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Change history

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3.1	01.03.2021	Formal adjustments to the header and footer No content adjustments to the previous version.	dei
3.0	01.01.2020	Clarification in section 5.4.1 on the retrievability of data, deletion of a sentence in section 5.9 and various changes to wording.	stb
2.0	29.05.2019	Inclusion of LMWH as biosimilars with corresponding additions in sections 1 to 4, 7.4 and 8, further details in section 5.4.1 explaining why it is appropriate to use a foreign comparator product instead of the Swiss reference product and clarifying that the DMF concept is not applicable to biological active substances (section 7.4). Correction: authorised by the European Commission not the EMA.	stb
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1 Definitions, terms, abbreviations

1.1 Definitions

1.1.1 Biosimilar

A biosimilar is a biological medicinal product having sufficient similarity with a reference product authorised by Swissmedic and which refers to its documentation (Art. 4 para. 1 let. a^{novies} TPA).

1.1.2 Reference product

The reference product is the biological medicinal product authorised in Switzerland and used in the biosimilar approval documentation as a reference for the comparability of its pharmaceutical quality, efficacy and safety (Art. 4 para. 1 let. a^{octies} TPA). It was authorised by Swissmedic on the basis of complete documentation in the procedure according to Article 11 TPA. Biosimilars themselves may not be used as reference products.

1.1.3 Comparator product

The comparator product is the product with which the biosimilar is compared, in respect of pharmaceutical quality, biological activity and safety, in comprehensive comparability exercises.

The reference product from Switzerland or the product authorised by the European Commission or US FDA, and still available on the market, may be used as the comparator product. Complementary studies can also be carried out with comparator products from other countries with comparable medicinal product control. In this context, Swissmedic currently recognizes the following countries, based on Art. 16 para. 4 TPO: Australia, EU and EFTA member states, Japan, Canada, New Zealand, Singapore and the USA, and publishes a corresponding list on its website (see *List of all countries with comparable human medicinal product control HMV4*).

If a foreign comparator product is used instead of the Swiss reference product, its suitability must be demonstrated according to chapter 5.4.

1.2 Abbreviations

CHMP	Committee for Medicinal Products for Human Use of the EMA
EFTA	European Free Trade Association
EMA	European Medicines Agency

ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHP	Medicinal product Information for healthcare professionals
INN	International Nonproprietary Name
LMWH	Low Molecular Weight Heparins
NAS	New Active Substance
PD	Pharmacodynamics
PI	Medicinal product Patient information
PK	Pharmacokinetics
RMP	Risk Management Plan
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (Therapeutic Products Ordinance, TPO) (SR 812.212.21)
TPLO	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the Simplified Licensing of Therapeutic Products and the Authorisation of Therapeutic Products by the Notification Procedure (SR 812.212.23)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (SR 812.212.22)
WHO	World Health Organisation

2 Introduction and objective

In accordance with Art. 2 para. 1 let. e in conjunction with Art. 12, para. 6 TPLO Swissmedic can, on the one hand and within the framework of the authorisation of biosimilars, grant facilitations with regard to documentation and evidence requirements in accordance with Art. 3 et. seq. TPLRO for biotechnological products as per Art. 12, para. 5 let. d TPLO. On the other hand, Swissmedic grants corresponding facilitations for medicinal products belonging to the group of low molecular weight heparins (LMWH) which, as biological medicinal products according to Art. 2 para. 1 let. d TPLO, are sufficiently similar to a reference product authorised by Swissmedic and where reference is made to their documentation. This guidance document specifies the conditions under which Swissmedic grants this. This document also describes:

- the requirements regarding the authorisation of biosimilars in Switzerland
- the valid regulatory framework conditions
- the justifications required in the case of requests to submit simplified documentation
- the requirements concerning the documentation to be submitted in the authorisation application

Swissmedic uses this guidance document primarily as a resource for applying the legal provisions in a uniform and equitable manner. The purpose of the document is to make transparent to the applicant, which requirements must be fulfilled so that Swissmedic can process corresponding applications as quickly and efficiently as possible. Swissmedic assesses the application documentation within the framework of this guidance document and in accordance with the current status of science and technology, and also takes into consideration the currently valid edition of the pharmacopoeia, the EU and FDA *Guidance Documents* listed in the Annex, and any other relevant guidelines issued by the *Committee for Medicinal Products for Human Use (CHMP)* or the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)*.

