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Guidelines on evaluation of similar biological products

Proposed revision of Annex 2 of WHO Technical Report Series, No. 977

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed revision of *Guidelines on evaluation of similar biotherapeutic products, Annex 2, WHO Technical Report Series No. 977* 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 ECBS. Written comments proposing modifications to this text MUST be received by 24 May 2021 using the Comment Form available separately and should be addressed to: Department of Health Products Policy and Standards (HPS), World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Comments may also be submitted electronically to the Responsible Officer: Dr Hye-Na Kang at kangh@who.int.

The outcome of the deliberations of the ECBS will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the second edition of the *WHO style guide* (KMS/WHP/13.1).

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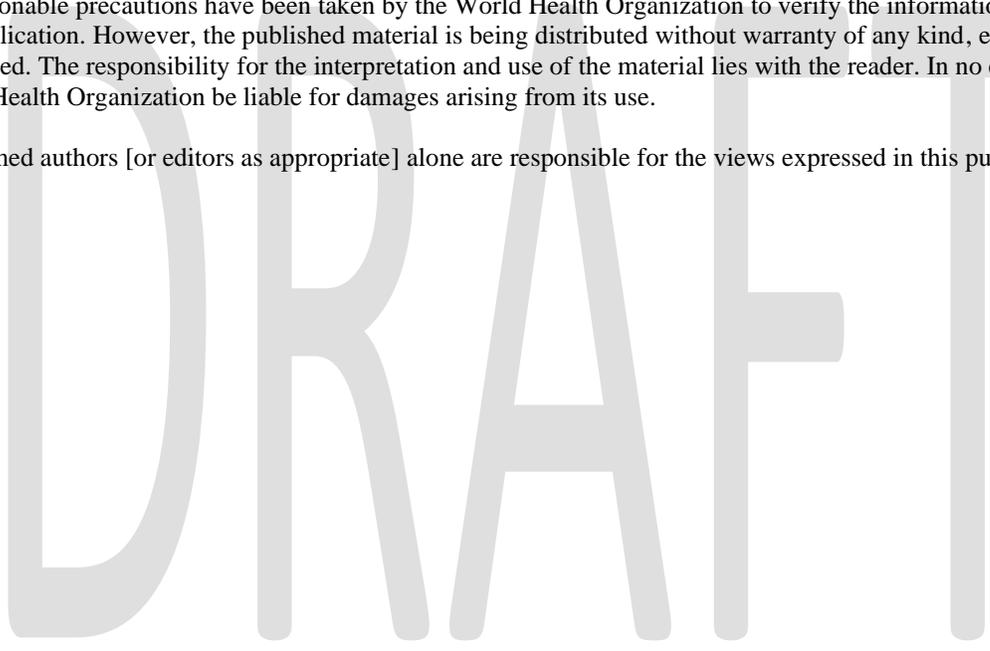
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Guidelines on evaluation of similar biological products (SBPs)

Proposed revision of Annex 2 of WHO Technical Report Series, No. 977

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19 Guidelines published by the World Health Organization (WHO) are intended to be scientific and
20 advisory in nature. Each of the following sections constitutes guidance for national regulatory
21 authorities (NRAs) and for manufacturers of DNA vaccines. If an NRA so desires, these WHO
22 Guidelines may be adopted as definitive national requirements, or modifications may be justified
23 and made by the NRA. It is recommended that modifications to these Guidelines are made only
24 on condition that such modifications ensure that the product is at least as safe and efficacious as
25 that prepared in accordance with these WHO Guidelines set out below.

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1. Introduction

Biotherapeutic products (biotherapeutics) have a successful record in treating many life-threatening and chronic diseases. However, their cost has often been high, thereby limiting their accessibility to patients, particularly in developing countries. The expiry of patents and/or data protection for originator's biotherapeutics has ushered in an era of products that are designed to be highly "similar" to a licensed originator product. Based on demonstrated close analytical similarity, these products can rely for their licensing partly on safety and efficacy information obtained with the originator products. A variety of terms have been used to describe these products, including: "similar biotherapeutic product", "similar biological medicinal products", "biosimilar products", and "biosimilars" (1).

The term "generic" medicine is used to describe chemical, small-molecule medicinal products that are structurally and therapeutically equivalent to an originator product whose patent and/or data protection period has expired. Demonstration of bioequivalence of the generic medicine to a reference product is usually appropriate and sufficient proof of therapeutic equivalence between the two. However, the approach established for generic medicines is not suitable for the development, evaluation and licensing of similar biotherapeutic products since biotherapeutics usually consist of relatively large and complex proteins, are more complicated to manufacture than small molecule and in most cases cannot be reproduced exactly.

As part of its mandate for assuring global quality, safety and efficacy of biotherapeutics, WHO provides globally accepted norms and standards for the evaluation of these products. Written standards established through the Expert Committee on Biological Standardization (ECBS) serve as a basis for setting national requirements for production, quality control and overall regulation of biological medicines. In addition, International Standards for measurement are, where available, essential tools for establishing the potency of biological medicines worldwide; they are often used as primary standards for calibration of the secondary standards that are directly used in the biological assays.

An increasingly wide range of similar biotherapeutic products was under development or was already licensed in many countries and a need for guidelines for their evaluation and overall regulation was formally recognized by WHO in 2007 (2). The WHO *guidelines on evaluation of similar biotherapeutic products* were adopted by the ECBS in 2009 (3). The document had provided the scientific principles including the stepwise approach which should be applied for demonstration of similarity between the similar biotherapeutic product and its reference biotherapeutic product. The document also provides guidance for the development and evaluation of such biotherapeutics; it should be viewed as a "living" document that will be developed further in line with advances in scientific knowledge and experience. It is anticipated that the increasing availability of similar biotherapeutic products worldwide will increase competition between manufacturers, thus bringing down prices and improving access to such medicines. In line with World Health Assembly resolution WHA67.21 on access to biotherapeutics (4), the ECBS at its meeting in October 2020 recommended that a review should be undertaken of current scientific evidence and experience in this field. The opportunity allowed a review of new developments and to identify areas where the current guidance could be more flexible without compromising its basic principles, providing

1 additional explanation regarding the possibility of further tailoring the amount of data needed
2 for regulatory approval (5). At its meeting in December 2020 the Committee was informed
3 that the review had taken into account a number of national and regional guidelines, and a
4 number of sections in the current WHO Guidelines had been identified for potential updating
5 and revision. Having been updated on progress in this area, the Committee expressed the
6 opinion that the review of existing regional guidance had been comprehensive and reiterated
7 its support for the continuation of the outlined revision process. It was intended that such
8 revision of the WHO Guidelines would result in greater flexibility and reduced regulatory
9 burden, while continuing to ensure the quality, safety and efficacy of such products (6).

10 The present guidelines are intended as a revision of those in Annex 2 of WHO Technical Report
11 Series, No. 977 (3) and will be developed through international consultations.

12
13 The main changes made to the previously published WHO Guidelines (3) include:

- 14 1. Updating the Introduction with the discussions held for the revision;
- 15 2. Expanding the scope of products from biotherapeutics to biologicals
- 16 3. Updating the considerations to use non-local reference biological products (RBPs);
- 17 4. Extensively revising the Quality, Non-clinical, and Clinical sections to make them
18 more consistent with current practices and with other guidelines as well as to provide
19 more clarity and flexibilities. It includes, but are not restricted to, the following:
 - 20 a. use of WHO international standards and reference reagents
 - 21 b. analytical considerations for quality
 - 22 c. considerations on the establishment of similarity ranges for quality comparisons
23 and on the conclusion on similarity
 - 24 d. new guidance on the determination of the need for in vivo animal studies and
25 implementation of the 3Rs principles (Replacement, Reduction and Refinement
26 of animal experiments)
 - 27 e. considerations for amount and type of necessary clinical data
- 28 5. Updating the sections of Pharmacovigilance, Prescribing information and label, and
29 Role and responsibilities of national regulatory authorities (NRAs) with additional
30 description and references.

31
32 For public health purposes, it is essential that the standard of evidence supporting the decisions
33 to license similar biological products (SBPs) is sufficiently high to ensure that the products
34 meet acceptable levels of quality, safety and efficacy. Elaboration of the data requirements and
35 considerations for the licensing of these products is expected to facilitate development of and
36 worldwide access to biologicals of assured quality, safety and efficacy at more affordable
37 prices. It is expected that these Guidelines on the scientific principles for evaluation of SBPs
38 will help to harmonize the requirements worldwide and lead to easier and speedier approval
39 and assurance of the quality, safety and efficacy of these products. It is important to note that
40 biologicals that are not shown to be similar to an RBP as indicated in these Guidelines should

1 neither be described as “similar” nor called SBPs. Such products could be licensed through
2 other pathways, e.g. via a full licensing application using more extensive nonclinical and
3 clinical data sets.

4 It was recognized that a number of important issues associated with the use of SBPs, including
5 but not limited to the following, need to be defined by NRAs:

- 6 • intellectual property issues;
- 7 • interchangeability and substitution of RBP with SBP; and
- 8 • labelling and prescribing information.

9 For this reason, these issues are not elaborated in this document.

10 2. Aim

11 The intention of this document is to provide globally acceptable principles for licensing
12 biological products that are claimed to be similar to biological products of assured quality,
13 safety, and efficacy that have been licensed based on a full licensing dossier. On the basis of
14 proven similarity, the licensing of an SBP will rely, in part, on nonclinical and clinical data
15 generated with an already licensed RBP. These Guidelines can be adopted as a whole, or
16 partially, by NRAs worldwide or used as a basis for establishing national regulatory
17 frameworks for licensure of these products.

18 3. Scope

19 An SBP is a biological product that is highly similar in terms of quality, safety and efficacy to
20 an already licensed biological product (the ‘RBP’). These Guidelines apply to well-
21 characterized biological products.

22 4. Terminology

23 The definitions given below apply to the terms used in these Guidelines. They may have
24 different meanings in other contexts.

25 **Comparability exercise.** Direct comparison of a biological product with a licensed originator
26 product with the goal of establishing similarity in quality, safety and efficacy.

27 **Comparability margin:** the largest difference that can be judged as being clinically acceptable.

28 **Comparability range.** Allowable differences on physicochemical and biologic activity level.

29 **Drug product.** A pharmaceutical product that contains a drug substance, generally in
30 association with excipients.

31 **Drug substance.** The active pharmaceutical ingredient and associated molecules that may be
32 subsequently formulated, with excipients, to produce the drug product.

1 **Equivalent.** Equal or virtually identical in the parameter of interest. Equivalent efficacy of two
2 medicinal products means they have similar (no better and no worse) efficacy and any observed
3 differences are of no clinical relevance.

