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Change history

Version	Valid and binding as of	Modified without version change	Description, comments (by author)	Author's initials
02	**01.01.18**		**Changes to content, incl. addition of possible foreign comparator products for the main studies: formerly EU/new: EU and USA and, for complementary studies: formerly: Japan/new: Japan and Canada.** **An ERA for biosimilars now also needs to be submitted (in line with EMA procedure).** **Various editorial adaptations and additional details in order to eliminate redundancies and improve comprehensibility.**	**nma**
01	**12.06.17**		**Formal adaptation to Swissmedic's requirements management: Administrative ordinance converted into Guidance document; content unchanged.**	**fua**

1 Definitions, terms, abbreviations

1.1 Definitions

1.1.1 Biosimilar

A biosimilar is a similar biological medicinal product, i.e. a biological medicinal product having sufficient similarity with an authorised biological medicinal product (reference product) and for which the applicant's own documentation refers to the reference product.

1.1.2 Reference product

The reference product is the biological medicinal product authorised in Switzerland which the application documentation for a biosimilar uses as a reference for the comparability of its pharmaceutical quality, biological activity, efficacy and safety. The reference product is, or has been, authorised by Swissmedic on the basis of complete documentation in accordance with Article 11 TPA[1]. Biosimilars may not be used as reference products.

1.1.3 Comparator product

The comparator product is the product with which the biosimilar is compared by means of comprehensive comparability studies on pharmaceutical quality, biological activity, safety and efficacy. The reference product, or a product from the EU, or a similar product from the USA, may be used as the comparator product. Complementary studies can also be carried out with comparator products from Japan or Canada. If the reference and comparator products are not identical, their equivalence must be proved (see section 8.3.1).

1.2 Abbreviations

TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (Therapeutic Products Licensing Requirements Ordinance, TPLRO; SR 812.212.22)
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
INN	International Nonproprietary Name
eCTD	Electronic submission in CTD format
FAP	First Applicant Protection
EMA	European Medicines Agency

[1] If the reference product is no longer authorised in Switzerland, it is essential to ensure that the required comparability studies were carried out with the reference product.

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ERA	*Environmental Risk Assessment*
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HD	Hilfsdokument = support document
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA; SR 812.21)
ICH	*International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*
INN	International Nonproprietary Name
NAS	New Active Substance
NCO	Nonclinical Overview
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PVP	Pharmacovigilance Planning
RMP	Risk Management Plan
TPO	Ordinance of 17 October 2001 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 (TPLO; SR 812.212.23)
WHO	World Health Organisation
WL	Wegleitung = guidance document
ZL	Zulassung

2 Introduction and objective

In accordance with Article 12, para. 5 TPLO, and within the framework of the authorisation of biosimilars, i.e. for products to which Article 12, para. 4 letter d TPLO applies, a simplification of the requirements regarding documents to be submitted in accordance with Article 3 et. seq. TPLRO is possible. This guidance document specifies the conditions to be met in order for Swissmedic to grant this possibility. 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 documentation to be submitted in the authorisation application

This document is primarily intended for administrative entities and does not directly address the therapeutic products industry and its service providers. For Swissmedic the document is primarily intended to provide assistance in applying the legal provisions in a uniform and equitable manner. Swissmedic assesses the application documentation within the framework of this 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 Guidance Documents* listed in the Annex, and any other relevant guidelines by the *Committee Medicinal Products for Human Use (CHMP)* or the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*.

3 Scope

This guidance document is valid for the authorisation of biosimilars and major variations thereto, provided that these variations were already authorised for the reference product.
The guidance document may be solely used for biosimilars containing only active substances manufactured using recombinant technologies and/or processes based on hybridomas and/or monoclonal antibodies (Art. 12, para. 4 letter d) in conjunction with Art. 12, para. 5 TPLO).

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4 Legal basis

Article 12, para. 4 letter d TPLO stipulates that medicinal products that are manufactured using recombinant technologies and/or processes based on hybridomas and/or monoclonal antibodies are not eligible for simplified authorisation.
In accordance with Art. 12, para. 5 TPLO, and in the case of submissions in accordance with Art. 12, para. 4 letter d TPLO, however, Swissmedic may, in justified cases, permit applicants to submit reduced documentation compared to that required in the provisions of Art. 3 et. seq. TPLRO.

5 Other valid documents

Document ID
ZL000_00_006e_WL Guidance document Time limits for authorisation applications
ZL105_00_001e_WL Guidance document Meetings for applicants held with the Authorisation sector
ZL101_00_001e_WL Guidance document Authorisation human medicine new active substance
ZL000_00_004d_WL_Instruction on the authorisation of human medicinal products already authorised in foreign countries (Art. 13 TPA)
eCTD documentation: see Swissmedic website: eSubmission Swissmedic: documentation
ZL000_00_001d_WL Formal requirements
ZL000_00_002e_VZ Overview of documents to be submitted
ZL000_00_010e_CL Formal control of application authorisation human medicines
ZL101_00_002e_WL_Procedure_with_prior notification
ZA000_00_001e_VZ_List_countries_with_comparable_medicinal product control

