



WHO Questions and Answers: Similar Biotherapeutic Products

(Proposed document to implement the WHO guidelines on evaluation of similar biotherapeutic products, Annex 2, WHO TRS No. 977, adopted in 2009)

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained. Publication of this **draft** is to provide information about the proposed WHO document on *Questions and Answers on similar biotherapeutic products* to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee on Biological Standardization (ECBS). Written comments proposing modifications to this text **MUST** be received by **23 February 2018** in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at email: kangh@who.int.

The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide, second edition" (KMS/WHP/13.1).

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CONTENT

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
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35
36
37
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Background

I. Concept for licensing similar biotherapeutic products (SBPs):

- QI-1 What is a similar biotherapeutic product (SBP)?
- QI-2 What is the evaluation concept for licensing a SBP?
- QI-3 What are the differences between SBPs and generic products (copies of chemical drugs)?
- QI-4 Which products can be approved as SBPs?

II. Reference biotherapeutic products (RBPs):

- QII-1 What is the so-called ‘reference biotherapeutic product’ referred to in biosimilar regulatory framework?
- QII-2 What are the criteria for selection of a RBP?
- QII-3 The guidelines say ‘the same RBP should be used throughout the entire comparability exercise’. Can the RBP from another manufacturing site be used?
- QII-4 Under what circumstances would it be acceptable to use a foreign-sourced RBP?
- QII-5 Can the SBP be approved with a RBP which is not available in the domestic market?

III. Quality:

- QIII-1 Should the expression system used in producing a SBP be the same as the one used to produce the RBP?
- QIII-2 Should a SBP have the same formulation as the RBP?
- QIII-3 Should the SBP have the same delivery device or container closure system as the RBP?
- QIII-4 Should the SBP have the same strength as the RBP and how can this be demonstrated?
- QIII-5 To prove the comparability, should the specifications of a SBP be the same as the RBP's ones?
- QIII-6 How many batches must be analysed in the comprehensive comparability studies?
- QIII-7 What is the role of pharmacopoeia monographs in the evaluation of SBPs?
- QIII-8 What is the role of reference standard materials in the evaluation of SBPs?
- QIII-9 How should the expiry date of a SBP be established?
- QIII-10 Are the comparability studies in accelerated and stress stability tests needed?
- QIII-11 When conducting a comparability exercise, head-to-head characterization studies are required to compare the SBP and the RBP. How much difference or which

1 kinds of differences can be accepted considering a high degree of similarity
2 between the SBP and the RBP?

3 QIII-12 How comprehensive evaluation of glycan structure (i.e. level of details) is required?

4 QIII-13 How could statistical analysis support a demonstration of biosimilarity of a SBP to
5 the RBP?

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7 **IV. Nonclinical evaluation:**

8 QIV-1 Which general aspects should be considered for the planning/conduct of the
9 nonclinical studies?

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11 **Nonclinical in vitro studies**

12 QIV-2 Which in vitro studies should be provided for the nonclinical evaluation of a SBP?

13 QIV-3 Which specific aspects should be observed for the planning/conduct of the
14 nonclinical in vitro studies?

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16 **Nonclinical in vivo studies**

17 QIV-4 Which aspects should be considered to decide whether in vivo animal studies are
18 required for nonclinical evaluation of a specific SBP?

19 QIV-5 Which specific aspects should be observed for the planning/conduct of in vivo
20 animal studies on pharmacodynamics and/or pharmacokinetics of a SBP?

21 QIV-6 Which specific aspects should be observed for the planning/conduct of in vivo
22 animal toxicity studies for a SBP?

23 QIV-7 Where no suitable animal model available, how can preclinical comparability
24 exercise be extended?

25 QIV-8 Under what circumstances/conditions would an additional of nonclinical
26 comparability study be required?

27

28 **V. Clinical evaluation:**

29 QV-1 Will SBPs be as safe as originator products?

30 QV-2 What is immunogenicity and why is it a special concern for a SBP?

31 QV-3 If there are differences in immunogenicity, how is this handled?

32 QV-4 In case the RBP showed higher rate of ADA positivity than the historical data,
33 what could be the data requirement for the SBP?

34 QV-5 If the comparability study of efficacy is waived, is a separate immunogenicity
35 study required or could immunogenicity assessment be conducted in the same
36 study with comparative PK/PD study?

37 QV-6 How can SBPs be approved for indications for which no clinical studies have been
38 done?

39 QV-7 What are the most important 'Points to Consider' in extrapolating clinical data
40 showing biosimilarity in one indication to other licensed indications?

41 QV-8 After a SBP has been approved, can a new indication added to the RBP be shared
42 with the SBP?

1 QV-9 How can a different regulatory decision regarding extrapolation be reached by
2 different national regulatory authorities when using the same regulatory data
3 package?

4 QV-10 How should inexperienced national regulatory authorities (NRAs) deal with
5 differing regulatory decisions of major experienced NRAs?

6 QV-11 Is there always a need for a clinical study of a SBP?
7

8 **VI. Pharmacovigilance:**

9 QVI-1 After a SBP has been approved, is the SBP required to maintain biosimilarity with
10 its RBP?

11 QVI-2 Would it be beneficial to review/discuss post marketing commitments from each
12 country after extrapolation of indications?

13 QVI-3 If safety information of the RBP (i.e. adverse events) is amended, how would it be
14 applied to the already approved SBPs?

15 QVI-4 Can the SBP license holder develop a new indication or dosage administration
16 which the RBP is not approved for?

17 QVI-5 Should cautions in use for a SBP be the same with those for the RBP for its
18 marketing approval?
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20 **Authors and acknowledgements**

21 **References**
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Guidance documents published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. It is recommended that modifications to these Guidelines are made only on condition that such modifications ensure that the product is at least as safe and efficacious as that prepared in accordance with the guidance set out below.

23

1 Background

2 WHO *guidelines on evaluation of similar biotherapeutic products* (SBPs, also called
3 ‘biosimilars’) adopted by the WHO Expert Committee on Biological Standardization (ECBS)
4 in 2009 have been instrumental in raising awareness of the complex scientific issues related
5 to the licensing of SBPs.

6 In May 2014 the Sixty-seventh World Health Assembly adopted a new resolution on access
7 to biotherapeutic products and ensuring their quality, safety and efficacy. One of requests is
8 for ‘WHO ECBS to update the 2009 guidelines, taking into account the technological
9 advances for the characterization of biotherapeutic products and considering national
10 regulatory needs and capacities’.

11 In response, WHO has convened meetings to identify the needs and text which should
12 specifically be updated. In April 2015, an informal consultation on the possible amendment
13 of the Guidelines was organized. All participants from national regulatory authorities (NRAs)
14 from both developing and developed countries, as well as industry recognized and agreed that
15 the evaluation principles described in the WHO Guidelines were still valid, valuable and
16 applicable in facilitating the harmonization of SBP requirements globally. It was therefore
17 concluded that there was no need to revise the main body of the existing WHO Guidelines on
18 SBPs. However, it was also agreed that there was a need for additional guidance on the
19 evaluation of monoclonal antibody products as biosimilars which was then developed and
20 adopted by the ECBS 2016. In May 2017, WHO held another meeting entitled ‘WHO
21 consultation on improving access to and use of similar biotherapeutic products’. From the
22 outcome of this meeting, WHO noted that developing questions and answers (Q&As) is more
23 appropriate than revising the Guidelines in order to further clarify and complement some
24 areas and points written in the Guidelines.

25 The Q&As would be produced for guidance only and should be read in conjunction with
26 relevant WHO guidelines. The Q&As are intended to provide clarity by addressing questions
27 that may arise in the use of WHO Guidelines. The questions in this document have been
28 selected based on addressed ones from regulators during the implementation workshops on
29 *WHO guidelines on evaluation of similar biotherapeutic products* in the past 8 years. The
30 intention is to update Q&As regularly to reflect new developments and issues that arise but
31 not to address the issues of interchangeability, switching, substitution, naming, or shortages
32 which are out of the scope of the original Guidelines.

