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Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)

Draft

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Once finalised, this guideline will replace 'The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005)'.

Comments should be provided using this template. The completed comments form should be sent to bwp.biosimilar.revision@ema.europa.eu

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Executive summary

The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues 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 medicinal product, analytical methods, physicochemical characterisation, biological activity, purity and quality attributes for relevant specifications of the similar biological medicinal product.

1. Introduction

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 a reference medicinal product, which has been granted a marketing authorisation in the Community. The development of a similar biological medicinal product (biosimilar) relies in part on the scientific knowledge gained from the reference medicinal product, provided that the active substance of the biosimilar has been demonstrated to be similar, in physicochemical and biological terms, to the active substance of the reference medicinal product.

Biosimilars are manufactured and controlled according to their own development, taking into account relevant and up-to-date information. The product development should be performed in accordance with relevant ICH and CHMP guidelines.

In contrast to the approach generally followed for generic medicinal products, a comparison of the biosimilar to a publicly available standard is not sufficient for the purpose of comparability. The biosimilar should be demonstrated to be similar to a reference medicinal product approved in the Community, which is selected by the company developing the biosimilar. Consequently, an extensive comparability exercise with the chosen reference medicinal product will be required to demonstrate that the biosimilar product has a similar profile in terms of quality, safety and efficacy to the reference medicinal product.

It is acknowledged that the manufacturer developing a biosimilar would normally not have access to all information that could allow an exhaustive comparison with the reference medicinal product, particularly with regards to the manufacturing process. Nevertheless the level of detail must be such that firm conclusions can be made.

If appropriately carried out, the comparability exercise at the quality level, including analysis of relevant quality attributes with sufficiently sensitive analytical tools, could allow for the submission of a Marketing Authorisation Application in accordance with Article 10(4) of Directive 2001/83/EC, as amended. In such situation, the applicant would normally be required to perform relevant non-clinical and clinical comparability program to complete the biosimilar development as laid down in the legislation and technical guidelines.

2. Scope

This guideline addresses quality aspects of the demonstration of comparability for similar biological medicinal products containing recombinant DNA-derived proteins and derivatives to support a Marketing Authorisation Application. Nevertheless, the principles explained in this document could apply to other biological products, on a case by case basis.

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 outlined by ICH Q5E.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part II of the Annex I to Directive 2001/83 as amended.

A full quality dossier (CTD Module 3) is required as detailed in current legislation and this should be supplemented by the demonstration of biosimilar comparability, as discussed in this guideline. Applicants should note that the comparability exercise for a biosimilar product versus the reference medicinal product is an additional element to the normal requirements of the quality dossier and should be discussed separately when presenting the data in Module 3.

4. Manufacturing process of a similar biological medicinal product

The development and documentation for biosimilars should cover two distinct but complementary aspects:

i) molecular characteristics and quality attributes (QA) of the target product profile should be comparable to the reference medicinal product;

ii) performance and consistency of the manufacturing process of the biosimilar on its own.

The quality target product profile (QTPP) of a biosimilar should be based on data collected on the chosen reference medicinal product, including publicly available information and data obtained from extensive characterisation of the reference medicinal product. The QTPP should be detailed at an early stage of development and forms the basis for the development of the biosimilar product and its manufacturing process. It is important to identify critical quality attributes that may impact the safety and efficacy of the product.

A biosimilar is manufactured and controlled according to its own development, taking into account state-of–the-art information on manufacturing processes and consequences on product characteristics. As for any biological medicinal product, the biosimilar medicinal product is defined by the molecular composition of the active substance resulting from its process, which may introduce its own molecular variants, isoforms or other product-related substances as well as process-related impurities. Potential risks introduced by the proposed manufacturing process, as compared to the reference medicinal product, should be kept in mind during the development of a biosimilar. For instance, the use of novel expression systems should be carefully considered, as they may introduce additional risk, such as atypical glycosylation pattern, higher variability or even a different impurity profile, as compared to the reference medicinal product.

The formulation of the biosimilar does not need to be identical to that of the reference medicinal product. The applicant should take into account state-of-the-art technology and, regardless of the formulation selected, the suitability of the proposed formulation with regards to stability, compatibility (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and strength of the active substance should be demonstrated. If a different formulation and/or container/closure system to the reference medicinal product is selected (including any material that is in contact with the medicinal product), its potential impact on the safety and efficacy should be appropriately justified.

