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Change history

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01	**12.06.17**		**Formal adaptation to Swissmedic's requirements management: Administrative ordinance converted into Guidance document; content unchanged**	**fua**

1 Terms, definitions, 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 medicinal product authorised in Switzerland which the application documentation of the biosimilar uses as a reference for the comparability of its pharmaceutical quality, biological activity, efficacy and safety, i.e. the product for which the test results serve as the basis for the application for the authorisation of a biosimilar. The reference product is a medicinal product that 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, efficacy and safety. The reference product, or a product from the EU, or – for complementary studies – also a product from the USA or Japan may be used as the comparator product (see Section 6.4, Requirements regarding the comparator product). The equivalence of the comparator product with the reference product must be proved (see Section 8.3.1, Requirements regarding proof of equivalence). For the definition of the terms **new active pharmaceutical ingredient (API) and major variations,** see the Guidance document *Authorisation of human medicine with new active substance and major variation.*

1.2 Abbreviations

AMZV	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Requirements for the Authorisation of Medicinal Products (Medicinal Products Authorisation Ordinance); SR 812.212.22)
API	Active Pharmaceutical Ingredient
AW	(Anweisung) Instruction
CTD	Common Technical Document for the Registration of Pharmaceuticals for Human Use
eCTD	Electronic submission in CTD format
EMA	European Medicines Agency

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

ERA	Environmental Risk Assessment
FAP	First Applicant Protection
FDA	Food and Drug Administration
GD	Guidance document
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Nonproprietary Name
NCO	Nonclinical Overview
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PVP	Pharmacovigilance Plan
RMP	Risk Management Plan
TPA	Swiss Federal Law on Medicinal Products and Medical Devices of 15 December 2000 (Therapeutic Products Act); SR 812.21
VAM	Ordinance of 17 October on Medicinal Products (Medicinal Products Ordinance); SR 812.212.21)
VAZV	Ordinance of the Swiss Agency for Therapeutic Products of 22 June 2006 on the simplified authorisation of medicinal products and the authorisation of medicinal products by the notification procedure; (SR 812.212.23)
WHO	World Health Organisation

2 Introduction and objective

In accordance with Article 12, para. 5, VAZV, and within the framework of the authorisation of biosimilars, (i.e. for products to which Article 12, para. 4, letter d applies), a simplification of the requirements regarding documents to be submitted in accordance with Article 3 et. seq., AMZV is possible. The present instructions specify the conditions to be met in order for Swissmedic to grant this possibility. The instructions also describe

- The requirements regarding the prerequisites for 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.

These instructions are primarily intended for administrative entities and do not directly address the therapeutic products industry and its service providers. For Swissmedic, the instructions are above all intended to provide assistance in applying the legal provisions in a uniform and equitable manner.
The Agency assesses the application documentation within the framework of these instructions 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

These instructions are valid for the authorisation of biosimilars and major variations thereto, provided that these variations were already authorised for the reference product.
The instructions may only be used for biosimilars containing only APIs manufactured using recombinant technologies and / or processes based on hybridomas and / or monoclonal antibodies (Art. 12, para. 4, letter d) in connection with Art. 12, para. 5, VAZV).

4 Legal basis

Article 12, para. 4, letter d, VAZV 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.

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In accordance with Art. 12, para. 5, VAZV, and in the case of submissions in accordance with Art. 12, para. 4, letter d, VAZV, however, Swissmedic may – in justified cases – permit applicants to submit reduced documentation compared to that required in the provisions of Art. 3 et. seq., AMZV.

