Questions and answers concerning the authorisation of similar biological medicinal products (biosimilars)

Version 2 of 17 February 2014

Question 1

Does the Administrative Ordinance (AO) / Instructions: *Authorisation of similar biological medicinal products (Biosimilars), hereinafter abbreviated to AO Biosimilars* also apply to veterinary medicines?

Answer 1

Yes

Question 2

Why does Swissmedic differentiate between the terms "reference product" and "comparator product"? This distinction could be misinterpreted or be confusing, and could be a cause of concern for patients: particularly for biosimilars for which the development work is expensive and for which no specific studies using the reference product can be carried out. For generics, **no** such difference is made, and only the concept of a "reference product" is used.

Answer 2

By choosing to use two different terms – reference product and comparator product – Swissmedic wishes to emphasise the fact that candidate biosimilars are characterised by documentary reference (the Swiss reference product) on the one hand, and on the other by batches of medicinal products actually used in practical experiments, with emphasis on their physico-chemical and biological characterisation, plus appropriate preclinical and/or clinical studies, whose results are compared with the biosimilar (the comparator product).

With regard to generics, Swissmedic also used two different terms "reference product" and "test product" in the English version of the Administrative Ordinance / Instructions: *Submission and authorisation of generics* that was valid until the end of 2013. In the currently valid, revised Administrative Ordinance / Instructions: *Authorisation of human medicines with known active pharmaceutical ingredients"* in force as of 1 January 2014, the terms "reference product" and "comparator product" are also used.

Question 3

Why are the foreign comparator products restricted to those from European Union Member States, the USA and Japan? The purpose for which a product from the USA or from Japan can actually be used is not clear. It is however clear that only the use of EU products is accepted for the pivotal trials. This contradicts the approach by the EU and the USA regarding biosimilars. Moreover, this would be a restriction regarding procedures in accordance with Article 13, TPA. For that reason, products from all countries with comparable control systems should be mentioned in order to be consistent and to be in line with Article 13, TPA.

Answer 3

The comprehensive comparability studies on quality, biological activity, safety and efficacy of the candidate biosimilar must be carried out using a reference product obtained from the Swiss market. Alternatively, these comparability studies may also be carried out using a comparator product with the same active pharmaceutical ingredient that is obtained from the European market and authorised there. In the latter case, it is also necessary to demonstrate equivalence (sufficient similarity) between the European comparator product and the Swiss reference product, since the documentation for the latter is the reference for the biosimilar.

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By using these rules, Swissmedic is currently taking same direction for the authorisation of biosimilars as stated in the requirement of the European Medicines Agency (EMA), which has considerable, long-standing experience in the authorisation of biosimilars and has drawn up the corresponding detailed, comprehensive guidelines.

In accordance with the *Guideline on Similar Biological Medicinal Products* (currently still in draft form) the EU also accepts an EU product only for the main comparability studies with the candidate biosimilar. The Swiss requirements thus do not contradict the EU's approach.

Question 4

Why is it not possible for the comparability studies to be carried out using US or Japanese products? As long as it can be demonstrated that the products are comparable, it should at least be possible to obtain them from various regions (EU, USA, Japan).

Answer 4

If the comprehensive comparability studies are not carried out with the Swiss comparator product (reference product), Swissmedic uses, as an alternative, the EMA requirements stating that the main comparison with the candidate biosimilar must be with the European reference product.

Comparator products from the USA and / or Japan may (as is the case in the EU) be used for additional studies, i.e. as a complement to the main, pivotal studies (PK studies, phase III trials).

Question 5

What is meant by "additional studies", and what are their value if the authorisation would be possible with the pivotal studies alone and since additional ones are only accepted if they are conducted using the EU comparator product or the Swiss reference product?

Answer 5

"Additional studies" are, for example, non-pivotal studies on pharmacodynamics, pharmacokinetics and supplementary clinical / nonclinical studies on efficacy and safety. In particular, they constitute supporting information for the main studies or make it possible to demonstrate specific aspects such as pharmacodynamics or pharmacokinetics more precisely.