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1 **I. Concept for licensing similar biotherapeutic products (SBPs):**

2
3 **QI-1 What is a similar biotherapeutic product (SBP)?**

4 According to the WHO *guidelines on evaluation of similar biotherapeutic products*, a SBP is
5 a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already
6 licensed reference biotherapeutic product (RBP).

7 In addition to “SBP”, a variety of terms, such as “similar biological medicinal products”,
8 “biosimilar products”, “follow-on protein products” and “subsequent-entry biologics” have
9 been used to describe these products. Since the main principles of developing SBPs are the
10 same, definitions of the SBP are complementary to the WHO definition. For example, the EU
11 definition states that a SBP is highly similar to its RBP product that is already marketed. High
12 similarity means that the quality characteristics, biological activity, safety and efficacy of the
13 SBP and its RBP have been shown to be comparable to the degree that the drug substance of
14 the SBP can be called a new version of the drug substance of the RBP.

15 According to the US FDA definition, there may be differences between the inactive parts of
16 the SBP and the RBP. However, there cannot be any clinically meaningful differences in the
17 safety, purity, and potency of the product.

18 Based on the above-mentioned definitions, a SBP is highly similar to an original
19 biotherapeutic product (RBP) that has been developed and assessed according to the
20 regulatory guidelines that ensure an adequate comparison of the SBP to its RBP. SBP and
21 RBP are therapeutic equivalents.

22 A medicinal product that has not been compared and shown to be similar to a reference
23 product as indicated in the WHO guidelines should not be called “similar” or SBP.

24

1 **QI-2 What is the evaluation concept for licensing a SBP?**

2 The development and evaluation philosophies of SBPs and products containing new active
3 substances, such as RBPs, are different. The RBP of a SBP has been licensed on the basis of
4 a full documentation of the pharmaceutical quality, pharmacology and toxicology as well as
5 of human safety and efficacy in all of its therapeutic indications.

6 The pharmaceutical quality of SBPs must meet the same regulatory requirements as any other
7 biotherapeutic products whereas the nonclinical and clinical development is abbreviated. This
8 is possible when the manufacturer can demonstrate that the active substances of the SBP and
9 the RBP are highly similar and, thus, can be expected to have same functional properties. In
10 these circumstances, the role of the abbreviated (non)clinical study program is confirmatory.

11 The extent of the (non)clinical program depends on the ability to demonstrate structural and
12 functional similarity between the SBP and its RBP. Thus, the development should be a
13 stepwise approach where the results of the previously conducted tests and studies will guide
14 the next steps. Extensive comparisons will inevitably reveal some differences that may be
15 true or just reflect limitations of the tests. Therefore, the overall assessment of similarity is
16 based on the evaluation of the whole data package consisting of quality, nonclinical and
17 clinical parameters (also called “totality of evidence”).

18 The quality and function of a biotherapeutic product are highly dependent on its
19 manufacturing process. The manufacturing process of a biotherapeutic product is changed
20 several, even tens of times, during its life-cycle. Each change has an impact on the product.
21 Therefore, regulatory authorities will require that the manufacturer will demonstrate by
22 comparability studies that the safety and efficacy of the product have not been changed. The
23 requirements of comparability studies after a manufacturing change are described in the
24 *WHO guidelines on procedures and data requirements for changes to approved*
25 *biotherapeutic products*.

26 Comparability studies may include physico-chemical and structural analyses as well as *in*
27 *vitro* functional, often cell-based tests. In more extensive changes, additional nonclinical and
28 clinical studies may be required. The experience of hundreds of manufacturing changes
29 during three decades shows that the safety and efficacy of biotherapeutic products can be
30 maintained over time in spite of the fact that the product itself has undergone some changes.
31 Certain general scientific principles of comparability assessment for manufacturing changes
32 are applicable to an assessment of similarity for SBPs.

33 The demonstration of high similarity is based on an extensive comparability exercise
34 consisting of comparative state-of-the-art physico-chemical, structural and *in vitro* functional
35 tests as well as nonclinical and clinical studies. The clinical experience and established safety
36 profile of the originator products facilitates the development of SBPs.

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1 **QI-3 What are the differences between SBPs and generic products (copies of**
2 **chemical drugs)?**

3 The term generic applies to chemically synthesized small molecule drugs. In contrast, SBPs
4 refer to large complex macromolecular drugs of biological origin which are much more
5 difficult to characterize. The abbreviated development of both generics and SBPs leans on the
6 data of their reference products. Both must have the same or highly similar active
7 pharmaceutical substance, dose, strength, and route of administration, and be therapeutic
8 equivalents. However, the development of a SBP requires much more extensive studies due
9 to the nature of biological substances.

10
11 In contrast to generics, the demonstration of adequate quality and bioequivalence of a SBP
12 with a reference product is usually not sufficient to ensure therapeutic equivalence between
13 the SBP and its RBP. Additional analytical, functional, and (non)clinical studies are needed
14 to demonstrate high similarity before concluding therapeutic equivalence. SBPs and RBPs, or
15 any other therapeutic proteins and their versions for that matter, cannot be shown to be
16 identical because of their large and complex structure and manufacturing process that
17 introduces product heterogeneity. SBPs and RBPs are produced in cells that generate a
18 product with some microheterogeneity that is unique for each cell type and manufacturing
19 process.

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22 **QI-4 Which products can be approved as SBPs?**

23 SBPs should be developed and evaluated according to the WHO *guidelines on evaluation of*
24 *similar biotherapeutic products* or similar national guidelines. The RBP must have been
25 licensed on the basis of full data on quality, safety, and efficacy.

26 The development of a SBP to a licensed original biotherapeutic product (i.e. RBP) depends
27 on the ability to characterize and compare their structure and function. To date, SBPs have
28 been developed for well-established and well-characterized biotherapeutic products, such as
29 recombinant DNA-derived therapeutic proteins with proven record of clinical safety and
30 efficacy. Vaccines and plasma-derived products and their recombinant analogues are not
31 considered in the WHO definition. However, biosimilar versions of low molecular weight
32 heparins, that are not proteins, have been licensed in some jurisdictions as SBPs. Vaccines,
33 plasma derived products, and their recombinant analogues cannot be licensed via the SBP
34 route.

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II. Reference biotherapeutic products (RBPs):

QII-1 What is the so-called ‘reference biotherapeutic product’ referred to in biosimilar regulatory framework?

A reference biotherapeutic product (RBP) is the comparator for head-to-head comparability studies with the SBP in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as an RBP. The term does not refer to measurement standards such as international, pharmacopoeial or national standards or reference standards. A manufacturer developing a SBP may be allowed an abbreviated (non)clinical development if it can be demonstrated that the SBP and the chosen RBP are comparable.

QII-2 What are the criteria for selection of a RBP?

The RBP should have been approved with a complete registration dossier, including safety and efficacy studies in each therapeutic indication. It should be fully identifiable (e.g. brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, number of batches, lot number, age of batches). Normally, the national regulatory authority (NRA) should have access to the registration dossier of the RBP. The RBP should also be widely marketed for a suitable duration in the jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of the biotherapeutic products and post-marketing surveillance activities.

In case the RBP is not licensed in a given country, the NRA may set other criteria for the selection of the RBP, such as licensing in another country with a complete dossier according to WHO *guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* or corresponding guidelines as well as significant duration and magnitude of exposure on the market. The manufacturer of the SBP should justify the use of a RBP that is not licensed locally. The same RBP should be used in all comparability studies of a given SBP.

QII-3 The guidelines say ‘the same RBP should be used throughout the entire comparability exercise’. Can the RBP from another manufacturing site be used?

Yes. The “same RBP” means that the use of production batches from different manufacturing sites must be supported by the same licence of the RBP. This guarantees that products from all manufacturing sites are approved by the relevant regulatory authority and that the production batches conform to the same specifications.

