active substance in the reference medicinal product, and cannot directly compare his active substance to the one used in the reference medicinal product.

Nevertheless, the manufacturer of the similar biological medicinal product should demonstrate, using state of the art analytical methods that the active substance used in the comparability exercise is representative of the active substance present in the reference medicinal product. In certain situations, the analytical tools used for characterisation may not be capable of directly comparing the active substance in the similar biological medicinal product versus the active substance present in the reference medicinal product. In these situations, the Applicant should use suitable approaches to isolate representative active substance derived from the reference medicinal product in order to perform the comparative analysis at the active substance level. These approaches should be appropriately validated in order to demonstrate the suitability of the sample preparation process.

5.2 Analytical methods for similar biological medicinal products

Extensive state-of-the-art characterisation studies should be applied to the similar biological and reference medicinal products in parallel at both the active substance and the medicinal product levels to demonstrate with a high level of assurance that the quality of the similar biological medicinal product is comparable to the reference medicinal product.

5.2.1 Considerations on analytical procedures

- Suitability of available analytical methods

Given the complexity of the molecule and its inherent heterogeneity, the set of analytical techniques should represent the state-of-the-art. It is the duty of the manufacturer to demonstrate that the selected methods used in the comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality.

- Validation of analytical methods

Methods used in the characterisation studies form an integral part of the quality data package and should be appropriately qualified for the purpose of comparability. Before entering the clinical trial(s) needed for comparability purposes, release tests should be validated in accordance with the ICH Harmonised Tripartite Guidelines “Validation of Analytical Procedures: Definitions and Terminology” and “Validation of Analytical Procedures: Methodology”.

If available, standards and reference materials (e.g., from Ph. Eur., WHO, etc.) should be used for method qualification and validation.

5.2.2 Physicochemical properties

The physicochemical comparison comprises the evaluation of physicochemical parameters and the structural identification of product-related substances and impurities, including the determination of degradation by performing stress and accelerated stability studies. A physicochemical characterisation program should include a determination of the composition, physical properties, primary and higher order structures of the active substance of the similar biological medicinal product. An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic process, therefore, the similar biological medicinal product can contain a mixture of post-translationally modified forms. Appropriate efforts should be made to investigate and identify these forms.

5.2.3 Biological activity

The comparability exercise should include an assessment of the biological properties of the similar biological medicinal product and the reference medicinal product. Biological assays using different approaches to measure the biological activity should be considered as appropriate (i.e. depending on the biological properties of the product). The results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate. These assays should comply with appropriate European Pharmacopoeia requirements for biological assays, if applicable.

5.2.4 Purity and impurities

The purity and impurity profiles of the active substance and medicinal product should be assessed both qualitatively and quantitatively by a combination of analytical procedures for both reference and similar biological medicinal products. It is acknowledged that the manufacturer developing similar biological medicinal products would normally not have access to all necessary information that could allow an exhaustive comparison with the reference medicinal product. Nevertheless the level of detail must be such that firm conclusions on the purity and impurity profiles can be made.

The product-related substances and impurities in the similar biological medicinal product should be identified and compared to the reference product using state-of-the-art technologies. Additionally, information based on the analysis of samples stored under stress conditions, inducing selective degradation (e.g., oxidation, dimerisation) should be used for identification. Comparison of product-related substances, and of product-related impurities should be based on specific degradation pathways and potential post-translational modifications of the individual proteins. Accelerated stability studies of the reference and of the similar biological medicinal product can be used to further define and compare stability profiles.

Process-related impurities (e.g., host cell proteins, host cell DNA, reagents, downstream impurities, etc.) are expected to differ qualitatively from one process to another, and therefore, the qualitative comparison of these parameters may not be relevant in the comparability exercise. Nevertheless, state-of-the-art analytical technologies following existing guidelines and compendial requirements should be applied, and the impact of these process-related impurities should be confirmed by appropriate studies (which may include non-clinical and/or clinical studies).

6. Specifications

As for any biotechnology-derived product, the selection of tests to be included in the specifications is product specific and should be defined as described in ICH Q6B: *Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*. The rationale used to establish the proposed range of acceptance criteria should be described. Each acceptance criterion should be established and justified based on data obtained from lots used in non-clinical and/or clinical studies, and by data from lots used for the demonstration of manufacturing consistency, data from stability studies, relevant development data and data obtained from the comparability exercise (quality, safety and efficacy).

The setting of specifications should be supported by global reasoning based on the Applicant's experience of the similar biological medicinal product (quality, safety and efficacy) and his own experimental results obtained by testing the reference medicinal product. These data should demonstrate, whenever possible, that the limits set for a given test are not wider than the range of variability of the representative reference product, unless justified.