3 Scope

This guidance document is valid for the authorisation of biosimilars, variations thereto and new therapeutic indications, provided these variations are already approved for the reference product.

The guidance document is also used if the authorisation of the biosimilar is applied for on the basis of Art. 13 TPA (Art. 17 para. 1 let. b TPO).

4 Legal framework

Art. 4 para. 1 let. a^{octies} and a^{novies} TPA define the reference product and biosimilar. Art. 2 para. 1 let. d and e TPLO define the biological and biotechnological medicinal products.

Art. 12 para. 5 let. d TPLO stipulates that biotechnological medicinal products are not eligible for simplified authorisation. However, in accordance with Art. 12, para. 6 TPLO, for authorisations of medicinal products according to Art. 12, para. 5 TPLO, Swissmedic may in justified cases lower the requirement for the submission of documentation and evidence in accordance with Art. 3 et seq. TPLRO.

If the authorisation of biosimilars is applied for on the basis of Art. 13 TPA, Art. 16–20 TPO, and particularly Art. 17 para. 1 let. b TPO, also apply.

5 General requirements and principles applied to assessments

5.1 Principle

For the authorisation of a biosimilar, the applicant must prove that the product is sufficiently similar to a reference product in respect of structure, pharmaceutical quality, biological activity, efficacy, safety and immunogenicity in order to exclude any clinically relevant differences with sufficient reliability. The scientific proof of sufficient similarity encompasses the entire physico-chemical and biological characterisation of the biosimilar and comparator product, comparative preclinical and clinical data and, as well as a critical assessment of the totality of evidence. A stepwise approach is recommended. Based on a comprehensive and comparative analysis, the applicant can show that the biosimilar and reference product are sufficiently similar, even with the possibly detected minor differences in the active substance molecules.

Clinical comparability should be demonstrated in at least one relevant sensitive patient population in one indication and with one dose for which the reference product is authorised. Clinically relevant differences relating to the indication and dose must be ruled out with adequate sensitivity and statistical probability. For this purpose, adequate endpoints, including scientifically justified equivalence and non-inferiority limits, should be selected for the clinical studies. Subject to an appropriate scientific review of all the data generated in comparability studies, including regulatory experience and an acceptable scientific rationale, the efficacy and safety can be extrapolated to other indications and doses that are authorised for the reference product. In order to clarify an appropriate strategy, obtaining Scientific Advice from Swissmedic at an early stage is recommended (see also Guidance document *Meeting for applicants held with the Authorisation sector HMV4*).

The similarity of the biosimilar to the reference product must be proved by means of comprehensive comparability studies, such as those described in the *Guideline on similar biological medicinal products* (CHMP/437/04 Rev. 1) in the ICH Guideline Q5E, and other guidelines listed in the Annex.

The dosage recommendation and route of administration of the biosimilar must be the same as those for the reference product. If the pharmaceutical form¹, dosage strength and/or the excipients of the biosimilar are different to those of the reference product, the difference must be justified and, if appropriate, proved by means of additional studies.

In the case of applications for the authorisation of a biosimilar with a corresponding request for the application of Art. 13 TPA, Swissmedic does not conduct its own scientific review if the biosimilar has already been approved by the European Commission or the medicines agency of the United States of America (US FDA).

¹ The description of the pharmaceutical form for a medicinal product, the type of use and the containers used is based on the glossary and the standard terms of the European pharmacopoeia.