4 **Generic medicine.** A generic medicine contains the same active pharmaceutical ingredient as,
5 and is bioequivalent to, an originator (comparator) medicine. Since generic medicines are
6 identical in the active pharmaceutical substance, dose, strength, route of administration, safety,
7 efficacy and intended use, they can be substituted for the originator product.

8 **Immunogenicity.** The ability of a substance to trigger an immune response or reaction (e.g.
9 development of specific antibodies, T cell response, allergic or anaphylactic reaction).

10 **Impurity.** Any component present in the drug substance or drug product that is not the desired
11 product, a product-related substance, or excipient including buffer components. It may be
12 either process- or product-related.

13 **Non-inferior.** Not clinically inferior to a comparator in the parameter studied. A non-
14 inferiority clinical trial is one that has the primary objective of showing that the response to
15 the investigational product is not clinically inferior to a comparator by a pre-specified margin.

16 **Originator product.** A medicine that has been licensed by the national regulatory authorities
17 on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted
18 on the basis of full quality, efficacy and safety data.

19 **Pharmacovigilance.** The science and activities relating to the detection, assessment,
20 understanding and prevention of adverse effects or any other drug-related problems.

21 **Reference biological product (RBP).** A reference biological product is used as the
22 comparator for direct comparability studies with the similar biological product in order to show
23 similarity in terms of quality, safety and efficacy. Only an originator product that was licensed
24 on the basis of a full registration dossier and has been marketed for a suitable period of time
25 with a proven quality, efficacy and safety can serve as an RBP. The term does not refer to
26 measurement standards such as international, pharmacopoeial or national standards or
27 reference standards.

28 **Similarity.** Absence of a relevant difference in the parameter of interest.

29 **Similar biological product (SBP).** A biological product that is similar in terms of quality,
30 safety and efficacy to an already licensed reference biological product.

31 **5. Scientific considerations and concept for licensing** 32 **SBPs**

33 The regulatory framework for the licensing of generic medicines is well established in most
34 countries. Demonstration of structural sameness and bioequivalence of the generic medicine
35 to the reference product is usually sufficient for therapeutic equivalence between the generic
36 and reference product to be inferred. However, the generic approach is not suitable for the
37 licensing of SBPs since biological products usually consist of relatively large and complex
38 proteins, are more complicated to manufacture than small molecules and in most cases cannot
39 be reproduced exactly. In addition, SBPs are manufactured and controlled by processes

1 established by the SBP manufacturer since the manufacturer of an SBP normally does not have
2 access to all the necessary manufacturing information on the originator product. Differences
3 in the manufacturing process may result in differences in the biologicals that affect the
4 pharmacokinetics, pharmacodynamics, efficacy and/or safety of biological products.

5 Characterization and evaluation of the quality attributes of the RBP should be the first step to
6 guide the development of the SBP. This is followed by a comparability exercise to demonstrate
7 structural, functional, and clinical similarity. Comprehensive characterization and comparison
8 showing similarity at the quality and nonclinical (*in vitro*) level are the basis for possible data
9 reduction in the clinical development. If differences between the SBP and the RBP are found
10 at any step, the underlying reasons for the differences should be investigated. Minor differences
11 should always be fully explained and justified and may lead to additional data (e.g. on safety)
12 being required, major differences preclude biosimilarity and a stand-alone development may
13 need to be considered. Stand-alone development is not discussed here.

14 In addition to quality and non-clinical (*in vitro*) data, clinical data are required for any SBP.
15 The amount of such data that is considered necessary will depend on the product or class of
16 products, on the extent of characterization possible using state-of-the-art analytical methods,
17 on observed or potential differences between the SBP and the RBP, and on clinical experience
18 with the product class (e.g. safety/immunogenicity concerns in a specific indication). A case-
19 by-case approach is needed for each class of products.

20 An SBP is intended to be similar to a licensed biological product for which substantial evidence
21 exists of safety and efficacy. Authorization of the SBP on the basis of reduced clinical data
22 depends on proof of its similarity to an appropriate RBP through the comparability exercise.
23 Manufacturers should demonstrate both a full understanding of their product and consistent
24 and robust manufacture, and should submit a full quality dossier that includes a complete
25 characterization of the product. Comparison of the SBP and the RBP with respect to quality
26 represents an additional element to the “traditional” full quality dossier. In addition, usually a
27 comprehensive comparison at the nonclinical *in vitro* level is required. A reduction in data
28 requirements is therefore possible only for the nonclinical *in vivo* and/or clinical parts of the
29 development programme. The dosage form and route of administration of the SBP should be
30 the same as for the RBP.

31 Studies must be comparative in nature and must employ analytical methods that are capable of
32 detecting potential differences between the SBP and the RBP. The main clinical studies should
33 use the final formulation of the SBP, i.e. derived from the final process material, otherwise,
34 additional evidence will be required to demonstrate that the SBP to be marketed is comparable
35 to that used in the main clinical studies.

36 If similarity between the SBP and the RBP has been demonstrated, the SBP may be approved
37 for use in other clinical indications of the RBP without performing additional clinical trials,
38 provided appropriate scientific justification is given for such extrapolation (see section 10.7).

39 **6. Key principles for the licensing of SBPs**

- 1 • Characterization of the quality attributes of the RBP should be the first step to guide
2 the development of the SBP. The subsequent comparability exercise should
3 demonstrate structural, functional and clinical similarity.
- 4 • A clinical bioequivalence trial with PK and PD parameters (if available) and including
5 assessment of immunogenicity in human subjects will always be part of the
6 comparability assessment
- 7 • Demonstration of close similarity of an SBP to an RBP in terms of structural and
8 functional aspects and nonclinical *in vitro* data is a prerequisite for reducing the
9 nonclinical *in vivo* and clinical data package required for licensure.
- 10 • The decision to license the SBP should be based on the evaluation of the whole data
11 package generated in the overall comparability exercise.
- 12 • If relevant differences between the proposed SBP and the RBP are found at the
13 structural, functional or clinical level, the product is unlikely to qualify as an SBP. In
14 such cases, a more extensive nonclinical and clinical data set will probably be required
15 to support an application for licensure.
- 16 • If comparability exercises are not performed as outlined in this document, the final
17 product should not be referred to as an SBP.
- 18 • SBPs are not “generic medicines” and many characteristics associated with the
19 authorization process of generics generally do not apply.
- 20 • Like other biological products, SBPs require effective regulatory oversight for the
21 management of the potential risks they pose and in order to maximize their benefits.

22 7. Reference biological product

23 Comprehensive information on the RBP provides the basis for establishing the safety, quality
24 and effectiveness profile to which the SBP is compared. The RBP also provides the basis for
25 dose selection and route of administration, and is used in the similarity studies required to
26 support the licensing application. The demonstration of a high level of analytical and functional
27 similarity between the SBP and RBP provides the rationale for a tailored nonclinical and
28 clinical data set to support the application for market authorization for the SBP.

29 The choice of an RBP is critically important for the evaluation of the SBP. Only one RBP
30 should be chosen for a specific SBP for licensing purposes. Traditionally, NRAs have required
31 the use of a nationally licensed reference product for licensing of generic medicines. This
32 practice may not always be feasible nor necessary for an SBP. The acceptability of an RBP
33 sourced from another jurisdiction with similar scientific and regulatory standards is, however,
34 in the responsibility of the NRA.

35 The posology and route of administration of the SBP should be the same as that of the RBP.
36 However, depending on the jurisdiction, the strength, pharmaceutical form, formulation,
37 excipients and presentation of the SBP might differ from the RBP, if justified.

38 Since the choice of RBP is essential for the development of an SBP, the following should be
39 considered.

- 1 • The RBP should have been licensed on the basis of a full set of quality, non-clinical,
2 safety, and efficacy data. An SBP should therefore not be accepted as an RBP.
- 3 • The RBP should have been marketed for a suitable duration and have a volume of
4 marketed use that is considered sufficient by the respective NRA to support its safe and
5 effective use.
- 6 • Only one RBP should be chosen for a specific SBP for licensing purposes. The
7 analytical/functional comparison is the mainstay of the comparability exercise and
8 should be performed with this RBP.
- 9 • Where an RBP marketed in another jurisdiction (non-local) is allowed by the NRA, the
10 following should be considered.
 - 11 • The RBP should be licensed and widely marketed in a jurisdiction that has a well-
12 established regulatory framework, as well as considerable experience with the
13 evaluation of biological products and post-marketing surveillance activities.
 - 14 • If the use of a non-local RBP containing the same active substance in clinical
15 studies requires bridging between the local and non-local RBP, suitable analytical
16 and functional bridging data should be provided to demonstrate the
17 representativeness of the non-local RBP for the local RBP. Additional PK bridging
18 studies may be required, e.g. if the two RBPs have different formulations that may
19 affect PK. Stringent similarity assessment should be applied for the analytical and
20 functional bridging studies (following the principles provided in section 8.3.1).
- 21 • It is important to note that the acceptance of an RBP for the evaluation of an SBP in a
22 particular country does not imply that the NRA of that country has approved the RBP
23 for use on the domestic market.

24 8. Quality

25 The comparison showing molecular similarity between the SBP and the RBP provides the
26 essential rationale for predicting that the clinical safety and efficacy profile of the RBP apply
27 to the SBP. Therefore, a high degree of analytical and functional similarity between the SBP
28 and the RBP is the basis for developing an SBP.

29 Development of an SBP involves thorough characterization of multiple RBP batches in order
30 to obtain understanding of the overall quality profile as well as the range of variability of the
31 RBP batches on the market. Based on the knowledge gained from the RBP characterisation
32 studies, as well as available in-house and public information, the manufacturing process of the
33 SBP is developed to produce a product that is highly similar to the RBP in all clinically relevant
34 quality attributes, i.e. attributes that may impact clinical performance.

35 The SBP documentation should comply with the standards required by NRAs for originator
36 products. A full quality dossier for both drug substance and drug product is always required.
37 (see relevant guidelines, such as those issued by the International Conference on
38 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
39 (ICH) and the WHO *Guidelines on the quality, safety, and efficacy of biotherapeutic protein
40 products prepared by recombinant DNA technology* (7) and *Guidelines on evaluation of*

1 *monoclonal antibodies as similar biotherapeutic products* (8). As an additional element, the
2 manufacturer of the SBP should carry out a comprehensive and comparative physicochemical
3 and biological characterization of the SBP and the RBP and document the results in the
4 submitted dossier.