6 General requirements and principles applied to assessments

6.1 Principle

For the authorisation of a biosimilar, the applicant must prove that the product is sufficiently similar in respect of structure, biological activity, efficacy, safety and immunogenicity in order to rule out relevant clinical differences with sufficient reliability. The scientific proof of sufficient similarity encompasses the entire physico-chemical and biological characterisation of the candidate biosimilar and of the reference product, comparative, targeted preclinical and clinical data and a critical assessment of all the results.
Based on a comparative comprehensive analysis of pharmaceutical quality and biological activity, the applicant must demonstrate, in a step-by-step procedure, that minor differences detected in the active substance molecules do not affect the (pre-) clinical efficacy or safety.
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. To this end, 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.
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 dosage form[2], dosage strength and/or the excipients of the biosimilar

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

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are different to those of the reference product, the difference must be justified and, if appropriate, sufficient similarity must be proved by means of additional studies.

6.2 General requirements regarding documentation

Full quality documentation on the biosimilar including analytical comparability studies using the comparator product is required for the authorisation of a biosimilar.
Concerning the preclinical and clinical study results, Swissmedic may accept reduced documentation. In such cases, the type of the biosimilar, the documentation submitted, the analysis process available, the manufacturing process used, and experience with the reference product from clinical, preclinical and pharmacovigilance perspectives are also taken into account.
Swissmedic reviews and decides on a case-by-case basis the extent and components of the validation and the authorisation application that are eligible for submission of reduced documentation. Studies on the quality, biological activity, safety and efficacy of the biosimilar in comparison to the corresponding properties of the comparator products must be coherent, and provide conclusive proof of comparability.
In addition to the results from the applicant's own preclinical and clinical comparability studies that provide sufficient proof of the similarity of the biosimilar to the comparator product, the applicant may also use published scientific data on the safety and efficacy of the reference or comparator product and regulatory statements as a basis. The influence of Scientific Advices provided by regulatory authorities on the development programme must be clearly shown in the documentation.

6.3 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 *Application for authorisation/Variation* form and in the cover letter.
Applicants must justify the reasons for requesting the acceptance of reduced documentation compared to the mandatory documentation specified for the medicinal product concerned, the extent of the reduction, and the extent to which the medicinal product submitted for authorisation (the biosimilar) demonstrates sufficient similarity with a biological medicinal product (reference product) that is 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 WL on *Authorisation of human medicine with NAS and major variations*).

6.4 Indications and extrapolation

In principle, an application for the authorisation of a biosimilar can be submitted for all those indications and corresponding dosage recommendations that are authorised for the reference product and that are not currently under first applicant protection (FAP). 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 risk to patient safety 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 both substance-relevant (e.g. modes of action, target cells and tissues) and patient-relevant factors (e.g. co-

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medication, co-morbidity, immunological status) and disease-relevant factors into consideration. Defining the extent of the data to be submitted must take into account all of the findings from the comprehensive comparability studies and any possible concerns that remain (in accordance with EMEA/CHMP/BMWP/42832/2005 Rev. 1).

6.5 First applicant protection

According to the valid legislation, no first applicant protection is granted for biosimilars[3].
On receipt of an application for the authorisation of a biosimilar, Swissmedic checks to see whether any ongoing first applicant protection in accordance with Article 12, TPA exists for the reference product. If the first applicant protection has not yet expired by 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 for the biosimilar.
Indications, new routes of administration, new dosage forms or new dosages for the reference product that are still protected may not be the subject of an application for the biosimilar. Swissmedic's practice is not to process such applications.

6.6 Product information (information for healthcare professionals and patient information)

All appropriate text passages of the product information for the biosimilar must be identical to those for the reference product at the time the application for authorisation for the biosimilar was submitted. Data that is exclusively relevant to the biosimilar (e.g. efficacy data, adverse reactions observed during clinical trials, toxicological data, data on immunogenicity) must also be included in the information for healthcare professionals and, if applicable, in the patient information, and should be clearly identifiable as such. The information for healthcare professionals must also clearly identify the data that specifically applies to the biosimilar. For biosimilars, the date for the "last update to the information" is independent from 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 and the possibility of referring to study results for the reference products, the authorisation holder of the biosimilar must keep the product information up to date (Article 16 TPO). In particular, the authorisation holder of the biosimilar 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 – spontaneously – must submit either an appropriate application for a variation requiring approval or provide clear scientific justification if the texts are not to be adapted.

6.7 Product name

The name of a biosimilar must comply with the provisions of Article 7, para. 3, 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).

6.8 Application for a major variation to a biosimilar

Applications for a major variation (e.g. additional indication) to a biosimilar, which has already been authorised for the reference product, are assessed on a case-by-case basis. If reduced documentation is submitted, the sufficient similarity with the reference product must be demonstrated again.
According to the requirements of the guidance document *Authorisation of human medicine with NAS and major variations*, certain major variations which are not authorised for the reference product can also be requested for a biosimilar.