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 and major variation
ZL000_00_004e_WL Guidance document Authorisation human medicine under Art 13 ATP
eCTD documentation: see Swissmedic website: eSubmission Swissmedic: documentation
ZL000_00_001e_WL Guidance document Formal requirements
ZL000_00_002e_VZ Overview of documents to submitted
ZL000_00_010e_CL Formal control of application authorisation human medicines

6 General requirements and principles applied to assessments

6.1 Principle

The development of a biosimilar depends on the capacity to manufacture a product (a biosimilar) that is sufficiently similar to a reference product. The scientific proof of sufficient similarity encompasses: the entire physico-chemical and biological characterisation of the biosimilar and the comparator product (or of the biosimilar and the reference and comparator product if the two latter products are not the same); comparative, targeted preclinical and clinical data; and the critical assessment of the results. It is recommended, when planning and developing a biosimilar, to obtain scientific advice from Swissmedic at an early stage.

The specific development of the biosimilar depends on the technological status of the analysis process, the manufacturing process used, the availability of sensitive clinical endpoints and specific models, and on clinical and regulatory experience in identifying the limits of the comparability.

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 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 (or the reference and the comparator product if these are not the same) 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 comparator product from clinical, preclinical and pharmacovigilance perspectives are also taken into account.
The Agency 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. A limited study programme for preclinical and clinical studies is possible.

[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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Studies on the quality, biological activity, safety and efficacy of the biosimilar in comparison to the corresponding properties of the comparator product (or of the reference and comparator product if these are not the same) must be coherent, and provide conclusive proof of comparability.
In addition to the results from preclinical and clinical comparability studies that provide sufficient proof of the similarity of the biosimilar to the comparator product (or to the reference product and the comparator product if these are not the same), applicants may also use published scientific data on the safety and efficacy of the reference or comparator product as a basis.

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, this should be stated 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 API (see GD *Authorisation of human medicine with new active substance and major variation*).

6.4 Requirements regarding the comparator product

The comparability studies on the biosimilar's quality, biological activity, safety and efficacy must be carried out using a comparator product (reference product) which is marketed in Switzerland. Alternatively, the comparability studies may also be carried out using a comparator product that has been authorised within Europe and that contains the same API.
If a comparator product from the European market is used, it is necessary to provide data that demonstrates the equivalence of the comparator product with the reference product in accordance with Section 8.3.1 below; this proof is necessary in order to demonstrate that the results of the comparability studies (biosimilar – comparator product) can be applied by analogy to the reference product.
For the main studies (pivotal trials, pharmacokinetic (PK) trials, phase III clinical trials), the same comparator product must always be used.
Other studies may be carried out using a comparator product authorised and marketed in the US or Japanese markets. In such cases, it is also necessary to provide data that demonstrates the equivalence of the US / Japanese comparator product with the reference product or the European comparator product in accordance with Section 8.3.1 below. Under such circumstances applicants may choose whether they wish to make this comparison using the Swiss reference product or the European comparator product. We recommend obtaining scientific advice from the Agency in this respect, in advance.

6.5 Indications and extrapolation

In principle, an application for the authorisation of a biosimilar can be submitted for all those indications that are authorised for the reference product and that are not currently under first applicant protection (FAP). A decision regarding whether an indication for the biosimilar can be authorised by extrapolating the indication for the reference product to the biosimilar can only be taken on a case-by-case basis. An extrapolation of indications for the reference product to the biosimilar is possible if it is scientifically justified and the risk to patient safety is acceptable. The comparability between the biosimilar and the reference product, and thus the extrapolation to further indications, must be demonstrated in at least one indication or, if required, separately for each of the indications applied for. In cases where a study is only carried out regarding a single indication, it must concern the most sensitive indication. The proof of safety and efficacy is based, for example, on clinical experience, on available data from literature, on the mechanism of action of the API of the reference product in each indication, or on the receptors involved. The binding of the reference substance to the same receptor

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can have varying effects in different target cells and varying intracellular signalling pathways. For the extrapolation of the safety data, applicants must take both patient-relevant factors (e.g. co-medication, co-morbidity, immunological status) and disease-relevant factors and responses of the target cell (e.g. tumour cell lysis) 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).

6.6 First applicant protection

In accordance with the valid legislation, no FAP is granted[3].