5 **8.1 International standards**

6 WHO provides International Standards (ISs) and Reference Reagents, which serve as reference
7 sources of defined biological activity expressed in an international unit (IU) or unit (U). They
8 are intended for calibration of bioassays and are available for a wide range of substances such
9 as hormones (e.g. EPO, FSH) and cytokines (e.g. G-CSF) as well as modified/long-acting
10 proteins (e.g. pegylated G-CSF, darbepoetin, etanercept) and monoclonal antibodies (mAbs).
11 For the latter product class, ISs are expanding and currently include adalimumab, rituximab,
12 bevacizumab, infliximab, rituximab and trastuzumab
13 (http://www.who.int/biologicals/reference_preparations/en/). They are produced to defined
14 criteria as per WHO recommendations (9) which optimize retention of biological activity and
15 other important characteristics as well as ensuring stability, where appropriate. These standards
16 are used to calibrate bioassays either directly or to calibrate secondary (national,
17 pharmacopoeial, manufacturer) standards and support assay performance throughout the life-
18 cycle of a product. The use of a single primary standard worldwide facilitates the comparability
19 of assay results. WHO International Standards/Reference Reagents are not clinical products
20 (even though the active substance in them may be derived from material that was produced at
21 clinical grade) and are distinctly different from the RBP (e.g. protein content, formulation etc).
22 Therefore, they are not intended for use as comparators for SBP development and should not
23 be used for such purposes (10, 11).

24 **8.2 Manufacturing process**

25 The manufacturing process of the SBP should be developed based on comprehensive
26 understanding of the RBP gained through detailed characterisation studies of a sufficient
27 number of RBP batches.

28 It is understood that a manufacturer developing an SBP will normally not have access to
29 confidential details of the RBP manufacturing process; thus, the process will differ from the
30 licensed process for the RBP. In order to achieve a high-quality product that is as similar as
31 possible to the RBP, the SBP manufacturer should assemble all available knowledge of the
32 RBP regarding the type of host cell, the formulation and the container closure system used for
33 marketing the RBP. In order to decrease the potential for critical changes in quality attributes,
34 it can be recommended that the SBP is expressed and produced in a similar host cell type as
35 the RBP (e.g. *Escherichia coli*, Chinese hamster ovary cells, etc.). This will minimize the
36 potential for critical changes in quality attributes of the protein as well as in the process-related
37 impurity profile that could potentially affect the clinical outcomes and immunogenicity. If a
38 different host cell is used, for example in order to avoid unwanted and potentially immunogenic
39 glycan structures present in the RBP, the changes introduced into the product-related variants
40 and the impurity profile need to be carefully considered.

1 The manufacturing process can considerably affect the structure and impact the potency of the
2 product. For example, in the case of mAbs, manufacturers should be guided by the potential
3 enzymatic and nonenzymatic modifications to mAbs including the common ones such as
4 incomplete disulfide bond formation, glycosylation, N-terminal pyroglutamine cyclization, C-
5 terminal lysine processing, deamidation, isomerization, and oxidation, and the less common
6 ones such as modification of the N-terminal amino acids by maleuric acid and amidation of
7 the C-terminal amino acid in deciding the expression system to employ.

8 The manufacturer must demonstrate the consistency and robustness of the manufacturing
9 process by implementing state of art quality control and assurance procedures, in-process
10 controls, and process validation. The manufacturing process should meet the same standards
11 as required for originator products, including manufacture under current good manufacture
12 practices (12, 13).

13 As for any biological product, if process changes are introduced during the development of an
14 SBP, the impact of the changes should be assessed through a comparability exercise (14, 15).
15 Although many of the same principles are followed, the assessment of manufacturing process
16 changes should be addressed separately from the comparability exercise performed to
17 demonstrate biosimilarity versus the RBP (see section 8.4). It is, however, strongly
18 recommended that the pivotal data to demonstrate biosimilarity is generated using SBP
19 batch(es) manufactured with the commercial manufacturing process and therefore representing
20 the quality profile of the batches to be commercialised.

21 **8.3 Analytical considerations**

22 Thorough characterization of both the RBP and the SBP should be carried out using state-of-
23 the-art chemical, biochemical, biophysical and biological analytical techniques. The methods
24 should be scientifically sound, and demonstrated to be of appropriate sensitivity and specificity
25 to fit their intended use.

26 Details should be provided on primary and higher-order structure, post-translational
27 modifications (including, but not limited to, glycoforms), biological activity, purity, impurities,
28 product-related (active) substances (variants), and immunochemical properties, where relevant.
29 Orthogonal methods should be used, as far as possible, i.e. variants and quality attributes of
30 the product should be analysed using analytical methods with different underlying chemical,
31 physical and biological properties. For example, polyacrylamide gel electrophoresis (PAGE),
32 ion exchange chromatography, isoelectric focusing, and capillary electrophoresis all separate
33 proteins based upon charge, but they do so under different conditions and on the basis of
34 different physicochemical properties. As a result, one method may detect variants that another
35 method does not. The goal of the comparability investigation is to be as comprehensive as
36 possible in order to minimize the possibility of undetected differences between the RBP and
37 the SBP that may affect safety and clinical activity. The analytical limitations of each technique
38 (e.g. limits of sensitivity or resolving power) should be considered when determining the
39 similarity between an SBP and an RBP.

1 Representative raw data should be provided for all analytical methods (e.g. high-quality
2 reproductions of gels and chromatograms) in addition to tabular data summarizing the
3 complete data set and showing the results of all release and characterization analyses carried
4 out on the SBP and the RBP.

5 The measurement of quality attributes in characterization studies (as opposed to batch release
6 tests) does not necessarily require the use of validated assays, but the assays should be
7 scientifically sound and qualified; that is, they should provide results that are meaningful and
8 reliable. The methods used to measure quality attributes for batch release should be validated
9 in accordance with relevant guidelines, as appropriate. A complete description of the analytical
10 techniques employed for release and characterization of the product, along with method
11 validation or qualification data (as appropriate) should be provided in the licence application.
12 The discussion outlined in the following sections should be considered when conducting the
13 comparability exercise.

14 Due to the unavailability of drug substance for the RBP, the SBP manufacturer will usually be
15 using a commercial drug product for the similarity exercise. The commercial drug product will,
16 by definition, be in the final dosage form, containing the active substance(s) formulated with
17 excipients. It should be verified that these excipients do not interfere with analytical methods
18 and thus have no impact on test results. If the active substance in the RBP needs to be purified
19 from a formulated reference drug product in order to be suitable for characterization, studies
20 must be carried out to demonstrate that product heterogeneity and relevant attributes of the
21 active moiety are not affected by the isolation process. The approach used for isolating the
22 active substance of the RBP and comparing it with the SBP should be justified and
23 demonstrated, with data, to be appropriate for the intended purpose.

24 **8.3.1 *Physicochemical properties***

25 The physicochemical characterization should include determination of primary and higher-
26 order structure (secondary/tertiary/quaternary) and product variants using appropriate
27 analytical methods (e.g. mass spectrometry, circular dichroism, spectroscopy etc.) and other
28 biophysical properties.

29 The amino acid sequence of an SBP should be confirmed to be the same as that of its RBP.
30 The manufacturer is, however, recommended to pay special attention to any sequence variants
31 present in the SBP. Although identical primary sequence between the SBP and the RBP is
32 expected, low level sequence variants may occur and should be identified if present. The
33 presence of such variants could be acceptable if properly described and controlled to a
34 reasonable level. An assessment of the potential clinical impact of the variants needs to be
35 considered.

36 An inherent degree of structural heterogeneity occurs in proteins as a result of the biosynthesis
37 process. These include; C-terminal processing, N-terminal pyroglutamation, deamidation,
38 oxidation, isomerisation, fragmentation, disulfide bond mismatch, and free sulphhydryl groups,
39 N-linked and O-linked oligosaccharide, glycation, and aggregation. The structural
40 heterogeneity present should be evaluated in the SBP relative to the RBP. Experimentally
41 determined disulfide bonding patterns, particularly in the case of mAbs, should be compared
42 to the predicted structure based on the class and subclass of the molecule.

1 **8.3.2 Biological activity**

2 Biological activity is the specific ability or capacity of the product to achieve a defined
3 biological effect. It serves multiple purposes in the assessment of product quality and is
4 required for characterization (see also section 9) and for batch analysis. Ideally, the biological
5 assay will reflect the understood mechanism of action of the active substance of the RBP and
6 will thus serve as a link to clinical activity. A biological assay is a quality measure of the
7 “function” of the drug substance and can be used to determine whether a product variant has
8 the appropriate level of activity (i.e. a product-related substance) or is inactive (and is therefore
9 defined as an impurity). The biological assay also complements the physicochemical analyses
10 by confirming the correct higher-order structure of the molecule. Thus, the use of relevant
11 biological assay(s) with appropriate precision, accuracy and sensitivity provides an important
12 means of confirming that there is no significant functional difference between the SBP and the
13 RBP.

14 For a product with multiple biological activities, manufacturers should perform, as part of
15 product characterization, a set of relevant functional assays designed to evaluate the range of
16 activities of the product. For example, certain proteins possess multiple functional domains
17 that express enzymatic and receptor-binding activities. In such situations, manufacturers
18 should evaluate and compare all relevant functional activities of the SBP and the RBP.

19 Potency is the measure of the biological activity, and the results of the potency assay should
20 be provided and expressed in units quantitatively calibrated against an international or national
21 standard or reference reagent, where available and appropriate. International or national
22 standards and Reference Reagents should therefore be used to determine the potency and to
23 express results in IU or U, where appropriate (see section 8.1).

24 Functional assays used may or may not be fully validated, but they must be scientifically sound
25 and provide consistent and reliable results. The available information about these assays,
26 including sensitivity, specificity, robustness, and extent of validation, should be confirmed
27 before they are applied to test and establish the biosimilarity between the SBP and the RBP. It
28 should be noted that many biological assays may have relatively higher variability that might
29 preclude detection of small but significant differences between the SBP and the RBP.
30 Therefore, it is encouraged to develop assays that are less variable and are sensitive to changes
31 in the intended biological activities of the product to be measured. These assays can include,
32 in addition to cell based assays, also target binding assays that usually are less variable.
33 Adopting automated lab equipment that can help minimize manual operations, applying good
34 analytical practices and appropriate control samples, and the use of critical reagents that are
35 calibrated against WHO or national reference standards where available (e.g. TNF- α for
36 neutralization assays for anti-TNF products), may all help in reducing the variability of
37 biological assays.

38 When immunochemical properties are part of the activity attributed to the product (e.g.
39 antibodies or antibody-based products), analytical tests should be performed to characterize
40 these properties and used in the comparative studies. For mAbs, the specificity, affinity and
41 binding kinetics of the product to relevant Fc receptors (e.g. FcRn, C1q and Fc γ R_s) should be
42 compared by suitable methods such as surface plasmon resonance and biolayer interferometry.