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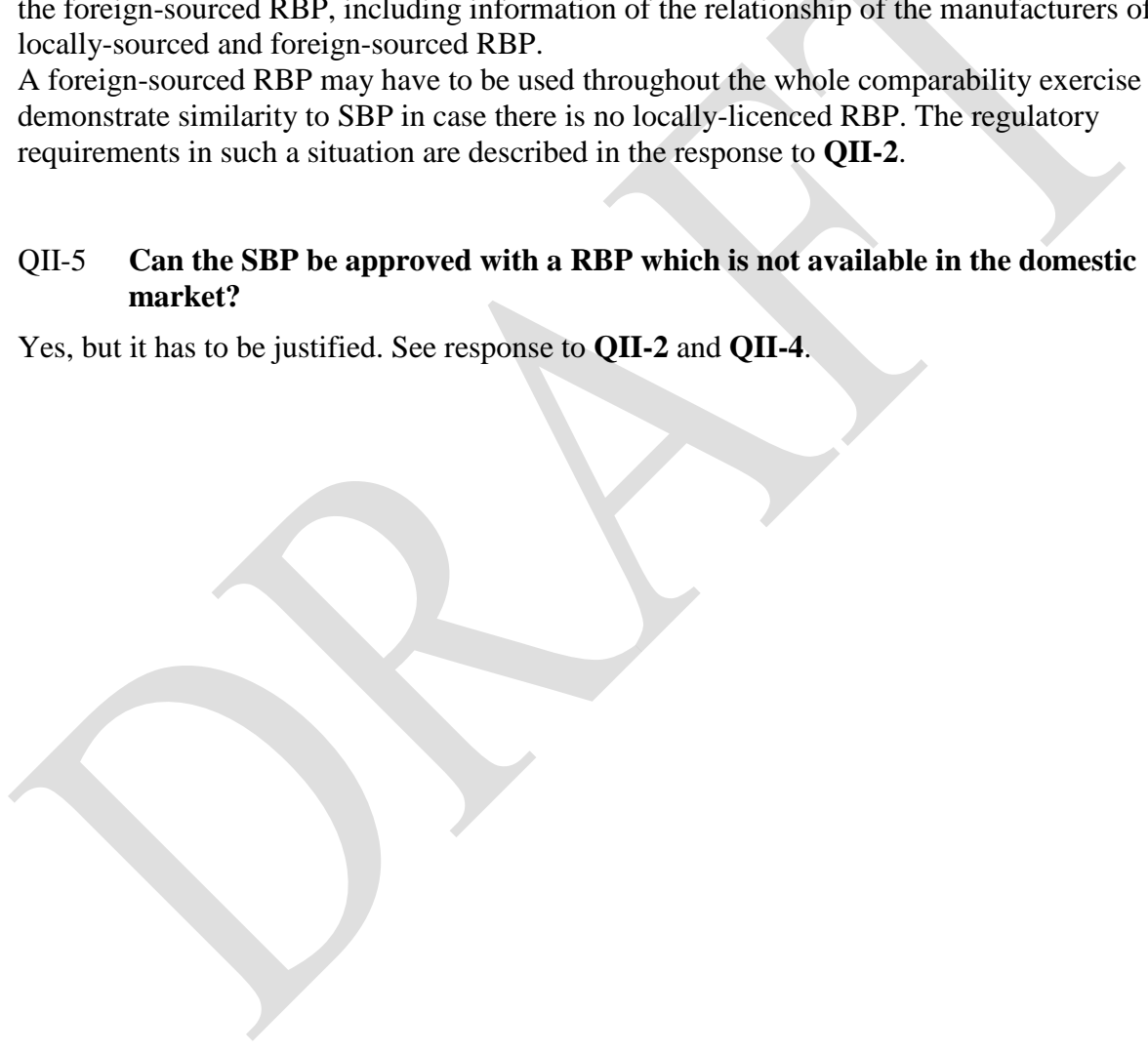
QII-4 Under what circumstances would it be acceptable to use a foreign-sourced RBP?

Normally, the analytical and *in vitro* functional comparability of the SBP and the RBP should be demonstrated by using the locally-licensed and sourced product. The use of a **foreign-sourced** RBP is feasible when the manufacturer plans for a global (non)clinical development plan. By using this approach, unnecessary repetition of (non)clinical studies can be avoided. The use of a foreign-sourced RBP in (non)clinical studies is possible if the manufacturer can demonstrate the comparability of the locally-sourced and foreign-sourced RBP by physico-chemical, structural and *in vitro* functional tests. NRAs may require additional pharmacokinetic and pharmacodynamic studies to support the “bridge” between the locally- and foreign-sourced RBPs. In addition, the manufacturer of the SBP should justify the use of the foreign-sourced RBP, including information of the relationship of the manufacturers of locally-sourced and foreign-sourced RBP.

A foreign-sourced RBP may have to be used throughout the whole comparability exercise to demonstrate similarity to SBP in case there is no locally-licensed RBP. The regulatory requirements in such a situation are described in the response to **QII-2**.

QII-5 Can the SBP be approved with a RBP which is not available in the domestic market?

Yes, but it has to be justified. See response to **QII-2** and **QII-4**.



1 **III. Quality:**

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3 **QIII-1 Should the expression system used in producing a SBP be the same as the one**
4 **used to produce the RBP?**

5 No. In general, a manufacturer of a SBP is not able to use the same clone of production cells
6 as the manufacturer of the RBP. The developers of a SBP must develop their own master cell
7 banks for their production cells.

8 The expression system (i.e. expression vector and production cells) need not to be same as for
9 the RBP if the expressed protein has the same amino-acid sequence as well as a comparable
10 higher order structure and post-translational modifications. It is recommended that the
11 manufacturers of SBPs use a similar expression system as the RBP, since each cell type will
12 synthesize proteins with a typical pattern of post-translational modifications.

13 This is particularly important when the RBP has significant post-translational modifications,
14 such as glycosylation. The manufacturers of SBPs should also consider expression system-
15 specific process impurities.

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18 **QIII-2 Should a SBP have the same formulation as the RBP?**

19 No. Not necessarily, as long as the differences do not have an impact on the quality of the
20 product and safety and efficacy of the SBP and RBP can be demonstrated to be comparable.
21 In addition, the manufacturer should justify possible differences between the formulations of
22 the SBP and the RBP. In general, the formulations should be state-of-the-art with regard to
23 stability, compatibility, integrity, and impact on activity and strength of the active substance.

24 It is important to justify the lack of adverse impact on the efficacy and safety of the SBP if a
25 different formulation and/or container/closure system, especially any material that is in
26 contact with the medicinal product, is selected. The aim of the biosimilar comparability
27 exercise is to demonstrate that the SBP and the RBP chosen by the manufacturer are
28 comparable at the level of both drug substance and the drug product.

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31 **QIII-3 Should the SBP have the same delivery device or container closure system as**
32 **the RBP?**

33 No. The lack of any adverse impact of the delivery device/container closure system on
34 quality, safety, efficacy, and usability should be demonstrated. The manufacturer of a SBP
35 should justify the differences between the delivery or container closure systems.

36 Thus, it is possible. For example to use different delivery device, such as pre-filled syringe or
37 autoinjector although the RBP has only a vial provided that the products are shown to be
38 comparable.