[3] Protection for 10 years in accordance with Article 12, para. 2, TPA in connection with Article 17, para. 1 letter b, TPO or for 3 years in accordance with Article 17, para. 2 letter b, TPO or for 5 years in accordance with Article 17, para. 3, TPO.

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6.9 Comments relating to interchangeability

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 process. 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. Such a decision must be made exclusively by the prescriber, i.e. the attending physician.

7 Pharmacovigilance

The same pharmacovigilance requirements as those pertaining to an NAS (see WL *Human medicine with NAS and major variations*) 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 connection with Arts. 32 and 34, 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). For that reason, all appropriate measures must be taken when sending such reports to identify the full product name and the batch number. Applicants must take these aspects into account as part of the risk management plan.

8 Requirements for the documents to be submitted

8.1 Administrative documents (Module 1)

The formal requirements regarding applications in general, and the formal requirements for Module 1 and the cover letter are laid down in the guidance document *Formal requirements* and in the associated directory, *Overview of documents to be submitted*.
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.

8.1.1 Environmental Risk Assessment (ERA, Module 1.6)

When applying for authorisation of biosimilars, an Environmental Risk Assessment (ERA) must be submitted or else an appropriate reason given for not submitting one.

8.1.2 Information relating to Pharmacovigilance (Module 1.8)

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

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

8.2 Overviews and summaries (Module 2)

8.2.1 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 reference or comparator product from Module 3.

8.2.2 Nonclinical Overview (2.4)

A *Nonclinical Overview* (NCO) according to ICH M4S should be submitted. This should include an integrated summary and risk assessment of the experimental and/or bibliographical data on pharmacology, pharmacokinetics 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* (EMEA/CHMP/BMWP/42832/2005 Rev. 1). 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 NCO, including in respect of their clinical relevance and extrapolation.

8.2.3 Clinical Overview (2.5)

The Clinical Overview consists of a summary of the key data on pharmacokinetics, pharmacodynamics, 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 pharmacokinetic studies must include information on the measurement methods used when determining the active substance levels. Pharmacokinetic studies must prove bioequivalence between the biosimilar and the comparator product. In addition, the PK parameters of 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,

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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, or of oversensitivity reactions, must be assessed. 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 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 possible concerns remaining into consideration (in accordance with EMEA/CHMP/BMWP/42832/2005 Rev. 1).

8.2.4 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 certain subsections of the *Nonclinical Summaries* if sufficient justification is provided for doing so.

8.2.5 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*.

8.3 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 WL *Authorisation of human medicine with NAS and major variations*).
The comparability between the biosimilar and the comparator product (procured from the Swiss, EU or US market) must be proved within the framework of characterisation/comparability studies reflecting the current status of science and technology, over several batches.
The document must present, on the one hand, the molecular properties and the quality attributes of the biosimilar in comparison with the comparator product or reference product (comparable product profile), and on the other, demonstrate the consistent manufacturing of the biosimilar.

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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, 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.

8.3.1 Requirements relating to proof of equivalence of the foreign comparator product with the Swiss reference product (*Bridging*)

If a comparator product from a foreign country (EU, USA, Japan or Canada) is used, the equivalence of the foreign comparator product with the Swiss reference product must be demonstrated in order to prove that the investigation results can be transferred to the reference product. To this end two options exist:

a) It must either be proved that the reference product is equivalent to the foreign comparator product with regard to composition, manufacturing process, primary container, manufacturer (for active substance and end product in each case)
b) or a comparability study between the foreign comparator product and the Swiss reference product is necessary, which always encompasses a comparative physico-chemical and biological characterisation. As described in ICH Guideline Q5E for process changes in the same product, the comparison between the comparator and reference products may also require clinical PK and/or PD studies if the equivalence alone is unsatisfactory because of quality attributes.

For proving equivalence between the foreign comparator product and the reference product (*bridging*) at least two batches should be used in each case.
If the product is obtained from the USA for the comprehensive comparability studies with the biosimilar – including safety and efficacy – *three-way bridging* between the biosimilar, the EU and the US comparator product must be carried out according to the *Guideline on similar biological medicinal products* (CHMP/437/04 Rev1). Therefore, *bridging* is usually required only between the EU comparator product and the reference product. In case of doubt *Scientific Advice* should be obtained.
If products are obtained from Japan or Canada for complementary studies, these should, as described above, usually be compared with the EU product. In this case, a direct *bridging* with the reference preparation is not required.

8.4 Documentation of 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 presented, from which any differences between the biosimilar and the reference product must be evident. The causes of such differences must be justified in the application, and their effects must be scientifically assessed.

8.5 Documentation of 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 biosimilars 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

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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.

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9 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	EMEA/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)	EMEA/CHMP/BMWP/301636/08
Reflection Paper: Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha	EMEA/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	EMEA/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	EMEA/CHMP/BMWP/94528/2005
Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues	EMEA/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	EMEA/CHMP/BMWP/101695/2006
Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins	EMEA/CHMP/BMWP/14327/2006
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins	CHMP/EWP/89249/2004

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FDA documents:

The current FDA documents on biosimilars can be downloaded via the following link:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
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
For biosimilars, the following documents are particularly relevant:

- 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

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