1 In addition, appropriate assays should also be employed to provide information on relevant Fc-
2 mediated functions (e.g. ADCC, ADCP, CDC).

3 The relationship across the observed effector functions, the Fc receptor or complement binding
4 activities, and the potential physicochemical characteristics (e.g. glycosylation and post-
5 translational modifications) should be considered, and whenever possible established. Such
6 analyses will facilitate the interpretation of subtle differences between the SBP and the RBP
7 and the prediction of their clinical impact.

8 **8.3.3 Purity and Impurities**

9 Process- and product-related impurities should be identified and quantified by orthogonal and
10 state-of-the-art technologies.

11 Product-related substances and impurities, such as those originating from protein degradation
12 (e.g. oxidation, deamidation, aggregation) and potential post-translational modification of the
13 protein, should be compared between the SBP and RBP. If a comparison reveals differences
14 in product-related substances and impurities of SBP and RBP, the impact of the differences
15 on the clinical performance of the drug product, including its biological activity, should be
16 evaluated. To obtain sufficient information of the product-related substances and impurities,
17 it is recommended that comparative stability studies under accelerated and/or stress conditions
18 are conducted (See section 8.6).

19 Process-related impurities such as host cell proteins, host cell DNA, cell culture residues,
20 downstream processing residues may be quantitatively and/or qualitatively different between
21 SBP and RBP because the drug products are produced by different manufacturing processes.
22 Nevertheless, process-related impurities should be kept at a minimum level by using state-of-
23 the-art manufacturing technologies. The risk related to any newly identified impurities
24 contained in the SBP should be evaluated.

25 **8.3.4 Quantity**

26 In general, an SBP should have the same concentration or strength of the active substance as
27 the RBP. Depending on the jurisdiction, deviation from the RBP might be possible if justified,
28 but the posology and route of administration of the SBP should be the same as those of the
29 RBP. The quantity of the SBP should be expressed using the same measurement system as the
30 RBP (that is, mass units or units of activity). A description with appropriate justification should
31 also be included to describe how quantity was calculated (e.g. the selection of extinction
32 coefficient).

33 **8.4 Comparative analytical assessment**

34 **8.4.1 Considerations for the RBP and the SBP**

35 The number of RBP batches needed for the comparative analytical assessment will depend on
36 the criticality of the quality attribute under investigation, the statistical approach applied, as
37 well as on the batch-to-batch variability present. In general, the manufacturer of the SBP
38 should aim at including at least 10 batches of the RBP into the comparability assessment. These

1 batches should also include the RBP batches used in the clinical studies. Under certain
2 conditions, for example for products indicated for rare diseases, fewer batches may be
3 considered, if justified. Where statistical approaches are used, the number of RBP batches
4 analyzed should be justified in terms of the risk of a false positive conclusion. In general,
5 sampling a higher number of RBP batches will provide a better estimate of the true batch-to-
6 batch variability of the RBP and will allow for a more robust statistical comparison.

7 Random sampling of the RBP batches is desirable, but considering the availability of RBP
8 batches, this may be difficult to achieve in practice. The RBP batches should be stored under
9 the recommended conditions and tested within their approved shelf life. Any exception from
10 this would have to be fully substantiated with experimental data. The shelf life of the RBP at
11 time of characterization should be considered. It is expected that RBP batches of different ages
12 will be included in the similarity assessment.

13 The SBP batches included in the comparability assessment should be manufactured using the
14 intended commercial manufacturing process and should preferably originate from different
15 drug substance batches. Generally, each value for an attribute being assessed for an SBP should
16 be contributed by an independent batch. For example, a single drug product batch produced
17 from a single drug substance batch would be considered an independent batch while different
18 drug product batches produced from the same drug substance batch may not necessarily be
19 considered independent. In addition, small or pilot scale batches can be included if
20 comparability between the small and commercial scale batches has been properly demonstrated.
21 Usually all commercial scale batches produced, including process validation batches (PPQ
22 batches) and batches applied in the clinical trial(s) should be included in the similarity
23 assessment. As for the RBP, the exact number of SBP batches depends on several factors, such
24 as the criticality of the quality attribute under investigation and the approach applied for
25 similarity evaluation. In general, the risk for a false positive conclusion on similarity will
26 decrease with increasing number of batches. A robust manufacturing control system and
27 demonstrated batch-to-batch consistency of the SBP (section 8.2) is a prerequisite for a
28 successful similarity assessment.

29 **8.4.2 Considerations for similarity assessment**

30 Prior to initiating the comparability exercise, it is recommended that the quality attributes of
31 the RBP are identified and ranked according to their impact on the clinical performance of the
32 product. For this purpose, a risk ranking tool could be developed. Such risk ranking tools
33 should consider the impact of the quality attribute on safety, efficacy, pharmacokinetics, and
34 immunogenicity. Furthermore, the degree of uncertainty should be taken into consideration. In
35 case the clinical relevance of a certain quality attribute is unknown (i.e. the uncertainty is high)
36 or if it is known that a quality attribute will impact the clinical performance (i.e. the uncertainty
37 is low but the impact high), the overall risk score should be high. Further guidance on the use
38 of risk ranking tools can be found in national and international guidelines (16).

39 The result of the risk ranking could be used to guide the data analyses and the overall
40 assessment of similarity. The most frequently used approach for similarity assessment relies

1 on demonstrating that the quality attributes of the SBP batches lay within the predetermined
2 similarity ranges established based on characterization data from multiple batches of the RBP.
3 Also other approaches, such as equivalence testing of means, can be used for similarity
4 assessment. Each statistical approach has, however, specific strengths and weaknesses which
5 should be discussed in the submission.

6 As the allowable differences in quality attributes between the SBP and the RBP most often are
7 difficult to establish based on clinical considerations alone, batch-to-batch variability of the
8 RBP is typically used for informing on acceptable differences in quality attributes. The
9 established similarity range should therefore tightly reflect the quality profile of the marketed
10 RBP batches. The ranges should normally not be wider than the batch-to-batch variability
11 present in the RBP, unless it can a priori be determined which difference would be acceptable
12 (e.g. less impurities is usually acceptable).

13 Statistical intervals for the establishment of similarity ranges

14 Different statistical intervals can be used to establish comparability ranges. Commonly used
15 approaches include the min-max range, tolerance intervals, and mean \pm xSD, these are
16 discussed further below.

17 A conservative approach would be to establish the similarity ranges directly based on the min-
18 max quality attribute data from the characterization studies of RBP batches. Such similarity
19 ranges could be viewed as clinically qualified (since the RBP batches are on the market and
20 taken by patients). However, the min-max approach suffers from the limitation that the
21 likelihood of claiming biosimilarity increases with decreasing number of SBP batches.
22 Consequently, a small sample size may result in a failure to detect differences between the
23 SBP and the RBP and therefore an increase in the rate of false positive conclusions.

24 Likewise, similarity ranges based on tolerance intervals (TI) would usually require a rather
25 high number of RBP batches for establishing meaningful ranges. With a limited number of
26 RBP batches characterized, the TI approach can result in an estimated range that is much wider
27 than the actual quality attribute ranges (i.e. the min-max range in the RBP). The risk for a false
28 positive conclusion on similarity may therefore also be unreasonably high when the similarity
29 ranges are based on TI intervals.

30 A commonly applied approach for establishing similarity ranges is the x-sigma interval, i.e.
31 mean \pm x*SD of the RBP batch data. The multiplier (X) used should be scientifically justified
32 and could be linked to the criticality of the quality attribute tested. While a smaller multiplier
33 would be used for high criticality attributes, low criticality attributes could be associated with
34 a higher multiplier.

35 Analytical similarity evaluation

36 The established similarity ranges should be accompanied by predefined similarity criteria. For
37 the similarity range approach, the most frequently applied similarity criteria require that a

1 certain percentage of the SBP batches (usually between 90% and 100%) fall within the
2 similarity range.

3 It is up to the manufacturer to justify the relevance of the established similarity ranges in
4 combination with the chosen similarity criteria. Ideally, the data analyses should be robust and
5 should minimize the risk of a false positive conclusion. In some jurisdictions, the use of
6 stringent comparability ranges and similarity criteria could also allow for a discussion with the
7 NRA on further tailoring of the clinical comparability program. Although decreasing the risk
8 for a false positive conclusion is, from a patient and regulatory point of view, of primary
9 importance, the risk of a false negative conclusion also needs to be managed by the
10 manufacturer and should be thoroughly considered during the planning of the data analyses.

11 Some minor differences between the RBP and the SBP are expected. Nevertheless, any quality
12 attributes not fulfilling the established similarity criteria should be considered as a potential
13 signal for non-similarity and should be assessed for an impact on clinical safety and efficacy.
14 However, the overall evaluation of analytical similarity should be based on the totality of data
15 available. A result, which does not meet the similarity criterion, does not preclude a conclusion
16 of similarity, but will usually require further justifications and/or further analytical assessments.
17 Confirmed differences in low criticality quality attributes also need to be adequately
18 considered, but for such differences, reference to available information, which could originate
19 for example from scientific publications is usually sufficient. Lower impurity levels in the SBP
20 (e.g. aggregates) or differences in quality attributes present at very low levels in both the RBP
21 and the SBP would in most cases be predicted to have no clinical relevance, and could therefore
22 be accepted without further assessments. For differences in quality attributes with higher
23 criticality, functional assays to thoroughly address the possible clinical impact of the detected
24 differences are generally expected. Where there are confirmed differences in the most critical
25 quality attributes, it will be more challenging to justify that the product is a true SBP. For
26 example, if differences are found in quality attributes that alter the pharmacokinetics of the
27 product and thereby change the dosing scheme, this product cannot be considered an SBP.

28 **8.5 Specifications**

29 Specifications are employed to verify the routine quality of the drug substance and drug
30 product rather than to fully characterize them. Specifications for an SBP, as for any biological
31 product, should be set as described in established guidelines. Furthermore, an SBP should show
32 the same level of compliance with a pharmacopoeial monograph as required for the RBP. It
33 should be noted that pharmacopoeial monographs may provide only a minimum set of
34 requirements for a particular product, and additional test parameters may be required.
35 Reference to analytical methods used and acceptance limits for each test parameter of the SBP
36 should be provided and justified. All analytical methods referenced in the specification should
37 be validated; the corresponding validation should be documented.