The stability of the biosimilar product should be determined according to ICH Q5C. Any claims with regard to stability and compatibility must be supported by data and cannot be extrapolated from the reference medicinal product.

It is acknowledged that the biosimilar will have its own lifecycle. When changes to the manufacturing process (active substance and/or finished product) are introduced during development, a comparability assessment (as described in ICH Q5E) should be performed. For the purposes of clarity, any comparability exercise(s) for process changes introduced during development should be clearly identified in the dossier and addressed separately from the comparability exercise versus the reference medicinal product. In addition, acknowledging the possible changes made to the process during the development of the biosimilar product, it is advisable to generate the required quality, safety and efficacy data for the biosimilar 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 medicinal product, quality aspects

5.1. Reference medicinal product

Several different batches of the reference medicinal product should be used to provide a robust analysis and to generate a representative quality profile. The relative age of the different batches of reference medicinal product should also be considered when establishing the target quality profile.

5.2. Comparability exercise

An extensive comparability exercise will be required to demonstrate that the biosimilar has a highly similar quality profile when compared to the reference medicinal product. This should include comprehensive side-by-side analyses of the proposed biosimilar and reference medicinal product using sensitive and orthogonal methods to determine not only similarities but also potential differences in quality attributes. Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy. If significant quality differences at the level of the active substance and/or the finished product are confirmed (e.g. atypical post-translational structure for which an impact on safety or efficacy cannot be excluded), it may be very challenging to claim similarity to the reference medicinal product, and thus, a full Marketing Authorisation Application may be more appropriate. Alternatively, the applicant could consider adequate revision of the manufacturing process to minimise these differences.

The aim of the comparability exercise is to demonstrate that the biosimilar product under development and the reference medicinal product chosen by the applicant are similar at the level of the finished product, i.e. the material that will be used to treat the patient. It is not expected that all quality attributes will be identical and minor differences may be acceptable, if appropriately justified. Particular attention should be given to quality attributes that might have a potential impact on safety or efficacy (e.g. impact on immunogenicity or potency) or that have not been identified in the reference medicinal product).

The applicant should demonstrate that the desired product and product-related substances present in the finished product of the biosimilar are highly similar to that of the reference medicinal product.

Where quantitative differences are detected, such differences should be demonstrated to have no relevance for the clinical performance of the product. Qualitative differences (i.e. presence or absence

of product-related substances and/or impurities) require a thorough justification, which may include non-clinical and/or clinical data, as appropriate. It is however preferable to rely on purification processes to remove impurities rather than to establish a preclinical testing program for their qualification.

The target acceptance criteria used in the comparability exercise should be justified. Quantitative limits should be established, where possible. The relevance of these limits should be discussed, taking into account the number of reference medicinal product lots tested, the quality attribute investigated and the test method used. These limits should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified. A descriptive statistical approach to establish target acceptance criteria for quality attributes could be used, if appropriately justified.

It should be noted that acceptance criteria used for the comparability exercise versus the reference medicinal product should be handled separately from release specifications (see also section 6 below).

As highlighted in section 4, it is advisable to generate the required quality, safety and efficacy data for the biosimilar comparability exercise with product manufactured with the final manufacturing process. While manufacturing changes may be expected during product development, it can be difficult to make a robust comparison with the reference medicinal product and various batches of biosimilar material manufactured using different/evolving processes.

It is acknowledged that the manufacturing process of the reference medicinal product may evolve through its lifecycle, and may lead to detectable differences in some quality attributes. Such events could occur during the development of a biosimilar medicinal product and may result in a development according to a QTPP which is no longer fully representative of the reference medicinal product available on the market. The ranges identified before and after the observed shift in quality profile could normally be used to support the comparability exercise at the quality level, as either range is representative of the reference medicinal product. Quality attribute values which are outside the range(s) of variability measured in the different profiles of the reference medicinal product should be appropriately justified with regard to their potential impact on safety and efficacy.

It should also be noted that there is no regulatory requirement for re-demonstration of biosimilarity once the Marketing Authorisation is granted.

An overview of the comparability exercise performed at the quality level should be provided, and should include an adequate description of the materials tested, the target acceptance criteria and analytical methods used.

The materials used in the comparability exercise (i.e. biosimilar and reference medicinal product) should be clearly identified (e.g. brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, number of batches, lot number, age of batches, use). Direct comparison of the biosimilar to a publicly available standard, e.g. Ph. Eur., WHO, is not sufficient for the purpose of comparability. Comparability should be demonstrated between the biosimilar and the reference medicinal product with an established safety and efficacy profile.