Question 6

Regarding the requirements for proof of equivalence of the foreign comparator product with the Swiss reference product (Section 8.4.1, letter a) of the AO biosimilars, it is not possible for an applicant for a biosimilar to know the manufacturing process for either the reference product or the comparator product. This information is strictly confidential and will never be made accessible. Why is information on the primary container relevant?

Answer 6

Swissmedic assumes that the information provided in Section 8.4.1, letter a) of the AO Biosimilars is only provided by the authorisation holder of the original product to designated partners.

The equivalence of the primary container of the foreign comparator product with that of the Swiss reference product is notably relevant when of different stopper materials (for vials) are used, which can affect the leachables.

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Question 7

One example case is that of a candidate biosimilar for which the comprehensive comparability studies were carried out with the EU comparator product. The Swiss reference product is not, however, marketed in Switzerland, meaning that it is no longer available for the bridging (proof of the equivalence of the EU comparator product with the Swiss reference product). Is it nevertheless possible to apply for the authorisation of a biosimilar with reduced documentation, in accordance to the instructions for biosimilars?

Answer 7

Proof of the equivalence of the foreign comparator product with the Swiss reference product is a mandatory aspect of the application for biosimilars if the Swiss reference product was **not** used for the comprehensive comparability studies. This applies because the applicant refers to the corresponding part of the documentation on the Swiss reference product for the reduced part of the documentation submitted for the biosimilar. Swissmedic only has documentation available for the Swiss reference product and not for the foreign comparator product.

If this proof in accordance with Section 8.4.1, letter a) of the AO Biosimilars can be provided (i.e. written proof by the authorisation holder of the originator product regarding the composition, manufacturing process, primary container and manufacturer), the equivalence of the foreign comparator product with the Swiss reference product is considered to be demonstrated.

If only the option available is that stated in Section 8.4.1, letter b) of the AO Biosimilars – i.e. bridging carried out using a series of tests that primarily consist of physico-chemical and biological characterisation – this proof cannot be provided when no Swiss reference product is available; as a result, the biosimilar application cannot be approved.

Question 8

How many batches must be analysed in the comprehensive comparability studies and, if applicable, in order to prove the equivalence of the EU comparator product with the Swiss reference product?

Answer 8

For the comprehensive comparability studies in accordance with the EMA *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)* (EMA/CHMP/BWP/247713/2012) with the candidate biosimilar and the Swiss reference product or the EU comparator product, it is usually necessary to analyse at least four batches.

If an EU comparator product is used for the above-mentioned comparison, at least two batches of each product should be analysed in each case in order to prove equivalence between the EU comparator product and the Swiss reference product.

Question 9

Is it possible for a product whose active pharmaceutical ingredient was manufactured with a different cell line (e.g. CHO instead of SP2) to that of the Swiss reference product to be authorised with reduced documentation in accordance with the AO Biosimilars?

Answer 9

The active pharmaceutical ingredient of the Swiss reference product and the candidate biosimilar must demonstrate identical amino acid sequences, i.e. the protein primary structures must be the same. Post-translational modifications must be comparable. Since the choice of the cell line affects the post-translational modifications – for example glycosylation – it can be assumed that if the production cells are changed (i.e. using another cell line), the resulting proteins / active pharmaceutical ingredients will no longer be sufficiently similar to qualify them as candidate biosimilars. If the recombinant proteins produced using different cell lines are nevertheless

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sufficiently similar, authorisation as a biosimilar is possible, i.e. the different cell line is not the primary decisive factor. The issue is much more one of the degree of similarity of the proteins / active pharmaceutical ingredients that are produced.

The applicant is free to decide whether to submit an application for the authorisation of a medicinal product with a new active pharmaceutical ingredient (NAS application with full documentation for the quality, preclinical and clinical modules), or an application for a biosimilar (with reduced documentation for the preclinical and clinical modules but with quality documentation that is expanded to include comprehensive comparability studies).

Question 10

Is it possible to submit applications for the authorisation of medicinal products with low molecular weight heparins as biosimilars, with reduced documentation?