38 Specifications for an SBP may not be the same as for the RBP since the manufacturing
39 processes will be different and different analytical procedures and laboratories will be used for
40 the assays. Nonetheless, the specifications should capture and control important known product
41 quality attributes of the RBP. The setting of specifications should be based upon the

1 manufacturer's experience with the SBP (e.g. manufacturing history; assay capability; quality
2 profile of SBP batches used in comparative clinical trials), the experimental results obtained
3 by testing and comparing the SBP and RBP, and on attributes with potential impact on product
4 performance.

5 8.6 Stability

6 Stability studies should comply with relevant guidance as recommended by the NRA.
7 Generally, stability studies should be summarized in an appropriate format, such as tables, and
8 they should include results from accelerated degradation studies and studies under various
9 stress conditions (e.g. temperature, light, humidity and mechanical agitation). There are
10 multiple specific purposes for performing stability studies.

11 First, the stability data should support the conclusions regarding the recommended storage and
12 shipping conditions and the shelf-life/storage period for the drug substance, drug product, and
13 process intermediates that may be stored for significant periods of time. Real-time/real-
14 temperature stability studies will determine the storage conditions and shelf life for the SBP,
15 which may or may not be the same as for the RBP. Results from forced degradation, accelerated,
16 and stress conditions may also show that additional controls should be used in the
17 manufacturing process and during shipping and storage in order to ensure the integrity of the
18 product.

19 Secondly, stability studies should be carried out to show which release and characterization
20 methods are stability-indicating for the product.

21 Thirdly, comparative stability studies conducted under accelerated, and in some cases, stress
22 and forced degradation conditions (e.g. freeze-thaw, light exposure, and agitation) can be
23 valuable in determining the similarity of the products by showing a comparable degradation
24 profile and rate, with consideration for formulation, volume, concentration and container
25 differences.

26 Stability studies on drug substance should be carried out using containers and conditions that
27 are representative of the actual storage containers and conditions. Stability studies on drug
28 product should be carried out in the intended drug product container-closure system.

29 9. Nonclinical evaluation

30 The nonclinical part of the Guidelines addresses the pharmaco-toxicological assessment of the
31 SBP.

32 It is important to note that, to design an appropriate non-clinical study programme, a clear
33 understanding of the reference product characteristics is required.

34 The nature and complexity of the RBP have an impact on the extent of the nonclinical studies
35 to confirm biosimilarity. Any differences observed in the physico-chemical and biological
36 analyses will guide the planning of the nonclinical studies. Other factors that need to be taken
37 into consideration are the mode(s) of action of the active substance (e.g. receptor(s) involved)
38 in all the authorized indications of the RBP and pathogenic mechanisms involved in the
39 disorders included in the therapeutic indications.

1 As regards nonclinical development, a stepwise approach should be applied to evaluate the
2 similarity of the SBP and the chosen RBP. *In vitro* studies should be conducted first and a
3 decision then made whether additional *in vivo* animal studies will be required

4 The following approach may be considered and should be tailored on a case-by-case basis to
5 the SBP concerned. The approach should be scientifically justified in the application dossier.

6 **9.1 *In vitro* studies**

7 In order to assess any relevant difference in pharmaco-toxicological activity between SBP and
8 chosen RBP, data from a number of comparative *in vitro* studies, some of which may already
9 be available from quality-related assays (see section 8.3.2), should be provided. In
10 consideration of this overlap, it is suggested to address the *in vitro* nonclinical studies alongside
11 of the related quality data in the quality module of the dossier.

12 Since experience has shown that *in vitro* assays are in general more specific and sensitive to
13 detect differences between SBP and RBP than *in vivo* studies in animals, these assays are
14 paramount for the nonclinical biosimilar comparability exercise.

15 For the *in vitro* studies, the following general principles apply:

- 16 – Usually, a battery of receptor-binding studies and of cell-based assays should be
17 performed in order to assess if any (clinically) relevant differences in reactivity
18 between SBP and RBP are present and, if so, to determine the likely causative factor(s).
- 19 – Together, these assays should cover the whole spectrum of pharmaco-toxicological
20 aspects with potential clinical relevance for the RBP and for the product class. The
21 manufacturer should discuss to what degree the *in vitro* assays used can be considered
22 representative/predictive of the clinical situation according to current scientific
23 knowledge.
- 24 – The studies should be comparative and designed to be sufficiently sensitive, specific
25 and discriminatory to allow to detect (clinically) relevant differences in pharmaco-
26 toxicological activity between SBP and RBP or, vice versa, provide evidence that any
27 differences observed in quality attributes are clinically not relevant.
- 28 – The studies should compare the concentration–activity/binding relationship of the
29 SBP and the RBP at the pharmacological target(s), covering a concentration range
30 where potential differences are most sensitively detected.
- 31 – A sufficient number of RBP batches and SBP batches, preferably representative of
32 the material intended for commercial use, should be evaluated. Assay and batch-to-
33 batch variability will affect the number needed. The number tested should be
34 sufficient to draw meaningful conclusions on the variability of a given parameter for
35 both the SBP and the RBP and on the similarity of both products (see also section
36 8.4.1).
- 37 – Where available, international reference standards can be used to support assay
38 characterization, calibration and performance (see also section 8.1)

1 The nonclinical *in vitro* program for SBPs should usually include relevant assays for the
2 following topics:

3 – Binding studies:

4 Evaluation of the binding of the SBP to cell membrane receptors or to other
5 membrane bound or soluble targets that are known/assumed to be involved in the
6 pharmaco-toxicological effects of the RBP in the clinically approved indications (e.g.
7 for IgG-based mAbs Fab-associated binding to the antigen and Fc-associated binding
8 to representative isoforms of the relevant Fc receptors and to complement C1q (see
9 also ref 8).

10 – Functional studies/determination of biological activities:

11 Studies should evaluate signal transduction and/or functional activity/viability of cells
12 or isolated tissues known to be of relevance for the pharmaco-toxicological effects of
13 the RBP. Together these assays should broadly cover all known modes of action of
14 the RBP in the clinically authorized indications (e.g. for IgG-based mAbs directed
15 against membrane-bound antigens evaluation of Fab-associated functions and of Fc-
16 associated functions like ADCC, ADCP and CDC, see ref 8).

17 Such assays are often technically demanding and the models chosen should be appropriately
18 justified by the manufacturer.

19 For additional guidance on these topics, see also section 8.3.

20 **9.2 Determination of the need for *in vivo* animal studies**

21 On basis of the totality of quality and nonclinical *in vitro* data available and the extent to
22 which there is residual uncertainty about the similarity of SBP and RBP, it is under
23 consideration of the NRAs to ask for additional *in vivo* animal studies.

24 The decision of the involved NRA to waive or not to waive the request for nonclinical *in vivo*
25 studies should take into account the following aspects:

- 26 – If the quality biosimilar comparability exercise and the nonclinical *in vitro* studies are
27 considered satisfactory and no issues are identified which would block a direct start
28 of clinical evaluations, an additional *in vivo* animal study is not considered necessary.
- 29 – If a need is identified to reduce remaining uncertainties concerning the similarity of
30 SBP and RBP before the initiation of clinical evaluations, additional *in vivo* animal
31 studies may be considered, however only: (i) when it is expected that such studies
32 would provide relevant additional information; and (ii) if the needed additional
33 information can **not** be obtained by an alternative approach, not involving *in vivo*
34 animal studies.

35 In this respect, factors to be considered could include for example:

- 36 – qualitative and/or quantitative differences in potentially relevant quality attributes
37 between SBP and RBP (e.g. qualitative and/or quantitative differences in post-
38 translational glycosylation of proteins)

1 – relevant differences in formulation (e.g. use of excipients in the SBP not widely
2 used in medicinal products).

3 On basis of the regulatory experience gained with marketing authorization
4 applications for SBPs so far, the need for additional *in vivo* animal studies is expected
5 to represent a rare scenario.

- 6 – If the quality and nonclinical *in vitro* comparability exercise indicates relevant
7 differences between the SBP and the RBP, making it unlikely that biosimilarity will
8 eventually be established, a stand-alone development to support a full marketing
9 authorization application should be considered instead (see section 6).

10 **9.3 *In vivo* studies**

11 **9.3.1 General aspects to be considered**

12 In the exceptional case that an *in vivo* evaluation is deemed necessary by the involved NRA,
13 the focus of the study/studies (PK and/or PD and/or safety) depends on the type of additional
14 information needed.

15 Animal studies should be designed to maximize the information obtained. The 3R principles
16 (replacement, reduction, and refinement of animal experiments) should always be obeyed.

17 To address the residual uncertainties, the use of conventional animal species and/or of
18 specific animal models (e.g. transgenic animals, transplant models) may be considered.

19 Animal models are often not sensitive enough to detect small differences. If a relevant *in vivo*
20 animal model cannot be identified, the manufacturer may choose to directly proceed to
21 clinical studies by taking into account strict principles to mitigate any potential risk.

22 Effects of RBPs are often species-specific. In accordance with ICH S6(R1) (17) and WHO's
23 *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by*
24 *recombinant DNA technology* (7), *in vivo* studies should be performed only in relevant species,
25 i.e. species which are pharmacologically and/or toxicologically responsive to the RBP.

26 The duration of the study/studies should be justified, taking into consideration the PK behavior
27 of the RBP, the time to onset of formation of anti-drug antibodies (ADAs) in the test species
28 and the clinical use of the RBP.

29 **9.3.2 Specific aspects**

30 *9.3.2.1 PK and/or PD studies*

31 In case such studies are considered necessary, the PK and/or PD of the SBP and the RBP
32 should be compared quantitatively, when the model allows by a dose-response assessment
33 that includes the intended exposure in humans.

34 The studies may include animal models of disease to evaluate functional effects on disease-
35 related PD markers or efficacy measures.

36 *9.3.2.2 Safety studies*

1 In case *in vivo* safety studies are deemed necessary, a flexible approach should be considered.
2 If appropriately justified, a repeated dose toxicity study with refined design (e.g. using just one
3 dose level of SBP and RBP, and/or just one gender and/or no recovery animals, and/or only
4 in-life safety evaluations such as clinical signs, body weight and vital functions) may be
5 considered. Depending on the chosen endpoints, it may not be necessary to sacrifice the
6 animals at the end of the study.

7 Repeated dose toxicity studies in non-human primates are not recommended as well as toxicity
8 studies in non-relevant species (e.g. to assess unspecific toxicity due to impurities).

9 9.3.2.3 Immunogenicity studies

10 Qualitative or quantitative difference(s) in product-related variants (e.g. glycosylation
11 patterns, charge variants, aggregates, impurities such as host-cell proteins) may have an
12 effect on the immunogenic potential and the potential to cause hypersensitivity. These effects
13 are usually difficult to predict from animal studies and should be better assessed in clinical
14 studies.