(see Art. 16 to 20 TPO and the Guidance document *Authorisation human medicinal product under Art. 13 TPA HMV4*).

5.2 General requirements regarding documentation

For the authorisation of a biosimilar, the applicant should always submit complete documentation on the analytical, chemical and pharmaceutical tests relating to the biosimilar in accordance with Art. 3 TPLRO (Quality), as well as analytical comparability studies with the comparator product.

Concerning the preclinical and clinical study results, Swissmedic may accept reduced documentation. In such cases, the type of the biosimilar, the available analytical methods, the manufacturing processes used, and experience with the reference product from clinical, preclinical and pharmacovigilance perspectives are also taken into account.

Studies on the quality, biological activity, safety and efficacy of the biosimilar in comparison with the corresponding properties of the comparator products must be coherent, and provide conclusive proof of comparability. Therefore, the same comparator product should be used throughout. The use of additional comparator products should be justified, and the corresponding practice is specified in section 5.4.

In addition to the results from the applicant's own preclinical and clinical comparability studies, the applicant may also refer, in its application, to published scientific data on the safety and efficacy of the reference product or comparator product and regulatory statements. The influence of Scientific Advice provided by regulatory authorities on the development programme must be clearly shown in the documentation.

5.3 Request for submission of reduced documentation

If applicants intend to request the acceptance of reduced documentation for the authorisation of a medicinal product as a biosimilar, Swissmedic should be informed accordingly when submitting the application in the corresponding forms, i.e. *New authorisation of human medicinal product HMV4* and *Variations and authorisation extensions HMV4*, and in the cover letter. Applicants must justify the reasons for requesting the acceptance of reduced documentation and evidence for the medicinal product concerned, and the extent to which the medicinal product submitted for authorisation (biosimilar) demonstrates sufficient similarity with a biological medicinal product (reference product) authorised in Switzerland. If the differences compared to the reference product are so significant that the medicinal product submitted for authorisation cannot be considered to be a biosimilar, an application must be submitted for a medicinal product with a new active substance (see also Guidance document on *Authorisation of human medicinal product with new active substance HMV4*).

5.4 Requirements for comparator products

5.4.1 Comprehensive Comparability Exercise (incl. pivotal studies)

A single comparator product should be used for the comprehensive comparability studies. This should preferably be the reference product from Switzerland, although a similar product from the EU² or US market is also acceptable.

If the applicant uses a foreign comparator product even though a reference product is already authorised in Switzerland, its suitability compared to the Swiss reference product must be shown as follows:

- a) active substance name (INN), pharmaceutical form, dosage strength, qualitative composition and route of administration must be identical, and
- b) for the indications of the reference product authorised in Switzerland, a comparison with the corresponding clinical trials for the comparator product must be presented.
Corresponding information should be taken from the relevant Information for healthcare professionals, the EU SmPC, EPAR or US Label.

² A product from Norway, Iceland or Liechtenstein (EFTA) is accepted provided it is also authorised in the EU.

If an additional comparator product from the EU³ or US market is used for a clinical efficacy trial, a *three-way bridging* between the biosimilar, the EU³ and the US comparator product should be submitted in accordance with the *Guideline on similar biological medicinal products (CHMP/437/04 Rev 1)*. Clinical PK and/or PD data for all three products may also be required on a case-by-case basis. The suitability of the additional comparator products should also be justified, as described above under a) and b).

Reasons should be provided in module 1 (1.5.2) and any analytical data (*three-way bridging*) in Module 3.2.R.

If necessary, specific questions on this matter can be clarified during a Scientific Advice or Presubmission Meeting.

5.4.2 Supplementary *in vivo* studies

If products from other countries with comparable medicinal product control are used for supplementary clinical or *in vivo* preclinical studies, a *three-way bridging* is also required here.

