Questions and answers concerning the authorisation of biosimilars

Question 1
What is meant by "supplementary studies", and what is their value given that it would be possible to obtain authorisation with the pivotal studies alone, but pivotal studies are only accepted if they are conducted using the EU or US comparator product or Swiss reference product?

Answer 1
"Supplementary studies" mentioned in section 5.4.2 of WL Biosimilar are, for example, non-pivotal studies on pharmacodynamics, pharmacokinetics and supplementary clinical/non-clinical studies on efficacy and safety. They provide complementary information in support of the main studies or to focus on specific aspects such as pharmacodynamics or pharmacokinetics.

Question 2
For a biosimilar candidate the comprehensive comparability studies were carried out with a foreign (i.e. EU or US) comparator product. The Swiss reference product is not marketed in Switzerland, meaning that it is not available for bridging (proof of the equivalence of the EU/US comparator product with the Swiss reference product). Is it nevertheless possible to apply for authorisation of a biosimilar with reduced documentation on a case-by-case basis, in accordance with WL Biosimilar?

Answer 2
This is now possible as there is no longer a “bridging” requirement. However, the suitability of the foreign comparator product must be demonstrated in accordance with section 5.4.1 of WL Biosimilar. However, authorisation as a biosimilar is not possible if a reference product was never authorised in Switzerland. In this case, the medicinal product would correspond to new authorisation with a new active substance (NA NAS).

Question 3
Is it possible for a product whose active substance was manufactured using a different cell line (e.g. CHO instead of SP2/0) from the one used to produce the Swiss reference product, to be authorised with reduced documentation in accordance with WL Biosimilar?

Answer 3
Yes, provided the active substances – and thus the medicinal products – demonstrate sufficient similarity.

Question 4
Is it possible to apply for authorisation of medicinal products with low-molecular-weight heparins (LMWH) as biosimilars?

Answer 4
Yes, under the revised Therapeutic Products Act and associated ordinances, it has been possible to authorise low-molecular-weight heparins as biosimilars since 2019.

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Question 5
Can applications for the authorisation of biosimilars also be submitted under Article 13 TPA?

Answer 5
Yes, it has been possible to apply Art. 13 TPA since the beginning of 2019 provided the EU Commission or US FDA have authorised the biosimilar in question and fulfilled the requirements set out in the guidance document “Authorisation in accordance with Art. 13 TPA” (e.g. documents not more than five years old, etc.; see also Art. 17 of the Therapeutic Products Ordinance, TPO; SR 812.212.21 and sections 1.1.3 and 4 of WL Biosimilar).

Question 6
A product that was authorised on the basis of reduced documentation in accordance with WL Biosimilar (a biosimilar) has a ‘creative’ (self-coined) name. In accordance with Art. 12, para. 1 in combination with Annex 1, number 1, paragraph 4 of the Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (TPLRO; SR 812.212.22), the outer packaging of human medicinal products must carry the name of the active substance, with its international non-proprietary name (INN), directly below the trade name. Generics must carry the active substance names above their trade or company name. In concrete terms, what does this mean for biosimilars?

Answer 6
For biosimilars, the product name must be either a ‘creative’ (self-coined) name or the name of the active substance (INN) combined with a company name. If a creative name is adopted, the active substance name (INN) must be placed below the trade name. In cases where the complete (unabbreviated) active substance name is already integrated in the product name as an INN, the name of the active substance does not need to be repeated.

Question 7
References made to the Swiss reference product must always be up to date.
Does this mean that changes to the reference product’s labelling or warnings also have to be included in the product information for the biosimilar?

Answer 7
In its decision on whether to authorise a biosimilar, Swissmedic states that under the applicable therapeutic products legislation – particularly the provisions of the TPLRO – parts of the documentation that refer to the reference product must be modified immediately in the event of changes to the reference product.
In particular, holders of marketing authorisation for biosimilars have to monitor changes to the safety sections in the product information texts of the Swiss reference product (Contraindications, Warnings and precautions, Interactions and Undesirable effects in the case of the Information for healthcare professionals). If the changes affect their biosimilar, they then have to submit an appropriate application for modification of the texts for the biosimilar; specifically C.I.2. If a holder of marketing authorisation for a biosimilar decides not to submit an application for a variation, it must notify Swissmedic of its decision immediately and without being asked, justifying the reasons for its decision (see also WL Biosimilar, last paragraph of section 5.7).

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Question 8:
The product information for a biosimilar has to 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 8
The product information for a biosimilar is not an exact copy of that for the Swiss reference product. However, all appropriate sections of the product information text for the biosimilar must be identical to the corresponding sections of the product information for the reference product. Since a biosimilar does not need to have all the indications of the reference product, the information for healthcare professionals may differ in the "Indications / usage" section, for example.