15 However, determination of (neutralizing) antibody formation against the study drugs may be
16 required for interpretation of pharmacokinetic (PK)/toxicokinetic (TK) data in case *in vivo*
17 animal studies are needed.

18 9.3.2.4 Local tolerance studies

19 Studies on local tolerance are usually not required. However, if excipients are introduced for
20 which there is little or no experience with the intended clinical route of application, local
21 tolerance may need to be evaluated. If other *in vivo* animal studies are conducted, the
22 evaluation of local tolerance may be integrated in the design of those studies.

23 9.3.2.5 Other studies

24 In general, safety pharmacology and reproductive and development toxicity studies are not
25 warranted for nonclinical testing of SBPs.

26 In accordance with ICH S6 (R1) (17) and WHO's "*Guidelines on the quality, safety and*
27 *efficacy of biotherapeutic protein products prepared by recombinant DNA technology*" (7),
28 genotoxicity and carcinogenicity studies are not required for SBPs.

29 10. Clinical evaluation

30 The main clinical data should be generated using the SBP product derived from the final
31 manufacturing process, which reflects the product for which marketing authorization is sought.
32 Any deviation from this recommendation needs to be justified and additional data may be
33 required. For changes in the manufacturing process, relevant guidelines should be followed
34 (14, 15). Similarly, a single RBP should be used as the comparator throughout the
35 comparability programme for quality, safety and efficacy studies during the development of
36 an SBP in order to allow the generation of coherent data and conclusions.

37 If certain clinical and *in vivo* non-clinical studies of the development programme are performed
38 with comparators licensed in different legislations, the manufacturer should provide adequate
39 data or information to scientifically justify the relevance of these comparative data and

1 establish an acceptable bridge from analytical studies (e.g. structural and functional data) that
2 compare all three products (the proposed SBP and the RBP from different legislations).

3 Clinical studies are valuable to confirm similarity. The goal is to document that there are no
4 clinically meaningful differences between the proposed SBP and the RBP.

5 Clinical studies should be designed to demonstrate comparable safety and efficacy of the SBP
6 and the RBP and therefore need to employ testing strategies that are sensitive enough to detect
7 any relevant differences between the products.

8 If relevant differences between the SBP and the RBP are detected at any stage of the
9 development, the reasons need to be explored and justified. If this is not possible, the new
10 product may not qualify as an SBP and a full licensing (standalone) application should be
11 considered.

12 A comparative bioequivalence study involving PK and/or PD comparability is required for
13 clinical evaluation. A comparative clinical phase 3 trial will not be necessary if sufficient
14 evidence of biosimilarity can be drawn from other parts of the comparability exercise. The type
15 and need for a phase 3 comparative clinical safety and efficacy trial for the proposed SBP will
16 be influenced by factors such as:

- 17 – Clinical history of RBP (including immunogenicity)
- 18 – how well it can be characterized;
- 19 – the availability of sufficient number of orthogonal assays to perform multiple adequate
20 analytical and functional tests;
- 21 – degree of analytical and functional similarity of the SBP to the RBP(s);
- 22 – the degree of understanding of the MOA(s) of the biological product in different
23 indications and how well these can be investigated in binding and functional in vitro
24 test.

25 Current examples (including but not limited to) for biological products that can be
26 comprehensively characterized and have a well-established mechanism of action would be
27 teriparatide, insulin, G-CSF and somatotropin.

28 With the advancement in the analytical sciences and clinical experiences also more complex
29 products as mAbs and mAb-like biologicals (fusion proteins) increasingly fall into this
30 category.

31 **10.1 Pharmacokinetic studies**

32 The clinical comparability exercise should always include a comparative PK study, if the active
33 substance can be measured in the blood, and should also include the measurement of PD
34 markers if available and also immunogenicity data

35 The PK study should be designed to demonstrate similar PK profiles of the SBP and the RBP.
36 The sample size should be appropriate taking into account PK variability in the study
37 population, and consideration should be given to whether a crossover or a parallel group design

1 is most adequate. If appropriate population PK or PK-PD models are available for the RBP in
2 the literature, modelling and simulation should be considered for optimising study design - for
3 example, selection of the most sensitive dose(s) and study population to detect potential PK
4 differences, and choice of sample size.

5 Pharmacokinetic studies should preferably be performed in healthy volunteers (if considered
6 ethical) and care should be taken to standardize the population with regard to factors that may
7 influence variability (e.g. ethnic origin, gender, weight). If the drug substance under
8 investigation is associated with risks or tolerability issues that are considered unacceptable for
9 healthy volunteers, it will be necessary to perform the PK studies in patients.

10 The preferred design is a randomised, two-period, two-sequence, single-dose, crossover
11 pharmacokinetic study using a dose within the therapeutic range at which the sensitivity to
12 detect differences is large enough to observe meaningful differences. The treatment periods
13 should be separated by a wash out phase that is sufficiently long to ensure that drug
14 concentrations are below the lower limit of bioanalytical quantification in all subjects at the
15 beginning of the second period, i.e. at least 5 times the terminal half-life.

16 When a crossover design is not suitable, e.g. for biologicals with a very long half-life, a
17 parallel-group study should be considered. The cross-over design eliminates inter-subject
18 variability and therefore, compared with the parallel design, reduces the sample size necessary
19 to show equivalent pharmacokinetic profiles of the SBP and RBP. In parallel group designs,
20 care should be taken to avoid imbalances between treatment groups that may affect the
21 pharmacokinetics of the drug substance under investigation (e.g. ethnic origin, body weight,
22 gender).

23 A multiple dose study in patients is acceptable as pivotal PK study if a single dose study cannot
24 be conducted in healthy volunteers due to risks or tolerability reasons, and a single dose study
25 is not feasible in patients. Multiple dose studies may also be acceptable in rare situations, where
26 problems with sensitivity of the analytical method preclude sufficiently precise plasma
27 concentration measurements after a single dose administration. However, given that a multiple
28 dose study is less sensitive in detecting differences in C_{max} than a single dose study, this will
29 only be acceptable with sound justification.

30 Pharmacokinetic comparison of the SBP and the RBP should not only include rate and extent
31 of absorption but also descriptive analysis of elimination characteristics, i.e. clearance and/or
32 elimination half-life, which could differ between the SBP and the RBP. Linear (nonspecific)
33 clearance and nonlinear (target-mediated) clearance should be evaluated by assessment of
34 partial areas under the curve (pAUCs).

35 Acceptance criteria for the demonstration of pharmacokinetic similarity between the SBP and
36 the RBP must be predefined and appropriately justified. It should be noted that the criteria used
37 in standard clinical pharmacokinetic comparability studies (bioequivalence studies) may not
38 necessarily be applicable for all biotherapeutic products. However, the traditional 80–125%
39 equivalence range will in most cases be sufficiently conservative to establish similar PK
40 profiles. Correction for protein content may be acceptable on a case-by-case basis if pre-
41 specified and adequately justified, with the results from the assay of the test and RBPs being
42 included in the protocol. If adjustments for covariates are intended for parallel group studies

1 (e.g. for adalimumab, stratification for body weight, gender), they should be predefined in the
2 statistical analysis plan rather than having post hoc analyses.

3 Other pharmacokinetic studies, such as interaction studies (with drugs likely to be used
4 concomitantly) or studies in special populations (e.g. children, the elderly and patients with
5 renal or hepatic insufficiency), are not required for an SBP.

6 Historically, limitations in the assay methodology for pharmacokinetic evaluation of peptide
7 or protein products have restricted the usefulness of such studies. There should consequently
8 be special emphasis on the analytical method selected and its ability to detect and follow the
9 time course of the protein (the parent molecule and/or degradation products) in a complex
10 biological matrix that contains many other proteins. The method should be optimized to
11 provide satisfactory specificity, sensitivity and a range of quantification with adequate
12 accuracy and precision.

13 In some cases, the presence of measurable concentrations of endogenous protein may
14 substantially affect the measurement of the concentration–time profile of the administered
15 exogenous protein. In such cases, the manufacturer should describe and justify the approach to
16 minimize the influence of the endogenous protein on the results (e.g. baseline correction).

17 In some instances it may not be possible to establish PK similarity due to the nature of the
18 substance (e.g. fractionated and unfractionated heparin cannot be measured in blood), the route
19 of administration (e.g. intra-ocular administration of aflibercept or ranibizumab), or an
20 unacceptably high PK variability (e.g. romiplostim). In such cases, clinical similarity should
21 be supported by PD, immunogenicity and/ or additional clinical parameters.

22 10.2 Pharmacodynamic studies

23 Pharmacodynamic parameters should preferably be investigated as part of the comparative PK
24 studies. In some instances, PK studies cannot reasonably be conducted in which case PD
25 markers may play a more important role. This is for example the case for heparins¹, where
26 serum concentrations cannot be measured and similarity needs to be established for the most
27 important PD endpoints anti-FXa and anti-FIIa activity.

28 Pharmacodynamic effects should be investigated in a suitable population using a dose or doses
29 within the steep part of the dose–response curve in order to maximize the chance of detecting
30 potential differences between the SBP and the RBP. Pharmacodynamic markers should be
31 selected on the basis of their clinical relevance.

32 10.3 Confirmatory pharmacokinetic and/or pharmacodynamic studies

33 In addition to analytical and functional similarity, comparative pharmacokinetic and/or
34 pharmacodynamic studies are appropriate to establish similar clinical performance of the SBP
35 and the RBP, provided that the mechanism of action of the RBP is well understood and at least
36 one PD marker is linked to efficacy (e.g. an accepted surrogate marker for efficacy).

¹ biologicals in most legislations except USA (ref, <https://doi.org/10.1016/j.biologicals.2020.02.005>)

1 Euglycaemic clamp studies would be an example for acceptable confirmatory
2 pharmacokinetic/pharmacodynamic studies for comparing the efficacy of two insulins. In
3 addition, absolute neutrophil count and CD34+ cell count are the relevant pharmacodynamic
4 markers for the activity of granulocyte colony stimulating factor (G-CSF) and could be used
5 in pharmacokinetic/pharmacodynamic studies in healthy volunteers to demonstrate the similar
6 efficacy of two G-CSF-containing medicinal products.

7 The study population and dosage should represent a test system that is known to be sensitive
8 to detect potential differences between the SBP and the RBP. In the case of insulin, for example,
9 the study population should consist of non-obese healthy volunteers or patients with type 1
10 diabetes rather than insulin-resistant obese patients with type 2 diabetes. Otherwise, it may be
11 necessary to investigate more than one dose to demonstrate that the test system is
12 discriminatory (18).