5.5 Indications and extrapolation

In principle, an application for the authorisation of a biosimilar can be submitted for all those indications and corresponding dosage recommendations for the reference product that are not under document protection. A decision regarding the specific indications or dosage recommendations that can be authorised for the biosimilar by extrapolation from the reference product to the biosimilar can only be taken on a case-by-case basis. An extrapolation of indications and dosage recommendations for the reference product to the biosimilar is possible only if it is scientifically justified and the associated safety risk to patients is acceptable. The comparability between the biosimilar and the reference product, and thus the extrapolation to further indications and dosage recommendations, must be demonstrated in at least one sensitive indication and dosage or, if required, separately for each of the indications and dosage recommendations applied for. Sensitive clinical or pharmacodynamic endpoints should be selected depending on the indication and the nature of the biosimilar. The proof of safety and efficacy is based, for example, on clinical experience with the reference product and already authorised biosimilars, on available data from literature, on the mechanism of action of the active substance of the reference product in each indication, or on the receptors involved. Depending on the cell and co-receptors involved, the binding of the reference substance to the same receptor can have varying effects in different target cells and activate varying intracellular signalling pathways (e.g. normal cells compared to malignant cells or effect in arthritis compared to vasculitis). For the extrapolation of the safety data, applicants must take substance-relevant (e.g. modes of action, target cells and tissues) as well as patient-relevant factors (e.g. co-medication, co-morbidity, immunological status) and disease-relevant factors into consideration. The scope of the data to be submitted must be established taking all the findings from the comprehensive comparability studies and any possible concerns remaining into consideration (in accordance with EMEA/CHMP/BMWP/42832/2005 Rev. 1).

5.6 Document protection

Document protection according to Art. 11a TPA is not granted for biosimilars authorised for the first time, although special cases exist according to Art. 11b TPA.

On receipt of an application for authorisation of a biosimilar or new indication, new route of administration, new pharmaceutical form, new dosage strength and/or new dosage recommendation, Swissmedic checks for any existing document protection for the reference product according to Art. 11a, 11b and 12 TPA. If the document protection is still valid for at least two years on the date on which the application is received, or if the authorisation holder of the reference product has not provided the relevant permission, Swissmedic will not process the application.

If the authorisation holder of the reference product does not consent to any referencing to its protected data, the application for the biosimilar can be approved at the earliest on the first day after expiration of the protection period (see also Guidance document *Document protection HMV4*).

5.7 Medicinal product information (information for healthcare professionals and patient information)

The medicinal product information for the biosimilar must be identical, in the relevant passages, to that for the reference product, subject to regulatory-related changes, e.g. indications dosage strengths and/or dosage recommendations that are still covered by document protection for the reference product.

The following sentence must appear after the ATC code in the Information for healthcare professionals (IHP) in section *13 Properties/Effects*: "XY is a biosimilar".

For a newly authorised biosimilar, an equal-sided black inverted triangle must be included in the Information for healthcare professionals and the Patient information, accompanied by the remark "This medicinal product is subject to additional monitoring" (Art. 14a TPLRO and Guidance document *Product information for human medicinal products HMV4*).

For biosimilars, the date stated in the IHP section *Date of revision of the text* is independent of that for the reference product.

Changes to the product information for the reference product must, if applicable to the biosimilar, be the subject of a variation application and be adopted as necessary. Given the special authorisation procedure for biosimilars, the possibility of referring to study results for the reference product and the general updating obligation stated in Article 28 TPO, the authorisation holder of the biosimilar must keep the product information up to date. In particular, the authorisation holder must actively monitor changes to the safety sections in the product information for the reference product (Information for healthcare professionals: Contraindications, Warnings and precautions, Interactions and Undesirable effects) and must submit – spontaneously – either an appropriate application for a variation requiring approval or provide clear scientific justification if the texts are not to be adapted.