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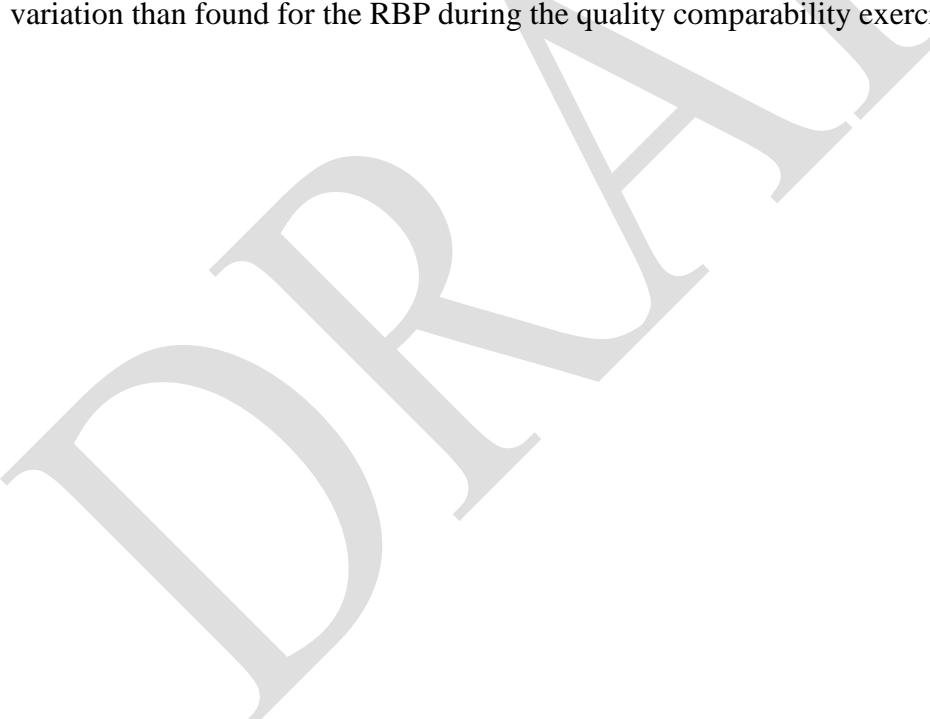
QIII-4 Should the SBP have the same strength as the RBP and how can this be demonstrated?

Yes. SBPs are injectable products that should have the same total content and concentration of drug substance as the RBP. The total content and concentration should be expressed by using in the same measurement system as the RBP, i.e. mass units or units of activity.

QIII-5 To prove the comparability, should the specifications of a SBP be the same as the RBP's ones?

No. The specifications will control the most important quality attributes concerning identity, purity, potency and molecular heterogeneity of the RBP and SBP. Nevertheless, specifications of SBP and RBP are likely to be somewhat different because of different manufacturing processes and analytical methods. Thus, the specifications reflect the experience of the manufacturer's own product. The specifications should be based on relevant guidelines (*WHO guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology*).

It should be noted that pharmacopoeial monographs provide only minimal requirements. It is expected that the specifications of a SBP do not allow significantly wider batch-to-batch variation than found for the RBP during the quality comparability exercise.



1 **QIII-6 How many batches must be analysed in the comprehensive comparability**
2 **studies?**

3 The analysis of multiple batches of the RBP by the manufacturer is necessary for developing
4 an optimal manufacturing process for its candidate SBP. For this purpose, the manufacturer
5 of a SBP needs to collect a representative set of batches of the RBP over an extended time
6 period to justify comparability ranges for quality attributes. The relevance of the ranges
7 should be discussed, taking into account the number of RBP lots tested, the quality attribute
8 investigated, the age of the batches at the time of testing and the evolution of quality
9 attributes over time as well as the test method used.

10 At the next stage, comprehensive physico-chemical, structural and *in vitro* functional
11 comparisons are performed for multiple representative batches of RBP and SBP to confirm
12 representative and comparable quality profiles. It is impossible to set a definite number for
13 batches of the comprehensive comparability exercise as it depends on multiple factors, such
14 as availability and variability of batches. The number of batches needed to show similarity of
15 each quality attribute and to establish the range of SBP specifications should be sufficient to
16 generate an acceptance range of quality attributes. The manufacturers may request for advice
17 from the relevant regulatory authority on the appropriate number of batches when preliminary
18 results from the degree of variability have been obtained.

19 Where several strengths or presentations are available, their selection should be appropriately
20 justified. The age of the different batches of the RBP (relative to the expiry dates) should also
21 be considered when establishing the target quality profile.

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24 **QIII-7 What is the role of pharmacopoeia monographs in the evaluation of SBPs?**

25 Pharmacopoeia monographs set the minimum technical requirements for quality of medicinal
26 products. Monographs for biotherapeutic products have been issued in various jurisdictions.
27 A SBP must comply with the same requirements of a pharmacopoeia monographs as the RBP.
28 However, compliance with pharmacopoeia monographs will not be sufficient to demonstrate
29 biosimilarity.

30

1 QIII-8 What is the role of reference standard materials in the evaluation of SBPs?

2 When available, the manufacturers can use international/ pharmacopoeial reference standards
3 and reagents for qualification and standardisation of the tests used to characterise and
4 quantify SBP and RBP. For example, potency assay should be calibrated against an
5 international or national standard or reference reagent, when available and appropriate. WHO
6 provides International Standards and Reference Reagents, which serve as reference sources of
7 defined biological activity expressed in an international unit (IU) or unit (U). International
8 Standards and Reference Reagents are intended for calibration of national reference standards
9 (http://www.who.int/biologicals/reference_preparations/en/). International or national
10 standards and Reference Reagents should therefore be used to determine the potency and to
11 express results in IU or U. However, the reference standards cannot be used instead of the
12 RBP for demonstration of comparability.

13

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15 QIII-9 How should the expiry date of a SBP be established?

16 The expiry date of a SBP is based on its shelf-life. The shelf-life of the SBP should be
17 justified based on full real-time and real-temperature stability data obtained according to the
18 relevant guidelines (ICH Q5C *Quality of Biotechnological Products: Stability Testing of*
19 *Biotechnological/Biological Products*; WHO *guidelines on the quality, safety, and efficacy of*
20 *biotherapeutic protein products prepared by recombinant DNA technology*).

21

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23 QIII-10 Are the comparability studies in accelerated and stress stability tests needed?

24 Stability testing of SBPs should comply with the relevant guidelines (ICH Q5C guideline:
25 *Stability testing of biotechnological/biological products*; WHO *guidelines on the quality,*
26 *safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA*
27 *technology*). Stability studies on drug product should be carried out in the intended drug
28 product container-closure system.

29 **Real-time/real-temperature stability tests** will determine the conditions for storage and the
30 shelf-life for the SBP. These conditions may or may not be the same as those of the RBP.
31 Comparative real-time, real-temperature stability studies between the SBP and RBP are not
32 required.

33 **Comparative accelerated stability tests** will not only provide important information on
34 degradation pathways of the active substance and on the suitability of the formulation and the
35 container closure system but may also uncover differences between the degradation profiles
36 of the SBP and RBP. Therefore, it is useful to add relevant quality attributes that should be
37 used in the manufacturing process and during shipping and storage in order to ensure the
38 integrity of the product.

39 **Stress stability testing** is necessary for a SBP in order to further investigate the appropriate
40 conditions of shipping and storage. However, comparative stress testing of SBP and RBP
41 may not be of added value.

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2 **QIII-11 When conducting a comparability exercise, head-to-head characterization**
3 **studies are required to compare the SBP and its RBP. How much difference or**
4 **which kinds of differences can be accepted considering a high degree of**
5 **similarity between the SBP and its RBP?**

6 It is important to remember that the conclusion of high similarity is based on the totality of
7 evidence and not on an individual variable or physico-chemical test. Previous experience, for
8 example generated from changes introduced into manufacturing processes may help to
9 understand the functional and clinical impact of a particular physico-chemical difference
10 between the SBP and its RBP.

11 The results of physico-chemical tests should always be interpreted in the light of the
12 performance of a particular analytical method and the batch-to-batch variability of the results.
13 When available, orthogonal analytical techniques should always be used in order to
14 strengthen the evaluation of comparability.

15 *In vitro*, usually cell-based functional assays may be helpful in understanding the significance
16 of a difference detected in the analytical testing. It is important to understand the factors that
17 have an impact on the functional tests. The sensitivity of some of functional tests, such
18 reporter gene based assays, has been increased to the degree that they do not correspond to
19 the physiological situation. In these situations the manufacturer need to justify whether the
20 assay used is for the right purpose and understand the difference between robust release assay
21 and bio-analytical assay in terms of mechanism of actions as well as for sensitivity. It is also
22 important to consider other tests that may be helpful for the interpretation of the observed
23 difference

24 In general, *in vitro* functional tests are more sensitive than clinical studies. Nevertheless,
25 results of physico-chemical and structural tests should be considered in the planning of the
26 clinical comparability program, especially in pharmacokinetic and pharmacodynamic as well
27 as in immunogenicity studies.