13 The acceptance ranges for confirmatory pharmacokinetic and/or pharmacodynamic parameters,
14 i.e. if they are primary endpoints, should be predefined and appropriately justified. If PD
15 comparison is not essential for a conclusion of biosimilarity but the results are still expected to
16 reasonably support biosimilarity, a purely descriptive analysis of the PD results may be
17 justified. This may be the case for biological substances that have been extensively
18 characterized and biosimilarity can already be concluded from the analytical, functional and
19 PK comparison. If appropriately designed and performed, such pharmacokinetic/
20 pharmacodynamic studies are usually more sensitive in detecting potential differences in
21 efficacy than trials using hard clinical endpoints.

22 However, PD markers may also be used as endpoints in clinical efficacy studies in patients.

23 Examples could be hemoglobin for measuring efficacy of an epoetin, or LDH, which is a
24 sensitive biochemical marker of intravascular haemolysis, for evaluating efficacy of a complex
25 drug such as eculizumab. For denosumab, investigation of bone formation and resorption
26 markers as part of the pharmacokinetic study may be useful or possibly sufficient. This model
27 can be used to simulate s-CTX time-concentration profiles after denosumab administration.

28 A stand-alone PK trial may suffice in certain cases to provide sufficient safety and
29 immunogenicity data in a scenario where no meaningful PD markers exist.

30 10.4 Efficacy studies

31 A comparative clinical phase 3 trial will not be necessary, if sufficient evidence of biosimilarity
32 can be drawn from other parts of the comparability exercise. A comparative clinical trial, if
33 necessary, should confirm that the clinical performance of the SBP and the RBP are
34 comparable. Demonstration of comparable potency, pharmacokinetic and/or
35 pharmacodynamic profiles provide the basis for use of the RBP posology in the comparative
36 clinical trial.

37 If a phase 3 comparative clinical trial of the SBP and the chosen RBP is deemed necessary,
38 then it is expected to be an adequately powered, randomized and controlled clinical trial. The
39 principles of such trials are laid down in relevant ICH guidelines (18-20). Clinical studies
40 should preferably be double-blind or at a minimum observer blind. In the absence of any
41 blinding, measures should be prospectively put in place to minimise bias.

1 In principle, equivalence designs (requiring lower and upper comparability margins) are
2 preferred for comparing the efficacy and safety of the SBP and the RBP. Non-inferiority
3 designs (requiring only one margin) (18) or trials with an asymmetrical margin may be
4 considered if appropriately justified (21).

5 Regardless of which design is selected in a particular case, the comparability margin(s) must
6 be pre-specified and justified on the basis of clinical relevance; that is, the selected margin
7 should represent the largest difference in efficacy that would not matter in clinical practice.
8 Treatment differences within this margin would thus, by definition, be acceptable because they
9 have no clinical relevance.

10 Similar efficacy implies that similar treatment effects can be achieved when using the same
11 posology; in the comparative trial(s), the same dosage(s) and treatment schedule of SBP and
12 RBP should be used.

13 Generally, equivalence trials are preferable to ensure that the SBP is not clinically less or more
14 effective than the RBP when used at the same dosage(s).

15 A non-inferiority design could be acceptable, if justified by the applicant, e.g.

- 16 – for biologicals with high efficacy (e.g. over 90%), making it difficult to set an upper
17 margin; or
- 18 – in the presence of a wide safety margin.

19 When using asymmetric margins, the narrower limit should rule out inferior efficacy and the
20 broader limit should rule out superior efficacy.

21 Whatever the predefined study design, the real results obtained from the comparative clinical
22 trial(s) along with comparative analytical, functional and PK data will determine whether the
23 SBP and the RBP can be considered to be clinically similar. If clinically relevant differences
24 are found, a root cause analysis should be performed. If a plausible cause that is unrelated to
25 the product (e.g. inadvertent baseline differences between treatment groups that could not be
26 prevented by randomisation) cannot be found, the new product should not be considered to be
27 similar to the RBP and should be developed as a stand-alone product.

28 Careful consideration should be given to the design of the comparative study(ies) including
29 the choice of primary efficacy endpoint(s). The study should be conducted using a clinically
30 relevant and sensitive endpoint within a homogenous population that responds well to the
31 pharmacological effects of the biological product of interest to show that there are no clinically
32 meaningful differences between the SBP and the RBP. Clinical outcomes, surrogate outcomes
33 or a combination of both can be used as primary end-points in biosimilar trials. The same study
34 end-points used to establish efficacy of the RBPs may be used because a large body of
35 historical data is generally available in the public domain for setting the comparability margin(s)
36 and calculating the sample size. However, the primary endpoint could be different from the
37 original study endpoint for the RBP if it is well justified and relevant data is available to support
38 the determination of the comparability margin(s). A relevant PD end-point can be used as the
39 primary end-point, e.g. when it is a known surrogate of efficacy or when it can be linked to the
40 mechanism of action of the product. The primary or secondary endpoints can be analyzed at
41 different time points compared to those used in clinical trials with the RBP, if these are known

1 to be on the steep part of the dose response curve and therefore are considered to be more
2 sensitive to capture the pharmacological action(s) of the biological product (e.g. adalimumab
3 efficacy could be measured by the American College of Rheumatology 20 (ACR 20) response
4 at week 12 or 16 in addition to week 24).

5 The sample size for and duration of the comparative clinical study should be adequate to allow
6 for the detection of clinically meaningful differences between the SBP and RBP. When a
7 comparative clinical trial is determined to be necessary, then adequate scientific justification
8 for the choice of study design, study population, study endpoint(s), estimated effect size for
9 the RBP, and comparability margin(s) should be provided and may be discussed with
10 regulators in order to obtain agreement at least in principle prior to trial initiation.

11 10.5 Safety

12 Pre-licensing comparative safety data should be obtained from a sufficient number of healthy
13 volunteers +/- or patients (22). Safety data should be captured throughout clinical development
14 from PK/PD studies and also in clinical efficacy trials where conducted. Knowledge of the
15 type and severity of safety issues with the RBP, whether these are due to exaggerated
16 pharmacological actions, the degree of analytical and functional similarity of the SBP and the
17 RBP and the presence of novel impurities in the SBP will inform on the extent of data required
18 to characterise the safety profile of the SBP.

19 If the clinical programme of the SBP is limited to confirmatory pharmacokinetic/
20 pharmacodynamic studies, a risk assessment should be conducted to determine the need to
21 obtain additional safety data for the SBP. For example, for insulins, the most relevant safety
22 issue is hypoglycaemia which can be attributed to the pharmacological action of insulin.
23 Highly similar physicochemical characteristics and PK / PD profiles of the SBP and the RBP
24 in the euglycaemic clamp study would provide sufficient reassurance that the hypoglycaemic
25 risk is also similar, obviating the need for further safety data. Similar examples are teriparatide,
26 filgrastim or somatropin. With the advancement in the analytical sciences and clinical
27 experiences more complex products as mAbs and mAb-like biologics (fusion proteins)
28 increasingly fall into this category.

29 If the SBP contains impurities that are not present in the RBP (e.g. because of the use of a
30 novel expression system), generation of further safety data may be necessary or scientific
31 justification should be provided why such data is not needed. Manufacturers should consult
32 with regulators when proposing a clinical program solely relying on PK/PD studies.

33 As for all medicinal products, further monitoring of the safety of the SBP is necessary in the
34 post-marketing phase (see section 11) and participation in existing disease registries is
35 encouraged.

36 10.6 Immunogenicity

37 Immunogenicity should be investigated as part of the clinical evaluation package of the SBP
38 relative to the RBP, unless the manufacturer can provide a scientific justification that human
39 immunogenicity data are not needed based on the degree of physicochemical similarity of the
40 SBP with the RBP and a thorough risk assessment of unwanted immunogenicity and clinical

1 consequences known for the RBP. Published information is useful to gain knowledge of the
2 immunogenicity risk of the RBP and to plan the immunogenicity strategy but is not generally
3 sufficient to support approval of the SBP. The goal of the immunogenicity program is to detect
4 an unacceptable/marked increase in the immunogenicity of the SBP when compared with the
5 immunogenicity of the RBP and to generate descriptive data in support of SBP approval and
6 its clinical use. If conducted, reporting data should include the antibody incidence, titre,
7 neutralization ability, whether transient/persistent and their impact on pharmacokinetics and
8 clinical correlates (23).

9 The marketing authorization application should include an integrated immunogenicity
10 summary, which would comprise a risk assessment, and if appropriate, testing using
11 appropriately validated and characterised assays, details on study duration, sampling schedules
12 and regimen, the results of the clinical studies along with an integrated clinical immunogenicity
13 assessment (23-25).

14 The immunogenicity studies should be tailored to each product and require a multidisciplinary
15 approach taking into account both quality and clinical considerations. The risk assessment
16 should include accumulated information on the immunogenicity of the RBP (nature, frequency
17 and clinical relevance of the immune response), considerations with respect to the quality
18 aspects (nature and complexity of the drug substance, non-glycosylated/glycosylated,
19 expression system, product- and process-related impurities, aggregates), excipients and
20 packaging and stability of the product, route of administration, dosing regimen, and patient-,
21 disease-related factors (immune-competent/compromised, concomitant immunomodulatory
22 therapy). Special emphasis on differences in product-related factors (e.g. impurities arising
23 from novel expression system, novel excipients) that could modify immunogenicity is crucial
24 in the risk assessment of the SBP.

25 Importantly, considerations on the type of product are a critical element of the risk assessment;
26 the risk being higher for a product that has an endogenous non-redundant counterpart. In this
27 case, special attention should be paid to the possibility that the immune response seriously
28 affects the endogenous protein and its unique biological function with serious adverse effects
29 (e.g. epoetin alfa). Real-time testing for neutralizing ADAs is recommended for epoetins (26)
30 and for other high risk products (e.g., enzyme replacement therapies). Conversely, for well
31 characterized biological substances (e.g. insulin, somatropin, filgrastim, teriparatide), where
32 extensive literature information and clinical experience are available indicating that
33 immunogenicity does not impact safety and efficacy, immunogenicity studies may not be
34 necessary, provided that the SBP is highly similar to the RBP. This may also be applicable to
35 other products, including mAbs. In such cases, manufacturers should consult with regulatory
36 authorities.

37 10.6.1 Immunogenicity testing

38 A multi-tiered approach, which comprises screening and confirmatory immunoassays that
39 detect binding anti-drug antibodies (ADAs) followed by assays which determine titre and
40 neutralization potential is generally necessary and deviation from this requires justification.