Answer 10

No. Low molecular weight heparin (LMWH) that emulate LMWHs that are already authorised do not fall under Art. 12, para. 4, letter d) of the Ordinance of the Swiss Agency for Therapeutic Products on the simplified authorisation of medicinal products and the authorisation of medicinal products with the notification procedure (VAZV; SR 812.212.23) since they are not manufactured using recombinant technologies and / or procedures on the basis of hybridomas and / or monoclonal antibodies. For this reason, authorisation cannot be granted for these products on the basis of reduced documentation (biosimilar applications).

Art. 14, para. 4, letter d), VAZV is different from EU legislation in this respect, which latter permits biosimilar applications for medicinal products with low molecular weight heparins (LMWHs) as the active pharmaceutical ingredient.

Question 11

Can applications for the authorisation of biosimilars (Art. 12, para. 4, letter d) in connection with Art. 12, para. 5, VAZV) also be submitted in application of Article 13, TPA?

Answer 11

Biosimilars are not considered to be known active pharmaceutical ingredients in accordance with Art. 14, para. 1, letter a) of the TPA and Art. 12, paras. 1 – 3, VAZV because by their nature, biotechnology substances differ among one another. Consequently, different medicinal products that are manufactured using these substances do not contain the same active pharmaceutical ingredient. Products to which Art. 12, para. 4, VAZV applies – including biosimilars – are not eligible for simplified authorisation. In justified cases, Swissmedic may however grant the possibility of submitting reduced documentation. The Agency carries out its assessment as described in the AO Biosimilars (Sections 6 to 8).

The implementing provisions for Art. 13, TPA can be found in Arts. 5a – 5d of the Medicinal Products Ordinance (VAM). According to Art. 5c, VAM, the Agency usually carries out a comprehensive examination of applications for the authorisation of a medicinal product with a new active pharmaceutical ingredient. For biosimilars, Art. 13, TPA can only be applied exceptionally, as indicated by the Agency's practices regarding the principle of taking the test results from foreign authorisation procedures in accordance with Art. 13, TPA into account (see, on this issue and on the following questions, the Administrative Ordinance / Instructions *Authorisation of medicinal products already authorised in foreign countries (Art. 13, TPA),* Section 3, part 2 in connection with Section 10.1 of Version 04). Art. 13, TPA is therefore only applied to biosimilars if the biosimilar authorised abroad has orphan drug status and is not an oncological.

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Question 12

Is the name of the Swiss reference product mentioned in the product information for the biosimilar?

Answer 12

No. For currently authorised biosimilars in Switzerland, the trade name of the reference product is not mentioned: the text only mentions "reference", "reference medicinal product" or "reference product".

For example.: *„…examined as the primary efficacy parameter compared to the reference and compared to the placebo…. The safety profiles observed in these studies on [product name of the biosimilar] and the reference medicinal product used in the study were consistent".*

NOTE:
EU-SmPCs for the recently authorised Infliximab biosimilars moreover do not state the name of the EU reference product.

Question 13

An authorised product for which authorisation was granted on the basis of reduced documentation in accordance with the AO biosimilars (a biosimilar) has a creative name. In accordance with Art. 12, para. 1 in connection with Annex 1, Section 1, para. 4 of the Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the requirements for the authorisation of medicinal products (AMZV; SR 812.212.22) a provision has existed as of 1 January 2013 stating that on the outer packaging of human medicines, the names of the active pharmaceutical ingredient, with the internationally accepted INN number, must be placed directly below the trade name. For generics, this must be placed above the trade or company name. In concrete terms, what does this mean for biosimilars?

Answer 13

For biosimilars, it is possible to select a creative name or the name of the active pharmaceutical ingredient (name according to INN) for the product, linked to a company name. If a creative name is selected, the active pharmaceutical ingredient name (INN) must be placed below the trade name (in accordance with the revised AMZV). In cases where the complete (unabbreviated) active pharmaceutical ingredient name is already integrated in the product name as an INN, the name of the active pharmaceutical ingredient need not be repeated.

Question 14

Is the medicinal product specifically authorised as a biosimilar?

Answer 14

No. Based on currently valid law, Swissmedic approves an application for a given medicinal product: here, in application of Article 12, para. 4, letter d) in connection with paragraph 5, VAZV.

Question 15

References made to the Swiss reference product must be up to date and kept updated. Does this means that changes regarding labelling of warnings for the reference product must also be made to the product information for the biosimilar?