28 The pharmacokinetics of the SBP and RBP are often compared in single-dose studies
29 involving healthy volunteers. The comparability range in the primary pharmacokinetic (PK)
30 parameters should be defined and justified prior to conducting the study. The criteria used in
31 the demonstration of bioequivalence of orally administered and chemically synthesized small
32 molecules, i.e. 90% confidence interval (CI) of ratios of SBP to RBP, are often used for
33 comparative PK studies of SBPs and RBPs in the absence of relevant historical data. If the
34 PK comparability criteria are met but the exposure to SBP is significantly lower or higher,
35 meaning that the CI of the SBP is entirely within either the higher or the lower side of the
36 equivalence range, a root cause analysis and possibly new data could be needed. It is
37 recommended that steady state pharmacokinetics is measured in the repeat dose safety and
38 efficacy studies. This may mitigate concerns of some PK differences observed after a single
39 dose study.

40 The equivalence design is recommended for confirmatory efficacy and safety studies. Non-
41 inferiority design may be used if superiority can be excluded otherwise. In both cases, the
42 acceptance range is defined by previous clinical trials with the RBP and means a difference
43 that is not clinically meaningful.

44

1 QIII-12 **How comprehensive evaluation of glycan structure (i.e. level of details) is**
2 **required?**
3

4 A **glycoform** is an isoform of a protein that differs from others only with respect to the
5 number or type of attached **glycans**. The biotechnological manufacturing process of a given
6 glycoprotein will always produce different glycoforms in spite of the same glycosylation
7 machinery. This glycoform pattern may to some extent vary from batch to batch. In addition,
8 production cells from different species may produce qualitatively different glycans that
9 should be identified and justified, especially if such glycan does not exist in man.

10 For glycoproteins, carbohydrate structures should be thoroughly compared; including the
11 overall glycan profile, site-specific glycosylation patterns as well as site occupancy. The
12 extent of the comparative analysis of the glycoform patterns of the SBP and RBP depends on
13 the knowledge in the glycoform pattern of the RBP and in the functional role of different
14 glycoforms. Knowledge in the variation in the glycoform pattern between batches of the RBP
15 will help in the assessment of differences between the SBP and RBP.

16 Differences in the glycans and glycan profiles may have an impact on the structure,
17 degradation pathways, potency, pharmacokinetics, safety and efficacy. For example,
18 sialylated, afucosylated and mannose-containing structures may display clinically significant
19 variation.

20 Monoclonal antibodies are glycoproteins with glycosylation sites in the Fc portion of the
21 heavy chains, with further possible glycosylation sites depending on the type of molecule.
22 Monoclonal antibodies display several glycoforms that have different functional properties,
23 such as differences in binding to Fc- and complement receptors. Therefore, a thorough
24 analysis of the glycans attached to the Fc-protein backbone is necessary. These data, together
25 with various binding and cell-based functional tests will be crucial in the demonstration of
26 comparability of SBP and its RBP. Glycans are rarely immunogenic unless they do not
27 normally exist in man. For example, alpha-gal-1, 3-gal that occurs on the carbohydrate
28 moiety of proteins produced by some mammalian but not human cells may trigger serious
29 hypersensitivity reactions in patients.

30

1 **QIII-13 How could statistical analysis support a demonstration of biosimilarity of a SBP**
2 **to the RBP?**

3 Statistical methods have a crucial role in interpreting comparative clinical data, especially
4 pharmacokinetics and efficacy. The role of statistics is less clear in the interpretation of
5 results of comparative physico-chemical, structural, and *in vitro* functional tests. It is obvious
6 that the statistical methods cannot be used in the same way in analysing quality and clinical
7 data.

8 Statistical methods are usually dealing with means whereas the analysis of quality data in the
9 context of comparability is often based on acceptable ranges. The means may change within
10 the acceptability range. Furthermore, working with probabilities, like confidence intervals is
11 problematic as it is expected that each batch of the product will be in the pre-defined range.
12 Nevertheless, in some jurisdictions it has been suggested that statistical analyses of
13 comparability data should be conducted in order to demonstrate similarity. There is a wide
14 acceptance of the view that descriptive statistical approach to establish ranges for quality
15 attributes could be used to support the scientific reasoning, if appropriately justified.

16 The establishment of similarity by statistical analysis is often hampered by the small number
17 of batches and observations, uncertainty of the clinical impact and distribution of results,
18 performance of the assays, source and age of the batch etc.

19 In conclusion, the use of statistics in defining comparability is still at an empiric stage in most
20 jurisdictions.

21

22

1 **IV. Nonclinical evaluation:**

2

3 **QIV-1 Which general aspects should be considered for the planning/conduct of the**
4 **nonclinical studies?**

5 The nonclinical development of SBPs has evolved from merely abbreviated versions of the
6 nonclinical development of original medicinal products to development programs tailored to
7 the specific features of SBP development.

8 Initially, significant emphasis was put on *in vivo* comparative nonclinical studies. The
9 original WHO *guidelines on evaluation of similar biotherapeutic products* required at least a
10 head-to-head repeat dose toxicity study. The newer WHO *guidelines on evaluation of*
11 *monoclonal antibodies as similar biotherapeutic products* promotes a stepwise nonclinical
12 development starting from the demonstration of the physico-chemical and *in vitro* functional
13 comparability and proceeding to the analysis of remaining uncertainties. If *in vivo* studies are
14 considered indicated, the developer should clarify the availability of relevant animal models.
15 If the drug substance candidate SBP show species-specific pharmacological activity only in
16 great apes, *in vivo* animal studies may not be feasible as such studies would not be in line with
17 the concept of avoiding pharmaco-toxicological testing in these species.

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1 **Nonclinical in vitro studies**
2

3 **QIV-2 Which *in vitro* studies should be provided for the nonclinical evaluation of a**
4 **SBP?**

5 The *in vitro* nonclinical studies should be comparative and measure relevant biological
6 activities of the drug substance. It is recommended that the tests are complementary or
7 orthogonal in order to support interpretation of results. Together, these assays should cover
8 the whole spectrum of pharmacological/toxicological aspects with potential clinical relevance
9 for the RBP and for the product class. The manufacturer should discuss to what degree the *in*
10 *vitro* assays used are representative/predictive of the clinical situation according to current
11 scientific knowledge.

12 Typically receptor binding assays and cell-based functional assays are used to compare
13 functions of SBP and RBP. The developer should justify the relevance, sensitivity and
14 discriminatory capability of the tests. Test results should be given in units of activity
15 calibrated against an international or national reference standard, when available.

16 For example, monoclonal antibodies have several functionally active sites. Fortunately, there
17 are assays for monoclonal antibodies to measure the binding affinity and activity as well as
18 cell-based functional assays for each active site. The standard assays can be tailored to reflect
19 better the physiological or pathological conditions in a particular therapeutic indication. A
20 detailed analysis of the biological activity including Fab- and/or Fc-mediated functions, such
21 as ability to bind to isoforms of Fc gamma and neonatal Fc receptors and to complement C1q,
22 should be provided even though some may not be considered essential for the therapeutic
23 mode of action. The corresponding cell-based functional assays, such as complement-
24 dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and
25 antibody-dependent cellular phagocytosis (ADCP) are important as they may play a different
26 role in different therapeutic indications.

27 Where available International Reference materials should be used to support bioassay
28 characterization, calibration and performance. See also **QII-8**.

1 **QIV-3 Which specific aspects should be observed for the planning/conduct of the**
2 **nonclinical *in vitro* studies?**

3 It is important to understand the mechanism of action of the molecule for the selection of the
4 relevant tests for the biological activity. The quality comparability studies may reveal
5 differences that may have an impact on the clinical performance, such as PKs or efficacy. The
6 nonclinical *in vitro* studies should be sensitive, specific and sufficiently discriminatory to provide
7 evidence that observed differences in quality attributes as well as possible differences that may not
8 have been detected during the comparative analytical assessment.