Question 9 (revised January 2024)
Biosimilars are not required to include an RMP. Does this mean that no additional risk minimisation measures need to be implemented for biosimilars?

Answer 9 (revised January 2024)
Applications for approval of biosimilars are not required to include an RMP.
If training materials or other additional risk minimisation measures are envisaged according to the RMP of the reference product, Swissmedic will review whether these should also be implemented for the biosimilar as part of the application for approval of the biosimilar. As a rule, it can be assumed that any measures necessary for the reference product will also be assessed as being necessary for the biosimilar; in this case, training materials or other additional risk minimisation measures will also be required as part of the application for approval of the biosimilar.
The applicant can also apply for additional risk minimisation measures directly together with the application for authorisation of the biosimilar. After review, their implementation will then be ordered as a condition.

Question 10 (revised January 2024)
Does Switzerland allow pharmacists to substitute biosimilars for biological medicinal products?

Answer 10 (revised July 2024)
Yes, the revision of the Health Insurance Act (HIA, SR 832.10) with effect from 1 January 2024 and the modification of Art. 52*a* therein make it possible for the dispensing pharmacist to substitute biosimilars[1].

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Art. 52*a* Right of substitution
[1] If several medicinal products with the same composition of active substances are included in the list of specialities, pharmacists may dispense a less expensive medicinal product if it is equally medically suitable for the insured person, unless the doctor or chiropractor expressly requests that the original product be dispensed.
[2] If the dispensing person replaces the prescribed medicine with a cheaper one, he or she shall inform the prescribing person accordingly.
[3] The Federal Council may specify the conditions under which medicinal products are deemed not to be equally medically suitable.

[1] In the Health Insurance Ordinance (HIO, SR 832.102) of 27 June 1995 (status as of 1 January 2024) the term "biosimilar" is now defined in Article 64*a* paragraph 5.

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Question 11 (deleted January 2024)

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Question 12
How should the issue of PIPs for biosimilars be handled where none is available because the EU does not require one?

Answer 12
The EU Paediatric Regulation 1901/2006 (11) does not extend to biosimilars. Applying Art. 5 TPO, PIPs are not required for biosimilars in Switzerland either, because the active substance is not new.

Question 13
Section 5.7 of WL Biosimilar states that the "product information for the biosimilar must be based on that for the reference product". It now transpires that no Patient information has been published for the reference product, only Information for healthcare professionals. Why is this?

Answer 13
Certain medicinal products (e.g. parenterals) do not require Patient information when they are authorised by Swissmedic (Art. 14 para. 2 of the Ordinance of the Swiss Agency for Therapeutic Products on the Licensing Requirements for Therapeutic Products, TPLRO; SR 812.212.22). Medicinal products that are not administered by patients but only by healthcare professionals do not require Patient information; the Information for healthcare professionals serves as a package insert.

Question 14
Do we only have to provide the Information for healthcare professionals when we submit our application, and can we omit the Patient information?

Answer 14
Patient information is generally required and should be submitted to Swissmedic in manuscript form with the rest of the application. This does not apply to medicinal products that do not require Patient information (see question and answer 13).

Question 15 (deleted January 2024)

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Question 16
As of 1 January 2019 (receipt of application), Information for healthcare professionals for biosimilars does not include specific clinical data for the product in question. Instead, the relevant passages in the medicinal product information for the biosimilar must be identical to the medicinal product information for the reference product (subject to regulatory modifications, such as indications for the reference product that are still under document protection).
What is the procedure for aligning the medicinal product information of biosimilars that have already been approved with the reference product?

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Answer 16
The holder of marketing authorisation for the biosimilar should submit an application for a variation C.I.2, and Swissmedic will determine whether the conditions for authorisation are still fulfilled.

Question 17
The current date of revision of the medicinal product information for the biosimilar is not the same as that for the reference product. Does the revision of the Therapeutic Products Act affect that in any way?

Answer 17
No, the date stated in the *Date of revision of the text* section of the Information for healthcare professionals for biosimilars is still independent of that for the reference product.

Question 18
If changes to the medicinal product information of the reference product are applicable to the biosimilar, an application for a variation must be submitted for them, and they must be adopted as necessary. Is there a time limit governing how long after publication of the revised medicinal product information for the reference product the application for the biosimilar has to be submitted? Within 90 days, as for generics?

Answer 18
Yes, as with generics, in line with Swissmedic practice, these changes should also be submitted within 90 days for biosimilars.