5.3. Analytical considerations

Extensive state-of-the-art characterisation studies should be applied to the biosimilar and reference medicinal products in parallel, to demonstrate with a high level of assurance that the quality of the biosimilar is comparable to the reference medicinal product.

It is the responsibility of the applicant 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. 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. If applicable, standards and reference materials (e.g. from Ph. Eur., WHO) should be used for method qualification and standardization.

For some analytical techniques, a direct or side by side analysis of the biosimilar and reference medicinal product may not be feasible or give limited information (e.g. due to the low concentration of active substance and/or the presence of interfering excipients such as albumin). In such cases, samples could be prepared from the finished product (e.g. extraction, concentration, and/or other suitable techniques). Where such preparation techniques are used, the preparation should be outlined, and the impact of the sample preparation process should be appropriately documented and discussed (e.g. comparison of active substances before and after formulation/deformulation preparation).

5.3.1. Physicochemical properties

The physicochemical comparison comprises the evaluation of physicochemical parameters and the structural identification of product-related substances and impurities. A physicochemical characterisation programme should include a determination of the composition, physical properties, primary and higher order structures of the biosimilar, using appropriate methodologies. The target amino acid sequence of the biosimilar should be confirmed and is expected to be the same as for the reference medicinal product. Any detected differences should be part of the micro-heterogeneous pattern of the reference medicinal product. The N- and C-terminal amino acid sequences, free SH groups and disulfide bridges should be compared, as appropriate. Any modifications/truncations should be quantified and any intrinsic- or expression system-related variability should be described, set at the minimum and justified.

If present, post-translational modified forms should be appropriately characterised. The carbohydrate profile, comprising the overall glycan profile, site-specific glycosylation patterns as well as site occupancy should be compared. The presence of unusual glycosylation structures (unusual monosaccharides, linkages or sequences) or variants not observed in the reference medicinal product may raise particular concerns and would require appropriate justification (see 5.2).

5.3.2. Biological activity

The comparability exercise should include an assessment of the biological properties of the biosimilar and the reference medicinal product as an essential step in establishing a complete characterisation profile. The biological activity is the specific ability or capacity of the product to achieve a defined biological effect. Biological assays using different and complementary approaches to measure the biological activity should be considered, as appropriate. Depending on the biological properties of the product different assay formats can be used, e.g. ligand or receptor binding assays, enzymatic assays, cell-based assays. Complementary approaches should be followed to accommodate the inherent limitations regarding validation characteristics of single bioassays. For biological assays, it should be demonstrated that the assay is sensitive and specific, and ideally sufficiently discriminatory to actually detect changes in biological activity. 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.

5.3.3. Immunochemical properties

In the case of monoclonal antibodies or related substances (e.g. fusion proteins based on IgG Fc), the immunological properties should be fully compared. This should normally include comparison of affinity of the products to the intended target. In addition binding affinity of the Fc to relevant receptors (e.g. FcγR, C1q, FcRn) should be compared. Appropriate methodologies should be employed to compare the ability to induce Fab- and Fc-associated effector functions.

5.3.4. Purity and impurities

The purity and impurity profiles of the active substance and medicinal product should be compared both qualitatively and quantitatively by a combination of analytical procedures. Appropriate orthogonal and state-of-the art methods should be used to compare the product-related substances and impurities. This comparison should take into account specific degradation pathways (e.g. oxidation, deamidation, aggregation) of the biosimilar product and potential post-translational modifications of the proteins. The age/shelf life of the reference medicinal product at the time of testing should be mentioned, and its potential effect on the quality profile should be discussed where appropriate. Comparison of relevant quality attributes, tested at selected time points and storage conditions (e.g. accelerated or stress conditions), could be used to further support the similarity of the degradation pathways of the reference medicinal product and of the biosimilar.

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 potential risks related to these newly identified impurities (e.g. immunogenicity) will have to be appropriately documented and justified.

5.3.5. Quantity

Quantity should be determined using an appropriate assay, and should normally be expressed in the same units as the reference medicinal product.

6. Specifications

As for any biotechnology-derived product, the selection of tests to be included in the specifications (or control strategy) for both drug substance and drug product, 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, any other relevant development data and data obtained from the biosimilar comparability exercise (quality, safety and efficacy).