5.8 Name of the medicinal product

The name of a biosimilar must comply with the provisions of Article 9, paragraph 4 TPO, and can be either a creative name or the name of the active substance (name according to INN) linked to a company name. The INN name must comply with the requirements of the World Health Organisation (WHO).

5.9 Application for an extension and/or new therapeutic indication for a biosimilar

Applications for extensions and/or new therapeutic indication(s) for a biosimilar that have already been authorised for the reference product are reviewed on a case-by-case basis.

5.10 Interchangeability in individual cases

The active substance in a biosimilar and its reference product is essentially the same biological substance, although minor differences may exist as a result of the manufacturing processes. The authorisation of a biosimilar constitutes the confirmation that the differences between the biosimilar and the reference product do not affect safety or efficacy. However, the authorisation issued by Swissmedic does not contain any statement regarding whether a biosimilar can be used interchangeably with the reference product in the individual therapeutic case. Such a decision must be made exclusively by the prescriber, i.e. the attending physician.

6 Pharmacovigilance

The same pharmacovigilance requirements as those pertaining to an NAS (see Guidance document *Authorisation of human medicinal product with new active substance HMV4*) apply to biosimilars. For a biosimilar, the authorisation is granted on condition that periodic safety update reports (PSUR) (in accordance with Art. 58, para. 2 TPA in conjunction with Arts. 58 and 60 TPO) must be submitted.

In routine clinical use, it is possible that a particular biological medicinal product may be substituted for another. When reporting suspected adverse reactions to biological medicinal products, the precise

identification of the product concerned with regard to the manufacturing process is of particular importance (clear differentiation regarding whether the report concerns the reference product or a biosimilar). Therefore, all appropriate measures must be taken when sending such reports to identify the full name of the medicinal product and the batch number. Applicants must take these aspects into account as part of the RMP.

7 Requirements for documents to be submitted

7.1 Administrative documents (Module 1)

The general formal requirements for application documents and the formal requirements for Module 1 and the cover letter are laid down in Guidance document *Formal requirements HMV4* and in the associated Directory *Overview of documents to be submitted HMV4*.

If the dosage form, dosage strength and/or the excipients of the biosimilar are different from those of the reference product, these differences must be justified in the cover letter. The reason for requesting the acceptance of reduced mandatory documentation must also be stated, as must the extent to which the biosimilar concerned by the authorisation application demonstrates sufficient similarity with the reference product.

7.2 Environmental Risk Assessment (ERA, Module 1.6)

When applying for authorisation of biosimilars, an Environmental Risk Assessment (ERA) is required or a justification for not submitting one.

7.2.1 Information relating to Pharmacovigilance (Module 1.8)

Module 1.8 of biosimilar applications requires documentation on the *Risk Management System*. This involves an RMP according to EU directives or comparable documents (see also information sheet: *MU103_10_002d_MB RMP / ICH E2E – Informationen für die Einreichung [Information for submissions]*).

Of particular importance is the information concerning immunogenicity, which must be given appropriate emphasis within the RMP, taking into account interdisciplinary aspects as necessary. Activities carried out to obtain additional immunogenicity data must be discussed.

A comprehensive plan for the continual monitoring of safety following marketing approval must be submitted. The identified and potential risks of the reference product, and any additional identified or potential risks discovered during the development programme for the biosimilar, must be taken into consideration. The way in which these risks will continue to be monitored and investigated must be described in detail.

If possible, as well as routine pharmacovigilance activities, the Pharmacovigilance Plan should encompass additional activities, e.g. entering registries in major databases, whereby the study data is recorded in a standardised way. In addition, participation in existing registries is recommended: this activity should also be shown in the RMP.

The need for additional risk mitigation measures (i.e. those going beyond the medicinal product information) must be evaluated, taking the requirements for the reference product into consideration. Risk-reducing measures that have already been introduced for the reference product should also be included in the RMP for the biosimilar.