9 Nonclinical studies may benefit from the potency assays included in the quality comparability
10 program. The clinical relevance of the selected assays should be justified.

11 Since *in vitro* assays may often be more specific and sensitive for detecting differences
12 between SBP and RBP than studies in animals, these assays can be considered as paramount
13 for the nonclinical biosimilar comparability exercise.

14

15

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1 **Nonclinical *in vivo* studies**

2
3 **QIV-4 Which aspects should be considered to decide whether *in vivo* animal studies**
4 **are required for nonclinical evaluation of a specific SBP?**

5 On the basis of the totality of available quality and nonclinical *in vitro* data and of the extent
6 to which there is residual uncertainty about the similarity of SBP and RBP, it is at the
7 discretion of NRAs to waive or not to waive a requirement for nonclinical *in vivo* studies. If
8 the quality-comparability exercise and nonclinical *in vitro* studies are considered satisfactory,
9 and no issues are identified that would block direct entrance into humans, *in vivo* animal
10 studies may be considered unnecessary.

11 In some jurisdictions, legislation requires the application of the 3R (Reduction, Refinement
12 and Replacement of animal experiments) principle in the product development in order to
13 reduce suffering of animals. In particular, studies with non-human primates should be
14 avoided if possible. *In vivo* animal studies should only be considered when it is expected that
15 such studies would provide relevant additional information. In general, the additional value of *in*
16 *vivo* nonclinical studies for the demonstration of comparability of SBP and RBP is
17 questionable when preceding physico-chemical, structural and *in vitro* functional tests have
18 demonstrated the close similarity of SBP and RBP.

19 There are a number of factors that reduce the need for *in vivo* studies in the development of a
20 SBP:

- 21
- 22 • the risk of the first-in-man use of a SBP can usually be estimated on basis of the
23 knowledge about the clinical safety profile of the RBP and the outcome of the physico-
24 chemical, structural and *in vitro* functional tests with the SBP.
 - 25 • most toxic effects of a therapeutic proteins are often related to an exaggeration of their
26 known pharmacological effects.
 - 27 • the functional activity of a biotherapeutic drug substance is often species-specific
28 making it difficult to identify a suitable animal species
 - 29 • being foreign, human drug substances are often immunogenic in the conventional
30 animal models which prevents or hampers the interpretation of repeat dose animal
31 studies
 - 32 • conventional animal models are often not sensitive enough to detect small differences
- 33
34
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1 **QIV-5 Which specific aspects should be observed for the planning/conduct of *in vivo***
2 **animal studies on pharmacodynamics and/or pharmacokinetics of a SBP?**

3 PK studies with the SBP should be justified on the basis of data of the RBP and the
4 interference of anti-drug antibodies.

5 If product-inherent factors that have an impact on PK and/or biodistribution (such as
6 glycosylation or pegylation) cannot sufficiently be characterized on a quality and *in vitro*
7 level, the manufacturer should carefully consider if *in vivo* animal PK and/or
8 pharmacodynamics (PD) studies should be performed in advance of clinical PK/PD testing.
9 Since relevant PK/PD data are obtained in humans, nonclinical PK/PD studies usually have
10 little additive value for the comparability exercise.

11 The WHO guidelines indicate that, if an *in vivo* PK/PD study is conducted, the PK and/or PD of
12 the SBP and the RBP should be compared quantitatively, including, if feasible, a dose-
13 response assessment that includes the intended exposure in humans.

14 *In vivo* assays may include the use of animal models of disease to evaluate functional effects
15 on PD markers or efficacy measures. Pharmacokinetic measurements may need to be
16 performed in parallel to ensure relevant drug exposure.

17

18

1

2 **QIV-6 Which specific aspects should be observed for the planning/conduct of *in vivo***
3 **animal toxicity studies for a SBP?**

4 Most toxic effects of therapeutic proteins are related to their pharmacological mechanism of
5 action which can be characterized by receptor binding assays and *in vitro* nonclinical
6 functional tests, including cell-based assays. Therefore, with regard to the conduct of
7 toxicological studies, the developer should focus on other types of adverse effects known to
8 occur following treatment with the RBP and adverse effects that could potentially be caused
9 by the differences observed during the preceding steps of the comparability exercise.

10 If a toxicity study is considered, the suitability of conventional toxicology models needs to be
11 evaluated. *In vivo* toxicological studies should only be conducted in an animal species in
12 which the SBP is pharmacologically active. However, many biological products may not be
13 pharmacologically/toxicologically active in the species used in conventional toxicology tests.
14 In addition, human proteins are often immunogenic in other species which restricts the
15 duration of toxicology studies and hampers the interpretation of study results. Finally, the
16 discriminatory ability of the *in vivo* model in a reasonably sized study, especially in multiple
17 dose studies, should be evaluated realistically.

18 If *in vivo* safety studies are deemed necessary, a flexible approach should be considered, e.g.
19 in accordance with the 3R principles. The conduct of repeat dose toxicity studies in non-
20 human primates is usually not recommended (see also **QIV-1**). If appropriately justified, a
21 study with refined design (for example, using just one dose level of SBP and RBP, and/or
22 just one biological sex and/or no recovery animals) and/or an in-life evaluation of safety
23 parameters (such as clinical signs, body weight and vital functions) may be considered.
24 Depending on the selected end-points, it may not be necessary to kill the animals at the end of
25 the study.

26 Local tolerance may be evaluated in the context of a repeat dose toxicity study.

27 Safety pharmacology, reproductive toxicology, genotoxicity, and carcinogenicity studies are
28 not needed.

1 **QIV-7 Where no suitable animal model is available, how can the preclinical**
2 **comparability exercise be extended?**

3 First of all, the developer needs to consider whether *in vivo* nonclinical studies are necessary
4 (see **QIV-4**). In this regard, it may be useful to consult the local regulatory authorities. If the
5 risk analysis based on data of the physico-chemical, structural and *in vitro* functional
6 comparability studies raises concerns about the transit to clinical studies, the developer may
7 consider the following options:

- 8 • optimisation of the manufacturing process to remove factors that raise concerns,
9 e.g. reduction of impurities or modification of the formulation
- 10 • perform additional tailored quality or nonclinical studies to reducing uncertainty
- 11 • apply specific risk mitigation measures upon the entry to clinical studies

12
13

14 **QIV-8 Under what circumstances/conditions would an additional nonclinical**
15 **comparability study be required?**

16 *In vivo* nonclinical studies should be considered if there is

- 17 • a significant functional difference suggested by nonclinical *in vitro* studies
- 18 • a novel excipient in the formulation of the SBP.
- 19 • a new expression system or purification process in the manufacturing process leading
20 to a significant change in the process-related impurities
- 21 • a narrow therapeutic window of the drug substance

22 Although the factors mentioned above will not necessarily always warrant *in vivo* testing,
23 these factors should be considered together to assess the level of concern and to determine
24 whether or not there is a need for *in vivo* testing.

1 **V. Clinical evaluation:**

2 **QV-1 Will SBPs be as safe as originator products?**

3 Yes, if they are developed according to the WHO and other corresponding guidelines and
4 assessed by regulatory agencies that have the necessary scientific expertise and experience.
5 For example, it is estimated that approximately 700 000 000 doses of SBPs authorised in the
6 EU were administered by 2016. In spite of the large exposure, no SBPs have been withdrawn
7 for safety reasons and no such new adverse effects have been reported that have not been
8 reported for the reference products as well. The equal safety of the SBP and its RBP is based
9 on the physico-chemical and structural similarity that is demonstrated by the extensive
10 comparability exercise comprised of analytical, structural, and functional tests, as well as
11 pharmacokinetic and clinical safety and efficacy studies. The safety of SBPs is monitored by
12 the pharmacovigilance systems and often by additional post-marketing risk detection and
13 minimisation measures.

