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

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This guideline replaces 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005)'

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

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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 biosimilar 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

As outlined in the Guideline on similar biological medicinal products, 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 on the basis of a complete dossier 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, using state-of-the-art approaches and taking into account relevant and up-to-date information. The product development should be performed in accordance with relevant ICH and CHMP Quality guidelines.

A comparison of the biosimilar to a publicly available standard, e.g. a pharmacopoeial monograph, 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 product 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 analytical data submitted should be such that firm conclusions on the physicochemical and biological similarity between the reference medicinal product and the biosimilar can be made.

If appropriately carried out, the biosimilar 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 a situation, the applicant would normally be required to perform relevant non-clinical and clinical comparability programmes 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 biosimilar comparability for similar biological medicinal products containing recombinant DNA-derived proteins and derivatives to support a Marketing Authorisation Application. Nevertheless, as the biosimilar approach is accessible to any

biological medicinal products, 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 and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles described in Article 10(4) and part II of the Annex I to Directive 2001/83/EC 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. It should be discussed separately in section 3.2.R when presenting the data in Module 3.

In particular the current versions of the following guidelines should be consulted:

- Guideline on similar biological medicinal products (CHMP/437/04)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)
- Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010)
- ICH guideline Q5E: Note for guidance on biotechnological/biological products subjected to changes in their manufacturing process (CPMP/ICH/5721/03)
- ICH guideline Q5C: Note for guidance on quality of biotechnological products: Stability testing of biotechnological/biological products (CPMP/ICH/138/95)
- ICH guideline Q6B: Note For Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96)
- General quality guidelines can be found at the EMA website under Home, Regulatory, Human medicines, Scientific guidelines, Biologicals (European Medicines Agency - Scientific guidelines - Biological guidelines)

4. Manufacturing process of a similar biological medicinal product

The development and documentation for biosimilars should cover two distinct 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 form the basis for the development of the biosimilar product and its manufacturing process. This QTPP should be considered

as a development tool for which some target ranges may evolve during development, as further information on the reference medicinal product becomes available.

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 manufacturing process, which may introduce its own molecular variants, isoforms or other product-related substances as well as process-related impurities. As a consequence, the manufacturing process should be appropriately designed to achieve the QTPP. The expression system should be carefully selected, taking into account expression system differences that may result in undesired consequences, such as atypical glycosylation pattern, higher variability or a different impurity profile, as compared to the reference medicinal product.

The formulation of the biosimilar should be selected taking into account state-of-the-art technology and does not need to be identical to that of the reference medicinal product. 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 efficacy and safety of the biosimilar 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 performed to demonstrate biosimilarity versus the reference medicinal product. Process changes may occur during the development of the biosimilar product, however, it is strongly recommended to generate the required quality, safety and efficacy data for the demonstration of biosimilarity against the reference medicinal product using product manufactured with the commercial 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

General requirements for the reference medicinal product including considerations for global development of biosimilars are outlined in the CHMP Guideline on Similar Biological Medicinal Products.

The reference medicinal product used in the biosimilar comparability exercise at the quality level must 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). Multiple different batches of the reference medicinal product should be used to provide robust comparability data in order to generate a representative quality profile. Where several strengths or presentations are available, their selection should be appropriately justified. The age of the different batches of reference

medicinal product (relative to the expiry dates) should also be considered when establishing the target quality profile.

Publicly available reference standards (e.g. Ph. Eur.) cannot be used as the reference medicinal product for demonstration of biosimilarity. However, as discussed in section 5.3 below, the use of these standards plays an important role in method qualification and standardisation.

5.2. Biosimilar 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 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. These analyses should include side-by-side comparative studies unless otherwise justified. Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy.

If relevant quality differences are confirmed (for which the absence of a clinically relevant impact will be difficult to justify) it may be 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 or avoid these differences.

The aim of the biosimilar comparability exercise is to demonstrate that the biosimilar product and the reference medicinal product chosen by the applicant are similar at the level of the finished medicinal product. It is not expected that all quality attributes of the biosimilar product will be identical to the reference medicinal product. However, where qualitative and/or quantitative differences are detected, such differences should be justified and, where relevant, demonstrated to have no impact on the clinical performance of the product. This may include additional non-clinical and/or clinical data, as outlined in the Guideline on similar biological medicinal products, as well as in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Particular attention should be given to quality attributes that might have an impact on immunogenicity or potency, or that have not been identified in the reference medicinal product.

The applicant should demonstrate that the desired product (including product-related substances) present in the finished product of the biosimilar is similar to that of the reference medicinal product. In contrast, process-related impurities may differ between the originator and biosimilar products, although these should be minimised. It is preferable to rely on purification processes to remove impurities rather than to establish a non-clinical testing program for their qualification. Differences that may confer a safety advantage (e.g. lower levels of impurities) should be explained but are unlikely to preclude biosimilarity.

Quantitative ranges should be established for the biosimilar comparability exercise, where possible. These ranges should be based primarily on the measured quality attribute ranges of the reference medicinal product and should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified. The relevance of the ranges should be discussed, taking into account the number of reference medicinal product lots tested, the quality attribute investigated, the age of the batches at the time of testing and the test method used. A descriptive statistical approach to establish ranges for quality attributes could be used, if appropriately justified. It should be noted that acceptable ranges used for the biosimilar comparability exercise versus the reference medicinal product should be handled separately from release specifications (see also section 6).

It is acknowledged that the manufacturing process of the reference medicinal product evolves through its lifecycle, which 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 biosimilar comparability exercise at the quality level, as either range is representative of the reference medicinal product. Quality attribute values which are outside or between the range(s) determined for a quality attribute 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.

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 biosimilar comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity). 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). Thus samples could be prepared from the finished product (e.g. extraction, concentration, and/or other suitable techniques). In such cases, the techniques used to prepare the samples should be outlined, and their impact on the samples 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. 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. Any detected differences between the biosimilar and the reference medicinal product should be justified with respect to the micro-heterogeneous pattern of the reference medicinal product (e.g. C-terminal lysine variability).

The presence and extent of post-translational modifications (e.g. glycosylation, oxidation, deamidation, truncation) should be appropriately characterised. If present, carbohydrate structures should be thoroughly compared; including the overall glycan profile, site-specific glycosylation patterns as well as site occupancy. The presence of glycosylation structures or variants not observed in the reference

medicinal product may raise concerns and would require appropriate justification, with particular attention to non-human structures (non-human linkages, sequences or sugars).

5.3.2. Biological activity

The biosimilar 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, functional assays), taking into account their limitations. Complementary or orthogonal approaches should be followed to accommodate limitations regarding validation characteristics of single bioassays. If relevant, separate assays should be employed to evaluate binding and activation of receptors. Where appropriate, cross-reference to non-clinical and/or clinical section(s) of the dossier may be made. It should be demonstrated that the biological assays are sensitive, specific and sufficiently discriminatory. 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

As detailed in the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, the immunological functions of monoclonal antibodies and related substances (e.g. fusion proteins based on IgG Fc) should be fully compared. This would normally include a 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, unless justified. Appropriate methodologies should also 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 biosimilar and the reference 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 identify and 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. Therefore, the qualitative comparison of these parameters may not be relevant in the biosimilar 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 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 be expressed in the same units as the reference medicinal product. A comparable strength should be confirmed for the biosimilar and 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. The rationale used to establish the proposed range of acceptance criteria for routine testing should be described.

The claimed shelf life of the product should be justified with full stability data obtained with the biosimilar medicinal product. Comparative real-time, real-condition stability studies between the biosimilar and reference medicinal product are not required.