Answer 15

Swissmedic grants authorisation to a biosimilar on condition that those parts of the document that refer to the reference product must be adapted immediately if changes are made to the reference product.

In particular, changes to the sections on safety in the product information texts (for the information for healthcare professionals: contraindications, warnings and precautionary measures, interactions and

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adverse reactions) for the Swiss reference products must be adopted by the authorisation holder of the biosimilar and a corresponding application for the adaptation of the text for the biosimilar must be submitted. If the authorisation holder of the biosimilar decides not to submit an application for a variation, the reasons for not doing so must be immediately and spontaneously justified in writing to Swissmedic.

Question 16

The product information for the biosimilar must be based on that for the Swiss reference product. A more precise definition is needed here. Does this mean that the biosimilar is a "copy of the originator product"? What is meant by the "additional text" required in the product information?

Answer 16

The product information for the biosimilar is not an exact copy of that for the Swiss reference product. All appropriate parts of the text of the product information for the biosimilar must however be identical to those for the reference product. There will however be text passages that are specific to the biosimilar and that are thus in its product information only (e.g. immunogenicity tests relevant for the biosimilar). Since a biosimilar need not have all the indications for the reference product and can also apply for specific indications of its own, the information for healthcare professionals in the section "Indications / areas of use" may, for example, differ.

Question 17

Can you confirm whether Pharmacovigilance Plan data (PVP data) that is sufficient for the EMA is also sufficient for Swissmedic?

Answer 17

Since Swissmedic does not directly apply EU law in this area, the Agency cannot confirm in advance whether data that is sufficient for the EMA is also sufficient for our Agency (which would constitute unauthorised, direct application of EMA decisions). It is however correct that for applications running parallel in Switzerland and the EU, requirements for PVP studies that go beyond the plan required by the EMA rarely arise in practice. The text in the AO Biosimilars is based closely on that of the EMA; a more in-depth specification on this level is not appropriate. Experts are fully aware of the typical possibilities that exist regarding PVP studies (e.g. PASS (*Post-authorisation safety studies),* various epidemiological designs).

Question 18

Is the automatic substitution[1] of a biological product by a biosimilar product allowed in Switzerland?

Answer 18

No, this is not explicitly permitted in Switzerland.
The substitution clause in the Federal Health Insurance Act (KVG) does not contain anything in this respect, and applies only to generics:
KVG / Art. 52a Right of Substitution (unofficial translation since English is not an official language of Switzerland):
http://www.admin.ch/opc/de/classified-compilation/19940073/index.html

Pharmacists may substitute less expensive generics for original products included in the List of Pharmaceutical Specialities unless the prescribing doctor or chiropractor explicitly states that the

[1] Automatic substitution in this context means the dispensing of a biosimilar instead of a prescribed reference biological product by the pharmacist without consulting or informing the prescribing doctor.

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originator product must be dispensed. If a substitution is made, the pharmacist informs the medical professional prescribing the product of which product was dispensed.

Section 4.4 of the following linked document (Federal Office of Public Health communication on biosimilars) regarding the modifications to the handbook regarding the List of Pharmaceutical Specialities (LS), version 1 March 2013 (available in German, French and Italian at http://www.bag.admin.ch/themen/krankenversicherung/06492/07568/index.html?lang=de) mentions that for reasons of patient safety and possible immunogenicity, biosimilars are neither interchangeable with one another nor with the reference product.
By authorising a biosimilar, Swissmedic confirms that the differences between the biosimilar and its reference product do not affect its safety and efficacy. Swissmedic's authorisation nevertheless contains no recommendation regarding whether a biosimilar can be substituted for the reference product. Such a decision must only be taken by the doctor in charge of the case.

Question 19

Are there any legal regulations in your country in relation to automatic substitution by biosimilar products?

Answer 19

There is no legal basis for this in Switzerland.

Question 20

A question on references in the information on biosimilar for healthcare professionals:
According to Section 6.9 of the AO Biosimilars, all relevant passages from the product information for the biosimilar must be identical with those in the product information for the reference product, supplemented by own passages specifically concerning the biosimilar. How should the product information be referenced in this case?