14

1 **QV-2 What is immunogenicity and why is it a special concern for a SBP?**

2 The purpose of the immune system is to recognise and eliminate foreign substances and
3 denatured structures of the body itself. Immunogenicity of a therapeutic protein means that
4 the immune system is capable of recognizing the protein as non-self and is able to generate an
5 immune response against it.

6 Immune system is a dedicated network of cells that have means to communicate with each
7 other. The immune system resembles the nervous system in that immune system can learn
8 and remember. Immune system is necessary for survival of an individual. Unfortunately, it
9 can sometimes recognise therapeutic proteins as foreign invaders and react against them. This
10 reaction may abolish the therapeutic effect and cause hypersensitivity and autoimmune
11 reactions.

12 Human immune system consists of two parts that collaborate to protect the body; an innate,
13 non-adaptive part and an adaptive antigen-specific part. The innate part is able to react
14 immediately to certain foreign substances, like bacterial polysaccharides. Macrophages have
15 an important role in the innate immune reaction as they can recognise and break down
16 foreign substances like bacteria and denatured proteins.

17 Macrophages and other similar cells can also alert the adaptive immune system of a foreign
18 invader by presenting parts of the digested foreign substance to T lymphocytes and by
19 secreting lymphocyte-stimulating cytokines. If the T-cell will recognise the presented parts of
20 the invader as foreign, “non-self”, T-cells will activate and become cytotoxic cells or helper
21 T-cells that stimulate B-cells to become plasma cells producing antibodies against the foreign
22 substances.

23 The human immune system has evolved to recognising proteins. All therapeutic proteins will
24 be recognised as either self or non-self. If a protein is deemed foreign, non-self, the immune
25 system will mount an immune response against the protein. If the protein is classified as a
26 normal body constituent, “self”, no reaction is triggered. In other words, there is an
27 immunological tolerance to the protein. The immunological tolerance varies between
28 individuals as it is partly genetically determined.

29 Many therapeutic proteins are similar to proteins of the body. Therefore, they are normally
30 recognised by the immune system as “self” and no activation of the immune system will take
31 place. However, an immune reaction may be triggered if the therapeutic protein is deemed
32 foreign or denatured. As a result, anti-drug antibodies (ADA) may neutralise the effect of the
33 therapeutic protein.

34 Safety problems may arise if the ADA-response will continue to evolve. Life-threatening
35 hypersensitive reactions may occur if the ADAs will have a class switch to IgE or if
36 pathogenetic immune complexes (protein + ADA) are formed. Another type of a serious
37 reaction is possible if the therapeutic protein has an endogenous counterpart. In this situation,
38 ADAs may cross-react with the endogenous protein, such as erythropoietin, and may cause a
39 serious complication, pure red cell aplasia.

40 According to WHO guidelines, all new therapeutic proteins, including SBPs, should be tested
41 for ADAs in clinical trials. The additional hurdle for SBPs is the need to demonstrate
42 comparable immunogenicity. Thus, an SBP is always compared head-to-head to its RBP in
43 pre-marketing clinical trials to demonstrate comparable immunogenicity, efficacy and
44 immune mediated adverse effects. An SBP cannot have more immune-mediated adverse
45 effects than its RBP. An RBP may have several therapeutic indications but SBP is tested

1 usually in one of them. Therefore, it is important to study a therapeutic indication and patient
2 population that provide a sensitive model for detecting differences in immunogenicity. To
3 date, no SBP has caused more adverse immune reactions than its RBP.

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2 **QV-3 If there are differences in immunogenicity, how is this handled?**

3 The purpose of the immunological studies is to detect harmful immunogenicity in the
4 clinically relevant population. The first step is to compare the incidence, titer, and
5 neutralising capacity. Secondly, the possible clinical correlations should be looked for.
6 Differences in efficacy and safety are not tolerated.

7 A root cause of a difference in immunogenicity should always be investigated, even if the
8 SBP appears to have less immunogenicity. First of all, ADA assay should be re-evaluated for
9 a possible bias. The most common problem in the ADA assays is drug interference in which
10 the residual product in the blood sample for ADA analysis will cause false negative results.
11 Therefore, the drug tolerance of the assay(s) should be revisited and the drug concentrations
12 in the samples compared.

13 If no technical problem is discovered, the responsible regulatory agency will ask the
14 manufacturer to review all differences observed in the analytical, structural, and functional
15 comparisons and discuss their possible role in immunogenicity.

16 If differences in ADA-incidences or titres, including neutralising ADAs, are observed, the
17 persistence of the ADA responses and possible clinical correlations should be explored by
18 comparing pharmacokinetics, recording relevant symptom complexes, such as
19 hypersensitivity or autoimmunity, as well as comparing cumulative drug doses of the SBP
20 and RBP in relevant clinical studies.

21 In case the SBP is really less immunogenic on the basis of ADA-assays, the manufacturer has
22 to ensure that that there is no impact on exposure. If there is more exposure due to reduced
23 immunogenicity, the manufacturer has to discuss the safety implications of the increased
24 exposure.

25 The burden of evidence is on the manufacturer who must convince regulators of the lack of
26 clinical impact. If no harmful effects are observed, the manufacturer will have to commit to
27 post-marketing studies to exclude potential rare immunological complications of the SBP to
28 ensure a positive benefit-risk ratio.

29

30

1 **QV-4 In case the RBP showed higher rate of ADA positivity than the historical data,**
2 **what could be the data requirement for the SBP?**

3 It is not uncommon that the incidence of ADAs is lower in older than in newer studies of the
4 RBPs. This can be explained by the higher sensitivity of current ADA assays. For this reason,
5 head-to-head comparisons using validated state of the art assays are the only way to
6 demonstrate comparable immunogenicity. Deviations from this rule are possible in low risk
7 situations after consultation of local competent authorities.

8
9

10 **QV-5 If the comparability study of efficacy is waived, is a separate immunogenicity**
11 **study required or could immunogenicity assessment be conducted in a**
12 **comparative PK/PD study?**

13 Immunogenicity studies should be integrated in the clinical comparability studies because the
14 purpose is to detect harmful immunogenicity. In principle, the analysis of immunogenicity
15 should be conducted in a population where differences can be detected and in a study that
16 allows the investigation of the possible clinical impact of ADAs.

17 ADAs should be investigated in PK studies because of the potential interference of ADAs.
18 PD studies in the target population are suitable for investigation of immunogenicity if a
19 surrogate PD marker is used.

20 If other kinds of PD studies are conducted, additional specific immunogenicity studies may
21 be needed pre- or post-marketing unless the product is expected to have a low risk of
22 immunogenicity. A consultation of the local regulatory authorities is warranted.

23
24

25 **QV-6 How can SBPs be approved for indications for which no clinical studies have**
26 **been done?**

27 The aim of the biosimilar comparability studies is to demonstrate a close similarity between
28 the SBP and RBP. If this is achieved, it can be expected that the function of the products is
29 also similar. Additional studies are needed only if the therapeutic indication that was
30 investigated in the clinical comparability study is not representative for other therapeutic
31 indications in terms of safety (see QV-7).

32

1 **QV-7 What are the most important ‘Points to Consider’ in extrapolating clinical data**
2 **showing biosimilarity in one indication to other licensed indications?**

3 Clinical studies of an SBP are a part of the overall comparability exercise. The ability to
4 extrapolate is based on the totality of evidence. If a close similarity has been demonstrated,
5 extrapolation is possible. Nevertheless, a scientific justification should be presented by
6 considering the following points:

7 • **The sensitivity of the studied clinical model** (therapeutic indication and patient
8 population) to detect differences:
9 This means that the therapeutic effect is significant and consistent across the clinical
10 trials as well as that there are sensitive clinical endpoints to compare the outcomes.

11 • **Are the same receptors or binding sites are involved in the effects of the drug**
12 **substance in all therapeutic indications claimed for the SBP?**

13 Extrapolation is easy if the same receptors or active sites are involved in the
14 therapeutic indications, for example epoetin alfa.