Question 19
Section 6.2 “Biosimilars” of the guidance document: Authorisation of human medicinal products under Art. 13 TPA HMV4 mentions that Swissmedic will not carry out its own scientific review if the EU Commission has already authorised the product. However, there is no explicit mention of whether this only applies to centralised procedures (CPs) or also to decentralised procedures (DCPs) and mutual recognition procedures (MRPs).

Answer 19
The EU Commission authorisation required in Art. 17 para. 1 let. b of the Therapeutic Products Ordinance (TPO; SR 812.212.21) refers to authorisation under the centralised procedure in accordance with EU Regulation 726/2004, which is to be applied in the EU to biotech biosimilars.
Within the EU, there are very few biosimilars that member states can authorise, including low-molecular-weight heparins (LMWH), which are obtained from the mucous membranes of pigs (see https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview, *Biosimilars in the EU – information guide to healthcare professionals*). LMWH biosimilars can only be notified for authorisation in Switzerland under Art. 13 TPA if the European Commission has authorised them in a centralised procedure.

Question 20
We are not clear about which fee will be applied under the new Fees Ordinance (FeeO-Swissmedic) for the new authorisation of a biosimilar. We assume that it will be the CHF 50,000 for biotech biosimilars (item 1.2 of FeeO-Swissmedic). What is the situation with low-molecular-weight heparins (LMWH) that are regarded as biosimilars in the EU but are not covered by Art. 12 para. 5 TPLO?

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Answer 20

Swissmedic applies the CHF 50,000 fee in Annex 1, no. I, no. 1.2 of the Swissmedic Fees Ordinance (FeeO-Swissmedic; SR 812.214.5) to the new authorisation of biosimilars. The same fee (no. 1.2, CHF 50,000) is applied to the new authorisation of LMWH biosimilars (see also question and answer 4).

Question 21

We have a query concerning the classification of a preparation, which is being submitted for new authorisation.

Situation:

- The preparation contains a biotech active substance (infliximab), which has been developed as a biosimilar.
- The reference product (Remicade) is authorised for IV administration in Switzerland.
- The product submitted for new authorisation is suitable for both IV and SC administration.
- The IV preparation will by definition be a biosimilar of infliximab.
- In a first stage, the SC administration route will be used in an indication of the IV product (at present, trials are only available for this indication). According to the trial, therapy will be initiated by IV administration, while maintenance doses will be administered SC.

Questions:

- How should we submit the SC administration route?
- Which preparation is the reference product?

Answer 21

The SC administration form cannot be classified as a biosimilar because a biosimilar must have the same dosage recommendations and administration routes as the reference product.

This is the only way that reference can be made to the documentation for the reference product (see definition of a biosimilar in Art. 4 para. 1 let. a^{novies} TPA).

Since the reference product is only authorised for intravenous (IV) administration, it is not possible to authorise an extension of the IV infliximab biosimilar to include the subcutaneous (SC) route (2.e) “Modification or addition of an administration route”).

The SC administration route must be submitted as a new authorisation application. There is no reference product. Adequate quality, preclinical and clinical data is required for the SC form and for every requested application (extrapolated data will not be accepted).

We recommend resolving specific questions on this point at a Scientific Advice or Presubmission Meeting.

Question 22

Why does Swissmedic only accept EMA and FDA decisions as the basis for applications for biosimilars under Art. 13 TPA?

Answer 22

The EMA and FDA have the most experience and/or competence in authorising biosimilars and have created and published guidelines that clearly set out the requirements that applications have to meet.This is duly reflected in Art. 17 para. 1 let. b TPO.

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Question 23
Is it possible to switch an ongoing authorisation procedure for a biosimilar to an Art. 13 TPA procedure?

Answer 23
Yes, but only for applications for biosimilars that Swissmedic receives on/or after 1 January 2019.

Question 24
If a biosimilar has been withdrawn after a “preliminary notice of rejection” but has been granted an authorisation in the EU and/or USA, can it be submitted and authorised under Article 13 TPA?

Answer 24
Yes, as long as there are no contradicting decisions from countries with comparable medicinal product control and Swissmedic has no major objections, authorisation under Art 13 TPA can be granted.

Question 25
Can bridging to the Swiss reference product be omitted from applications for biosimilars under Art. 13 TPA?

Answer 25
Yes, bridging can be omitted (see also Q&A 2).

Question 26
If there is no longer a bridging requirement, why must the Information for healthcare professionals be based on the Swiss reference product?

Answer 26
According to Art. 4 para. 1 let. a^{novies} TPA, biosimilars must demonstrate adequate similarity to a reference product authorised by the Agency and refer to that product’s documentation. Information for healthcare professionals is one of the documents that is relevant to authorisation. This is why a biosimilar submitted for authorisation in Switzerland must make reference to the Information for healthcare professionals of a medicinal product authorised by the Agency.

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