Answer 20

For identical text passages, the text for the reference product can be used, and for own text passages, the references must be taken from the documentation for the biosimilar, Modules 2 to 5.

Question 21

In the checklist *Formal Control, authorisation application for human medicinal products,* information on the foreign comparator product is required (pages 4 – 6). Should this information also be provided in an authorisation application for a biosimilar?

Answer 21

According to Section 8.2.2 of the AO Biosimilars, the following information on the reference and comparator product should be provided in the cover letter for biosimilar applications:

1. Name of the reference product authorised in Switzerland, with the authorisation number.
2. Name of the comparator product used in the main studies, stating the country of authorisation and country of source.
3. If applicable: name of other comparator products from the USA or Japan, stating the country of authorisation and country of source for the additional studies concerned.

The information on the foreign comparator product can also be included in the checklist *Formal control, authorisation application for human medicinal products,* however. The important aspect is for this information to be provided, either in the cover letter or the checklist.

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Question 22
Are there specific requirements regarding the form of proof to be provided with regard to the proof of equivalence between the reference product authorised in Switzerland and the comparator product (obtained from the EU) used in the comparability studies?

Answer 22
Documentation in accordance with ICH G5E should be provided to prove equivalence between the reference product authorised in Switzerland and the comparator product (obtained from the EU) that is used in the comparability studies. Swissmedic expects this to be provided either in CTD Module 1 (1.11, see also the checklist *Formal control, authorisation application for human medicinal products*) or in Module 3 (3.2.R). The cover letter should mention where the data (comparability studies and bridging data) can be found within the documentation.

Question 23
How should the issue of a biosimilar with a PIP be handled if there is no such plan available because it is not necessary in the EU?

Answer 23
If there is no PIP available, this should be mentioned under point 1.10 of the checklist *Formal control, authorisation application for human medicinal products* with a corresponding comment. Biosimilars do not fall within the EU Paediatric Regulation 1901/2006 (11).

Question 24
Section 6.9 of the AO Biosimilars indicates that the “product information for the biosimilars must be based on that for the reference product”. On checking the AIPS, the reference product of interest appears to have only the information for healthcare professionals available; the information for patients is missing. Why is this so?

Answer 24
Depending on the medicinal product (e.g. for parenteral medicinal products) patient information is not required. These medicinal products are not administered by the patient, but by the healthcare professionals and the information for healthcare professionals is used as a package insert.

Question 25
At the time of application, do we provide only the information for healthcare professionals for the biosimilar and no patient information?

Answer 25
Yes, but only in cases where no patient information for patient is required. In cases where patient information is required, however, the manuscript must be submitted to Swissmedic at the time of the application.

Question 26
Section 8.2.1 of the AO Biosimilars indicates the requirement for eCTD submission.
Does Swissmedic accept a NeeS for a biosimilar product?

Answer 26
No, NeeS are not accepted by Swissmedic (neither for biosimilars nor for other categories of medicinal products). Biosimilar submissions in Switzerland can be made either in eCTD format or as

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paper submissions (eCTD is preferred). As of 1 January 2014, Swissmedic accepts the eDok copy for submissions in paper format. An eDok copy means that Modules 1 to 5 are submitted to Swissmedic as a paper original biosimilar submission, together with an additional, electronic version of the biosimilar documentation on a data carrier. The electronic data replaces the paper copy that is required with a paper submission. Swissmedic bases its review exclusively on the electronic documents submitted, and archives the paper original biosimilar submission as a legally binding document. The structure of the eDok copy must correspond to that of the original. For that purpose, Swissmedic makes directory templates available on its website (see: https://www.swissmedic.ch/zulassungen/01520/01697/index.html?lang=en. Please also refer to the Guidance eDocumentation under the same url for the exact requirements).

Question 27

Are there any conditions for co-marketing applications that are specific to biosimilars?

Answer 27

No, there are no conditions for co-marketing applications that are specific to biosimilars. The same requirements apply as those for other co-marketing applications, e.g. same manufacturing process, same qualitative and quantitative composition of the finished product in terms of the active ingredients, excipients, and primary packaging. Simply using a different secondary packaging is acceptable: for security reasons (preventing confusion or errors), the imprints / logos must differ.

Version 2: 17.02.2014

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