15 For monoclonal antibodies, extrapolation is more complicated since there are several
16 receptors/functional sites that can mediate or modify therapeutic effects. It seems
17 obvious that the relative importance of individual receptors/active sites may vary
18 between the approved therapeutic indications of the RBP. Therefore, the binding and
19 function of the relevant receptors/functional sites should be addressed. In some cases,
20 functional tests need to be modified by using different target and effector cells to
21 better simulate the pathology of the target disease. Additional pharmacodynamic or
22 clinical efficacy and safety studies may be considered although their sensitivity is
23 usually inferior to *in vitro* functional tests.

24 • **Are there specific concerns in the therapeutic indications that were not**
25 **investigated or that cannot be addressed by data obtained in the conducted**
26 **clinical trial(s)?**

27 For example, immunogenicity may vary between therapeutic indications due to
28 differences in the state of the immune system. Another example is extrapolation from
29 one disease group such as autoimmune disease to another, such as cancer, where the
30 pharmacokinetics and posology may be different. In these cases, additional PK/PD or
31 clinical trials may be needed to address the prevailing uncertainty. Potential rare
32 adverse effects should be monitored post-marketing.

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35

1 QV-8 **After a SBP has been approved, can a new indication added to the RBP be**
2 **shared with the SBP?**

3 This is a regulatory decision made by the local NRA. In principle, adding a new therapeutic
4 indication is possible. However, it would need a justification and possibly some new data
5 along the same lines as with extrapolation before approval of the SBP.

6
7
8 QV-9 **How can a different regulatory decision regarding extrapolation be reached by**
9 **different national regulatory authorities when using the same regulatory data**
10 **package?**

11 It is not uncommon that there are some differences in the marketing authorisation conditions
12 granted by different regulatory authorities. In addition, it is not usually known whether the
13 same data to support extrapolation was submitted to different authorities, especially in case
14 the submissions took place at different times. The history of the RBP as well as local
15 guidelines and regulatory policies may also vary in different jurisdictions. Some regulatory
16 bodies have a lot of experience of extrapolation whereas some regulators have only recently
17 been exposed to it. In some areas, SBPs, including extrapolation, have been controversial
18 among stakeholders who are consulted by the regulatory bodies. Finally, the estimation of
19 benefit-risk ratio contains values and uncertainties that may be judged differently by different
20 regulatory experts.

21 Differences in the initial regulatory decisions on extrapolation will diminish over time, when
22 more post-marketing safety data and new clinical data become available. For instance, there
23 were initially differences between regulatory bodies concerning the extrapolation of efficacy
24 and safety of the first infliximab SBP from rheumatic diseases to inflammatory bowel
25 diseases. Within a couple of years, all main regulatory bodies reached the same conclusion on
26 the basis of scientific discussions and increasing experience.

27
28
29 QV-10 **How should inexperienced national regulatory authorities (NRAs) deal with**
30 **differing regulatory decisions of major experienced NRAs?**

31 In general, the major experienced regulatory bodies have reached similar conclusions and
32 decisions. However, national legislations may introduce some differences in the regulatory
33 approach. For instance, the U.S. legislation forces FDA to require interchangeability studies
34 of SBPs and RBPs whereas the European legislation prohibits EMA to take a position on
35 interchangeability. Therefore, it is important to understand the background of the regulatory
36 decisions.

37
38 True scientific differences in regulatory decisions exist (see QV-9). In such a case one should
39 read the publicly available assessment reports of the regulatory agencies that reached
40 different conclusions to understand the reasons for the different outcome. In addition, it is
41 useful to review post-marketing data on safety and efficacy from the NRA that made the
42 positive decision.

43

1

2 **QV-11 Is there always a need for a clinical study of a SBP?**

3 As mentioned in the WHO *guidelines on evaluation of similar biotherapeutic products*, the
4 demonstration of comparability of a SBP to its RBP in terms of quality is a prerequisite for
5 the reduction of the nonclinical and clinical data set required for licensure. Thus, the
6 reduction of clinical data is dependent on two issues: complexity of the product and the
7 performance of the analytical methods.

8 The analytical methodology is developing rapidly. As a result, even complex biotechnology-
9 derived products, such as monoclonal antibodies can be characterized to the degree that
10 allows an abbreviated clinical development.

11 For less complex proteins or polypeptides, such as insulin and filgrastim (G-CSF),
12 confirmatory PK/PD studies may be appropriate, provided that a PD marker can be regarded
13 as a surrogate for efficacy. Thus, euglycaemic clamp test is a suitable surrogate PD marker
14 for insulin SBPs and absolute neutrophil count (duration of severe neutropenia) has been used
15 in confirmatory studies of filgrastim SBPs. However, regulatory authorities may require
16 additional safety studies in the target population.

17 Very simple peptides may be licensed with only a small PK/PD bioequivalence study. For
18 example, teriparatide is a 34 amino acid peptide that can be synthesized both chemically and
19 by biotechnology. The peptide undergoes no post-translational modification. Synthetic and
20 genetically engineered versions of teriparatide have identical affinity for the parathyroid
21 hormone (PTH) surface receptors as well as the same biological activity. Thus, it is logical
22 that regulatory authorities have demanded only a simple bioequivalence study with
23 supportive PD markers.

24 In conclusion, confirmatory safety and efficacy studies are not always necessary.

1 **VI. Pharmacovigilance:**

2

3 **QVI-1 After a SBP has been approved, is the SBP required to maintain biosimilarity**
4 **with its RBP?**

5 No. Following approval, an SBP is considered independent from the reference product and
6 has its own life cycle. The manufacturer is not required to re-establish similarity to the
7 reference product when comparability exercises are conducted upon a manufacturing change
8 (*WHO guidelines on procedures and data requirements changes to approved biotherapeutic*
9 *products*). However, manufacturers of both SBP and RBP are required to keep their products
10 within the release specifications during the product life cycle. Every change in the
11 manufacturing process must be supported by a comparability exercise comparing the pre- and
12 post-change versions of the product to demonstrate that the safety and efficacy have not
13 suffered.

14 Thus, the manufacturers of both SBP and RBP are responsible to maintaining their products
15 as safe and efficacious by preventing significant changes to the product. Experience from
16 hundreds of manufacturing changes over several decades demonstrates that significant
17 changes to individual products over time are very rare. For time being, there are no data to
18 suggest that a SBP would have lost its comparability to the RBP.

19

20

21 **QVI-2 Would it be beneficial to review/discuss post marketing commitments from**
22 **each country after extrapolation of indications?**

23 Yes. The regulatory agencies may ask for specific risk detection measures to address possible
24 problems in the “extrapolated therapeutic indications” after licensing. These measures range
25 from the monitoring of adverse events to patient registries and specific clinical trials. These
26 measures are determined by each competent authority and may differ. It would be beneficial
27 to harmonise the post-marketing commitments in order to pool data and to identify a potential
28 problem as early as possible.

29

1 **QVI-3 If safety information of the RBP (i.e. adverse events) is amended, how would it**
2 **be applied to the already approved SBPs?**

3 This is a national regulatory decision. In principle, new safety information should be added to
4 SBP as well because an SBP refers to the safety and efficacy of the RBP. The manufacturer
5 of the SBP should send a variation to its safety information to the relevant regulatory
6 agencies unless it can be demonstrated that the new information on RBP is not relevant to the
7 SBP.

8

9

10 **QVI-4 Can the SBP license holder develop a new indication or dosage administration**
11 **which the RBP is not approved for?**

12 In principle yes, if the license holder will submit relevant data to support the application. The
13 manufacturer of the SBP should consult the local NRA when planning studies for the new
14 indication.

15

16

17 **QVI-5 Should cautions in use for a SBP be the same with those for the RBP for its**
18 **marketing approval?**

19 Yes. Cautions that are related to a therapeutic indication that was not applied for may also
20 have to be mentioned because of possible off-label use.

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