When an application for the authorisation of a biosimilar is received, Swissmedic checks to see whether any ongoing first applicant protection in accordance with Article 12, TPA exists for the reference product. If the FAP 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.

6.7 Legal consequences of reduced documentation

Swissmedic may permit the submission of reduced documentation for a biosimilar if the biosimilar in question is based on a reference product with regard to certain parts of the documentation. In the case of such reduced requirements, it is mandatory for the authorisation holder of the biosimilar to maintain the reference documentation up to date or, if the circumstances change, to adjust them. Swissmedic issues official decisions to authorise a biosimilar on condition that any parts of the document that are based on the reference product must be adjusted without delay in the case of changes to the reference product. In particular, the authorisation holder of the biosimilar must monitor any changes to the sections on safety in the product information texts for the reference product (in the information for healthcare professionals: contraindications, warnings and precautionary measures, interactions and adverse effects) and submit the modified text for the biosimilar together with the appropriate application. If the authorisation holder of the biosimilar decides not to submit an application related to the changes, this must be justified to the Agency in writing, immediately and spontaneously.

6.8 Application for a major variation to a biosimilar

Applications for a major variation (e.g. additional indication) for a biosimilar that have already been authorised for the reference product are assessed individually, on a case-by-case basis. When submitting reduced documentation, sufficient similarity with the reference product must again be demonstrated.
In accordance with the requirements of the Guidance document *Authorisation of human medicine with new active substance and major variation,* applications may also be made for variations specific to the biosimilar that are not authorised for the reference product.

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

The product information for the biosimilars must be based on that for the reference product. The appropriate text passages must be taken verbatim from the texts for the reference product, complemented by additional text specific for the biosimilar itself. 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

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

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healthcare professionals must also clearly identify the data that specifically applies to the biosimilar. For the 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 if necessary adopted. To this end, Article 16, VAM requires the authorisation holder to keep the product information up to date. In particular, the authorisation holder of the biosimilar must actively monitor changes to the safety text in the product information for the reference product and – spontaneously – must submit either an appropriate application for a variation or provide clear scientific justification if the texts are not to be adapted (see Section 6.7, Legal consequences of reduced documentation).

6.10 Product name

The name of a biosimilar must comply with the provisions of Article 7, para. 3, VAM and can be either a creative name or the name of the API (name according to INN) linked to a company name. The INN name must comply with the requirements of the World Health Organisation (WHO).

6.11 Comments relating to equivalence

The API(s) of a biosimilar and its reference product are 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. The authorisation issued by Swissmedic does not contain any statement regarding whether the 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 requirements as those regarding a new API (see GD *Authorisation of human medicine with new active substance and major variation)* 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, TAP in connection with Arts. 32 and 34, VAM) must be submitted.

A *Pharmacovigilance Plan* (PVP) in accordance with ICH Guideline E2R or comparable documents, such as – in particular – a *Risk Management Plan* (RMP) in accordance with EU Guidelines must be submitted with applications for biosimilars in Module 1.8.
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 regarding documentation to be submitted

8.1 Administrative documentation (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 list, *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, Modul 1.6)

No environmental risk assessment need be submitted for a biosimilar.

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8.1.2 Pharmacovigilance planning (Module 1.8)

A PVP in accordance with ICH Guideline E2R or comparable, such as – in particular – a *Risk Management Plan* (RMP) in accordance with EU Guidelines must be submitted with applications for biosimilars (see Section 8.2.4).
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.