7.3 Overviews and summaries (Module 2)

7.3.1 Quality Overall Summary (2.3)

A summary and critical assessment of all key data from Module 3 must be submitted as a Quality Summary. The use of synoptic tables and graphics to illustrate essential data is encouraged.

In particular, appropriate reference should be made to the analytical comparability studies between the biosimilar and the comparator product from Module 3.

7.3.2 Nonclinical Overview (2.4)

A Nonclinical Overview according to ICH M4S must be submitted. It includes an integrated summary and risk assessment of the experimental and/or bibliographical data on pharmacology, PK and toxicology. Information about the GLP status of studies should be provided. Furthermore, the test strategy (*Overview of the Nonclinical Testing Strategy (2.4.1)*) should be presented. For biosimilars, this strategy focuses on the clarification of any differences from the comparator product in respect of physicochemical properties, biological activity, immunological properties and purity. The use of excipients/formulations that differ from the comparator product should also be critically reviewed.

Studies should be carried out in accordance with the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMA/CHMP/BMWP/42832/2005 Rev. 1) and the other product-specific biosimilar guidelines. New experimental studies should be listed with the study titles and should also include the relevant *in vitro* studies that were carried out as part of the quality investigations. The results of these comparability studies should be discussed in the Nonclinical Overview, in respect of their clinical relevance and extrapolation.

7.3.3 Clinical Overview (2.5)

The Clinical Overview consists of a summary of the key data on PK, PD, efficacy and safety that permits an assessment of the biosimilar.

The development of the biosimilar in accordance with international guidelines, and the selection of the studies carried out, must be presented and discussed. It must be clear from the Clinical Overview whether the final version of the biosimilar product or a development version was used in the studies that have been carried out. The comparator products used in the clinical trials, their batch numbers and their comparability must also be described in the Clinical Overview.

The PK studies must include information on the measurement methods used when determining the active substance levels. PK studies must prove bioequivalence between the biosimilar and the comparator product. In addition, the PK parameters for the biosimilar and the comparator product in healthy test subjects and in patients must be described in sufficient detail. The biological activity of the biosimilar and the comparator product must be described using multiple pharmacodynamic parameters, in the form of a comparability exercise.

The choice of clinically relevant endpoints, as opposed to those from more sensitive surrogate parameters, must be carefully considered when comparing the efficacy of the biosimilar and the comparator product. A sufficiently long study duration is important both in order to prove comparable efficacy and to assess the safety of the biosimilar.

If the biosimilar has undergone clinical testing for some but not all of the indications authorised for the reference product, an opinion must be given extending to the extrapolation of the non-tested indications. Age-related differences of the subjects must be taken into consideration, and the non-submission of paediatric data must be justified.

Among other aspects, applicants must analyse the extent to which the indication(s) included in the application for the biosimilar is/are based on the same mechanism of action as that of the active substance (e.g. as an immunosuppressant or an oncological), and the extent to which the various target populations for which the biosimilar is indicated could differ based on their underlying disease, concomitant disease and co-medication. A discussion should also be provided regarding whether the indications tested using the biosimilar are in fact appropriate to differentiate between the biosimilar and the reference product and whether the trial parameters used are sufficiently sensitive. The methods used to identify antibodies in the clinical trials on immunogenicity and their sensitivity regarding the identification of any difference between the biosimilar and the comparator product must be described. Any relevant differences regarding the manufacturing (possibly with regard to impurities in the finished product), the composition (e.g. excipients) and the shelf life (degradation products, formation of aggregates) must be discussed. Here, the risk of sensitisation to the biosimilar's active substance with regard to loss of efficacy and hypersensitivity reactions must be assessed in

particular. The triggering of autoimmune reactions or immune complex diseases must be addressed separately. In the case of differing routes of administration, the risk of an immunisation must be discussed separately for each type of application. The number of exposed patients and the duration of the clinical trial must be selected in accordance with the risk profile of the reference product. Here, the fact that evidence of differences in immunogenicity between the biosimilar and the reference product is more difficult to obtain than that for pharmacodynamic or clinical endpoints should be taken into consideration.