1 Details on assays and formats as well as their benefits and limitations along with interpretation
2 of results are extensively reviewed in publications (27-29). The manufacturer will need to
3 justify the antibody testing strategy and the choice of assays to be used. Attention should be
4 given to selection of suitable controls for assay validation and to determination of cut-off points
5 for distinguishing antibody-positive from antibody-negative samples. Aspects relating to
6 potential interference by matrix components, including the target and the residual drug in the
7 sample are important. To mitigate interference, corrective measures should be implemented.
8 For example, for drug interference, which commonly occurs with samples from patients given
9 mAbs, measures such as allowing time for clearance of the drug from the circulation prior to
10 sampling, or incorporating steps for dissociating immune complexes, and/or removal of the
11 drug can be used. Care should be taken that inclusion of such measures does not compromise
12 ADA detection or patient treatment.

13 Where required, comparative immunogenicity testing should be performed using the same
14 assay format and sampling schedule. Ideally for immunogenicity assessment, antibody testing
15 is performed using the therapeutic given to the patient. In applying this concept to SBPs,
16 development of screening assays with a similar sensitivity for the two patient groups (SBP and
17 RBP) within the same study is very challenging. Therefore, in the SBP scenario, relative
18 immunogenicity is often assessed by using a single assay which employs the active substance
19 of the SBP as the antigen for sample testing for both groups. This approach allows detection
20 of all antibodies developed against the SBP. The manufacturer should demonstrate the
21 suitability of the method(s) used and provide data assuring that the methods measure ADA to
22 the RBP or the SBP to a similar extent (30).

23 Neutralization assays reflecting the mechanism of action are usually based on the potency
24 assay of the product. Non-cell ligand-based assays are relevant in cases where the therapeutic
25 binds to a soluble ligand and inhibits the ligand's biological action. For products with high risk
26 (e.g. those with non-redundant endogenous homologs) and those where effector functions are
27 important, functional cell-based bioassays are recommended. Advice on the need for a
28 neutralization assay and the appropriate format (cell-based, ligand based or based on enzyme
29 activity) may be sought from regulatory authorities where necessary.

30 Further characterization of antibodies (e.g. isotype) should be conducted if considered
31 clinically relevant, or in special situations, (for example, occurrence of anaphylaxis or use of
32 certain assay formats), taking into account the immunogenicity profile of the RBP. For
33 example, if the RBP does not elicit an IgE response, it is unlikely that the SBP would elicit one
34 if it uses the same expression system. Retention of patient samples under appropriate storage
35 conditions is necessary for retesting in case of technical problems in the original assay.

36 10.6.2 Clinical evaluation

37 ADAs can affect the pharmacology and/or pharmacokinetics of the administered product and
38 influence pharmacodynamics, safety and efficacy of the product. The severity of the ADA
39 response observed with the RBP, i.e. the incidence in the treated population as well as the
40 magnitude of the clinical effect, influences the risk/benefit balance for the therapeutic.

41 Comparability of immunogenicity is important throughout the clinical program. The most
42 sensitive patient population is preferred for investigating immunogenicity, therefore, if the

1 RBP is licensed for different patient populations (e.g. renal anaemia vs. oncology indication
2 for an epoetin), selection of anaemic patients is advised. If comparative PK and PD studies are
3 regarded as sufficient for the biosimilar program, these studies should be designed to also
4 collect immunogenicity data regardless of the population to be included (e.g. healthy
5 volunteers and patients). A PK/PD crossover design is possible for immunogenicity but needs
6 to ensure there are sufficient number of patients followed without crossover (4 arm design) or
7 the sponsor should propose a parallel design study.

8 If anti-drug antibodies (ADA) are known to affect the PK of the RBP, ADA rate and kinetics
9 as well as assessment of their impact on PK through prespecified subgroup analysis of ADA-
10 negative and -positive subjects could be performed but should be pre-specified.

11 The required observation period for immunogenicity testing will depend on the expected time
12 of antibody development and should be justified by the manufacturer. Sampling for
13 immunogenicity testing should include baseline (prior to treatment) for pre-existing antibodies,
14 during treatment and, in some cases post-treatment particularly if ADAs persist or are
15 undetectable at earlier time-points (due to immunosuppressive properties of the product or
16 technical problems e.g. drug interference). The sampling schedule should be synchronized for
17 evaluation of PK as well as for assessment of safety and efficacy to provide an understanding
18 of the impact of antibodies on clinical outcome. Generally, for chronic administration, 6-month
19 data are acceptable to exclude excessive immunogenicity, but in some cases a longer
20 evaluation may be appropriate pre-licensing to assess antibody incidence and possible clinical
21 effects.

22 If anti-drug antibodies (ADAs) are present, an analysis of clinical impact of ADAs (e.g. on PK
23 or efficacy) should be performed through prespecified subgroup analysis of ADA-negative and
24 -positive subjects.

25 Further, any large difference in immunogenicity between the SBP and RBP would require
26 further investigation of the underlying cause, and data and justification to support that the
27 difference noted is not clinically relevant.

28 As for the RBP, the SBP should undergo a robust post marketing surveillance that includes
29 assessment of serious adverse events related to immunogenicity.

30 **10.7 Extrapolation of efficacy and safety data to other clinical indications**

31 Efficacy and safety data gained with the RBP can be extrapolated to the SBP for all approved
32 indications if the SBP has been shown to be highly similar to the RBP in terms of analytical
33 characteristics and functional properties related to the mechanism(s) of action, supported by
34 clinical data as necessary.

35 For example, clinical efficacy may be extrapolated based on highly comparable functional data,
36 e.g. for mAbs such as infliximab and adalimumab if they show fully comparable activity,
37 including ADCC, CDC, reverse signalling and apoptosis, both in terms of binding to soluble
38 TNF and membranous TNF.

39 **11. Pharmacovigilance**

1 As for all medicinal products, further close monitoring of the efficacy and safety of an SBP in
2 all approved indications and a continued benefit–risk assessment are necessary in the post-
3 marketing phase.

4 The manufacturer should submit a pharmacovigilance plan describing safety specification,
5 pharmacovigilance activities and risk minimization activities at the time of submission of the
6 marketing authorization application or when a safety concern arises post-marketing. The
7 principles of pharmacovigilance planning can be found in relevant guidelines such as ICH E2E
8 (31). The safety specification should describe important identified or potential safety issues for
9 the RBP and for the substance class and any that are specific for the SBP. If there are remaining
10 uncertainties for the SBP candidate due to e.g. a novel excipient or device - these should be
11 included in the plan and followed up post-marketing.

12 Any specific safety monitoring imposed on the RBP or product class should be incorporated
13 into the pharmacovigilance plan for the SBP, unless a compelling justification can be provided
14 to show that this is not necessary. Post-marketing safety reports should include all information
15 on product safety received by the marketing authorization holder. The safety information must
16 be evaluated in a scientific manner and should include evaluation of the frequency and
17 causality of adverse events.

18 Manufacturers should ensure that, at the time of the marketing authorization, they have in place
19 an appropriate pharmacovigilance system, including the services of a qualified person
20 responsible for monitoring pharmacovigilance and the necessary means for notification of
21 adverse reactions that occur in any of the countries where the product is marketed.

22 After the marketing authorization is granted, it is the responsibility of the NRA to monitor
23 closely the compliance of manufacturers with their marketing commitments, where
24 appropriate, and particularly with their pharmacovigilance obligations (as previously
25 described).

26 In addition, as for all biologicals, an adequate system for ensuring specific identification of the
27 SBPs (i.e. traceability) is essential. The NRA shall provide a legal framework for proper
28 pharmacovigilance surveillance and ensure the ability to identify any biological marketed in
29 its territory that is the subject of adverse reaction reports. This implies that an adverse reaction
30 report for any biological should include, in addition to the International Nonproprietary Name
31 (INN) (32), other important indicators such as proprietary (brand) name, manufacturer's name,
32 lot number and country of origin.

33 12. Prescribing information and label

34 The SBP should be clearly identifiable by a unique brand name together with the INN. From
35 the perspective of the WHO, there is no specific nomenclature for SBPs, that is, there is no
36 part of an INN which indicates that a product is an SBP. SBPs are given INNs using the process
37 and rules used for all biologicals. In many cases, the INN for an SBP is the same as that for its
38 RBP, for example, for GCSF SBPs that have used Neupogen as an RBP, both the SBP and the
39 RBP have the INN “filgrastim” (33, 34). Provision of the lot number is essential; it is an
40 important part of production information and critical for traceability whenever problems with
41 a product are encountered.

1 The prescribing information for the SBP should be as similar as possible to that of the RBP
2 except for product-specific aspects, such as different excipient(s). This is particularly important
3 for posology and safety-related information, including contraindications, warnings and adverse
4 events. However, if there are fewer indications for the SBP than for the RBP, the related text
5 in various sections may be omitted unless it is considered important to inform doctors and
6 patients about certain risks, e.g. as a result of potential off-label use. In such cases it should be
7 clearly stated in the prescribing information that the SBP is not intended for use in the specific
8 indication(s) and the reasons why.

9 **13. Roles and responsibilities of national regulatory** 10 **authorities**

11 One of the responsibilities of an NRA is to set up appropriate regulatory oversight for the
12 licensing and post-marketing surveillance of SBPs that are developed and/ or authorized for
13 use in its area of jurisdiction. The experience and expertise of the NRA in evaluating biological
14 products is a key prerequisite for appropriate regulatory oversight of these products. The NRA
15 is responsible for clearly defining a suitable regulatory framework for licensing biological
16 products, including SBPs (35).

17 As development of biological products is a rapidly evolving area, NRAs may need regular
18 review for their licensing, for adequacy of their regulations for providing oversight, and for the
19 processes and policies that constitute the regulatory framework is an essential component of a
20 well-functioning and up-to-date regulatory oversight for biologicals. If problems arise during
21 the review, the NRA should take action to identify the problematic products in its market, to
22 assess the risk-benefit balance of their use and to decide whether additional evaluations are
23 needed (36). NRAs should develop a specific, appropriate, regulatory framework for approving
24 SBPs that is distinct from the regulatory procedures previously applied to copy-version
25 products where regulatory evaluation was not well-defined (37).

26 NRAs could improve access to SBPs of assured quality, safety and efficacy by improving
27 efficiency of their regulatory evaluation, e.g. making effort to reduce time for evaluation
28 without compromising the quality of the review process (35, 37). In addition, they should
29 provide an effort to avoid unnecessary duplication of studies.

30 Most countries either use or amend their existing legislation and applicable regulations or
31 develop entirely novel frameworks for the authorization of SBPs. In some jurisdictions,
32 regulations for licensing subsequent entry versions of biotherapeutic products are intricately
33 linked with policies for innovation. Hence an NRA may need to coordinate and communicate
34 with other stakeholders for consistency.

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