The PVP must include a comprehensive approach to the continual monitoring of safety following marketing approval. The identified and potential risks of the reference product, and any additional 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, the PVP 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 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 (Section 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 (Section 2.4)

A summary of the experimental and / or bibliographical data for pharmacodynamics, pharmacokinetics and toxicology (integrated summary and risk assessment in accordance with ICH M4S) must be provided in the *Nonclinical Overview (NCO).* In general the test strategy used - taking the regulatory guidelines into consideration – must be presented. The clinical relevance of nonclinical observations must be evaluated.
New experimental studies carried out for the application for the biosimilar must be listed separately in the *Overview of the Nonclinical Testing Strategy (Section 2.4.1),* with the study titles. The status of the Good Laboratory Practice (GLP) quality system must be stated. The GLP quality requirements must be used, if possible, in studies to define immunogenicity and toxicokinetics. For *in vivo* studies, a tabular overview of the safety intervals between safety-relevant, experimental trials on animals (*no observed adverse effect level* or *highest non-severely toxic dose* for substances to which ICH 29 can be applied) and details of therapeutic exposure in clinical practice must be provided.
The API, the formulation, and differences with regard to the comparator product must be described in detail in the NCO, and the corresponding cross-references to the quality part of the documentation must be provided. The use of excipients / formulations that are different from those of the comparator product must be critically assessed. The influence of the expression system, purification, and the final formulation (including the formation of aggregates or adducts) on the immunogenicity of the medicinal product must be analysed. The possibility of impurities / degradation products acting as adjuvants must be taken into consideration.
A comparison between the comparator product used in the nonclinical trials and the biosimilar must be carried out, and any differences analysed. The time schedule for obtaining pharmacokinetic samples used for the *in vivo* trials (if carried out) and any schedules for identifying antibodies must be justified.

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The analytical assays carried out and their underlying strategy and validation studies must be described in detail, including the corresponding validation results. Every known possibility of interaction between the analyte must be measured and the analytical method should be examined and discussed. The section on analytical methods in the pharmacokinetics section of the NCO may be used for this purpose.
The risk assessment presented in the NCO must always be aligned with the *Clinical Overview* and the *Risk Management Plan*.
Relevant results from the investigations regarding immunogenicity must be presented in an appropriate section of the information for health professionals concerning the biosimilar.

8.2.3 Clinical Overview (Section 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 PK studies must include information on the measurement methods used when determining the API level. 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 API (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 API 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 immunisation 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 analysing antibody- and cell-mediated immunogenicity. All relevant aspects must be presented in an integrated summary that includes data from human and animal studies. The risk of immediate reactions, transfusion reactions, sensitisation

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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 (Section 2.6)

The *Nonclinical Summary Written and Tabulated Summaries* (Section 2.6) must be provided in accordance with ICH M4S. All necessary findings / parameters with regard to the assessment of immunogenicity must be presented, including a listing of the test items and formulations used, with all the required details. In addition to pharmacological and toxicological effects, all findings for which a relationship with the test substance / study treatment is unclear must be shown (*noteworthy findings* in accordance with ICH M4S).
It may be possible to omit certain sub-modules (*Sections*) of the *Nonclinical Summary* if sufficient justification is provided for doing so.

8.2.5 Clinical Summary (Section 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, AMZV (see also GD *Authorisation of human medicine with new active substance and major variation*).
The comparability between the biosimilar and the comparator product (or the reference product and comparator product, if they are not the same) 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 (if the two are not the same: 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 API can be isolated from the end product.
The characterisation / comparability studies to prove comparability between the biosimilar and the comparator product (or the reference product and comparator product, if they are not the same) 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 API 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 API or finished

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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

There are two options for providing proof of the equivalence of the foreign comparator product with the Swiss reference product:

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

If comparator products are obtained from the USA or Japan for complementary studies, the equivalence with the European comparator product that is used in the main study in accordance with ICH Q5E can also be demonstrated instead of equivalence with the Swiss reference product.

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, AMZV. The application 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, AMZV. Module 5 must include all clinical trials on test subjects and on patients that are submitted as trial reports, with the corresponding annexes. 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.

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9 Annex

European Medicines Agency (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	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

Other references:

ICH documents:
The currently valid ICH guidelines (grouped by quality, efficacy and multidisciplinary 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
- 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
- S8: Immunogenicity Studies for Human Pharmaceuticals
- S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

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FDA Dokumente:

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

WHO Dokumente:

- 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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