When assessing safety, emphasis must be placed on the discussion of antibody- and cell-mediated immunogenicity, and all relevant aspects must be presented. The risk of immediate reactions, infusion reactions, sensitisation effects and possible autoimmune reactions must be analysed. The analysis of immunogenicity must be carried out taking the pharmacodynamic and pharmacokinetic parameters of separate individuals into consideration. In addition, the kinetics of the therapeutic target must be considered. A possible transfer of antibodies to the foetus or to the mother's milk, and the consequences thereof, must be analysed. Here, differences between the comparator product and the biosimilar must be shown.

Where necessary, reference must be made to other modules of the documentation. The data on immunogenicity must be summarised and analysed in a separate section within the structure of the Clinical Overview.

The scope of the data to be submitted must be established taking all the findings from the comprehensive comparability studies and any remaining concerns into consideration (in accordance with EMEA/CHMP/BMWP/42832/2005 Rev. 1).

7.3.4 Nonclinical Summary (2.6)

The *Nonclinical Written and Tabulated Summaries on Pharmacology, Pharmacokinetics and Toxicology* should be submitted, taking ICH M4S into account.

It may be possible to omit individual subsections of the *Nonclinical Summaries* if sufficient justification is provided.

7.3.5 Clinical Summary (2.7)

The statements and information provided in the *Clinical Overview* must be presented in more detail in the *Summaries*. Since information on pharmacokinetic, pharmacodynamic and clinical details must be provided for biosimilars, separate *Summaries* must be submitted for *Biopharmaceutics, Clinical Pharmacology, Efficacy, and Safety*.

7.4 Documentation for the analytical, chemical and pharmaceutical tests (Module 3)

The analytical, chemical and pharmaceutical quality of the biosimilar must be documented in accordance with Article 3, TPLRO (see also Guidance document *Authorisation of human medicinal product with new active substance HMV4*).

Since the authorisation holder is responsible for the end product, it must possess complete knowledge of the starting materials and active substance manufacture. In the case of heparins (incl. LMWH), the porcine intestinal mucosa constitutes the starting material. Therefore, the complete manufacturing process (collection of the mucosa, intermediates, in-process controls, process validation, etc.), including all test methods, must be described in Module 3. Safety aspects play an important role here since the porcine starting material can potentially contain viruses, bacteria or other contaminants. In this context, full traceability (country of origin, abattoir, cross-contamination, health of the animals) by the authorisation holder directly responsible, according to therapeutic products legislation is essential. For these reasons, a procedure involving a Drug Master File / Active Substance Master File is not applicable to biological active substances. For the same reasons, the existence of a Certificate of Suitability of Monographs of the European Pharmacopoeia is not sufficient for an LMWH or for a heparin sodium intermediate; see also the EMA Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products, EMA/CHMP/BWP/429241/2013.

The comparability between the biosimilar and the comparator product (procured from the Swiss, EU/EFTA or US market) must be proved over several batches within the framework of characterisation/comparability studies reflecting the current status of science and technology.

The document must present, on the one hand, the molecular properties and the quality attributes of the biosimilar in comparison with the comparator product (comparable product profile), and on the other, demonstrate the consistent manufacturing of the biosimilar.

The comparability studies must be carried out in accordance with the *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)* (EMA/CHMP/BWP/247713/2012), and whenever possible, with the end product; if applicable, the active substance can be isolated from the end product.

The characterisation/comparability studies to prove comparability between the biosimilar and the comparator product must be carried out in parallel. Here, the physico-chemical properties (e.g. primary structure, glycosylation, content), the biological activity, the immunological properties and the purity (e.g. product-related impurities, product-related substances) should be taken into consideration appropriately, see also the ICH Guideline Q5E.

The establishment of the specifications (including the analysis methods used) for the active substance and the finished product must be justified in detail (see also ICH Q6B), while taking into consideration the preclinical and clinical data, batch analysis data (on release and shelf life, for the active substance or finished product respectively), plus data from the comparability study between the biosimilar and the comparator product.

7.5 Documentation for the pharmacological and toxicological tests (Module 4)

The efficacy and safety of the biosimilar must be proved in accordance with the requirements relating to documentation stated in Article 4, TPLRO. The documentation may, if sufficiently justified, refer to the preclinical data for the reference product.

In addition, comparative preclinical data must be submitted, from which any differences between the biosimilar and the comparator product must be evident. The causes of such differences must be justified in the application, and their effects must be scientifically assessed.

7.6 Documentation for the clinical trials (Module 5)

The clinical properties of the biosimilar must be proved in accordance with Article 5, TPLRO. Module 5 must include all clinical trials on test subjects and on patients that are submitted as trial reports, with the corresponding annexes. All clinical trials relating to the various development versions of the biosimilar should be submitted. Swissmedic decides on the extent to which the data from earlier versions of the biosimilar are relevant for the proof of biosimilarity and authorisation. The origin of the comparator product must be stated precisely in each trial report. The trial reports must clearly indicate whether the final version or a development version of the biosimilar product was used. The relevance of any differences must be critically assessed and be supported by appropriate bridging data. The application documentation may, if sufficiently justified, refer to the clinical data for the reference product.

The immunogenicity risks must be presented in all cases, must be proved by means of clinical data, and must be justified.

8 Annex

EMA documents:

The currently valid EMA guidelines on biosimilars can be found using the following link:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp

Overarching Guidelines	Reference number
Guideline on similar biological medicinal products	CHMP/437/04 Rev. 1
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	EMA/CHMP/BMWP/42832/2005 Rev. 1
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)	CHMP/BWP/247713/2012
Product-specific biosimilar guidelines	
Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human follicle stimulating hormone (r-hFSH)	CHMP/BMWP/671292/2010
Guideline on similar biological medicinal products containing interferon beta	EMA/CHMP/BMWP/652000/2010
Guideline on similar biological medicinal products containing monoclonal antibodies- non-clinical and clinical issues	EMA/CHMP/BMWP/403543/2010
Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision)	EMA/CHMP/BMWP/301636/08
Reflection Paper: Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha	EMA/CHMP/BMWP/102046/2006
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor	EMA/CHMP/BMWP/31329/2005
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing somatropin	EMA/CHMP/BMWP/94528/2005
Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues	EMA/CHMP/BMWP/32775/2005_Rev. 1
Other guidelines relevant for biosimilars	
Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use	EMA/CHMP/BMWP/86289/2010
Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues	EMA/CHMP/BMWP/101695/2006
Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins	EMA/CHMP/BMWP/14327/2006
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins	CHMP/EWP/89249/2004
Other guideline relevant for LMWH	
Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products	EMA/CHMP/BWP/429241/2013

FDA documents

The current FDA documents on biosimilars can be downloaded via the following link:

<https://www.fda.gov/drugs/guidances-drugs/all-guidances-drugs>

Here is a selection of these documents:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015):
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015):
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (December 2016):
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf>

ICH documents:

The currently valid ICH guidelines (grouped by Quality (Q), Safety (S), Efficacy (E) and Multidisciplinary (M) Guidelines) can be found using the following link: <http://www.ich.org/products>

The following are particularly relevant for biosimilars:

- Q5C: Stability Testing of Biotechnological/Biological Products
- Q5E: Biotechnological/Biological Products Subject to Changes in their Manufacturing Process: Comparability of Biotechnological/Biological Products
- Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- M3 (R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- M4S (R2): Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4
- S6 (R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

WHO documents:

- WHO: Guideline on Evaluation of Similar Biotherapeutic Products (SBPs) 2009:
http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf