Guidelines on evaluation of similar biotherapeutic products (SBPs)

Proposed guidelines

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 WHO approach for evaluation of similar biotherapeutic products to a broad audience and to improve transparency of the consultation process.

A previous draft (WHO/BS/08.2101) was presented to the ECBS in October 2008. The Committee affirmed that the guiding principles outlined in the document will contribute to the assurance of the quality, safety and efficacy of similar biotherapeutic products worldwide and recommended further development of the document. Following the ECBS advice, an updated draft has been prepared for public consultation. After receiving comments from this consultative process, as well as from invited reviewers, further revision of the draft guidelines will be undertaken and presented to the ECBS 2009. Final draft for submission to the ECBS (BS document) will be posted on WHO Biologicals website (http://www.who.int/biologicals/en/) for public consultation in August 2009.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Comments proposing modifications to this text MUST be received by 15 July 2009 and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Quality Safety and Standards (QSS). Comments may also be submitted electronically to the Responsible Officer: Dr Ivana Knezevic at email: knezevici@who.int.

The outcome of the deliberations of the Expert Committee 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 "WHO style guide" (WHO/IMD/PUB/04.1).

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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 access to patients, particularly in developing countries. Recently, the expiration of patents and/or data protection for the first major group of originator’s biotherapeutics has ushered in an era of products that are designed to be ‘similar’ to a licensed originator product. These products rely, in part, for their licensing on prior information regarding safety and efficacy obtained with the originator products. The clinical experience and established safety profile of the originator products should contribute to the development of similar biotherapeutic products (SBPs). The amount and extent of data required for the licensing of SBPs is likely to be less than is normally required for the originator products. A variety of terms, such as 'biosimilar products', 'follow-on protein products' and 'subsequent-entry biologics' have been coined by different jurisdictions to describe these products.

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. The demonstration of bioequivalence of the generic medicine with the reference product is usually appropriate to infer therapeutic equivalence between the generic medicine and the reference product. However, the approach established for generic medicines is not suitable for development, evaluation and licensing of SBPs since biotherapeutics usually consist of relatively large, and complex proteins that are difficult to characterize.

As part of its mandate for assuring global quality, safety and efficacy of biotherapeutics, the World Health Organization (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 essential tools for the establishment of potency for biological medicines worldwide. Often they are used as primary standards for calibration of the secondary standards that are directly used in the biological assays.

An increasingly wide range of SBPs are under development or are already licensed in many countries and a need for guidelines for their evaluation and overall regulation was formally
recognized by the WHO in 2007\textsuperscript{4}. This document is intended to provide guidance for the
development and evaluation of such biotherapeutics.

It is essential that the standard of evidence supporting the decisions to license SBPs be sufficient
to ensure that the product meets acceptable levels of quality, safety and efficacy to ensure public
health. Also, it is expected that the elaboration of the data requirements and considerations for
the licensing of these products will facilitate development of and worldwide access to
biotherapeutics of assured quality at more affordable prices. In most cases, their authorization
will be evaluated on a case-by-case basis, and the amount of data required by a National
Regulatory Authority (NRA) may vary. However, it is expected that a guideline on the scientific
principles for evaluation of SBPs will help harmonize the requirements worldwide and will lead
to greater ease and speed of approval and assurance of the quality, safety and efficacy of these
products.

2 Aim

The intention of this document is to provide a globally acceptable set of principles to be applied
to the licensing of safe, efficacious, and high quality biotherapeutics that are claimed to be
similar to already licensed biotherapeutics and therefore may rely, in part, on information from
the already licensed products whose patents have expired. This guideline can be adopted as a
whole, or partially, by NRAs worldwide or used as a basis for establishing national regulatory
frameworks for licensure of these products.

3 Scope

This guideline applies to well-established and well-characterized biotherapeutic products such as
recombinant DNA-derived therapeutic proteins.
Vaccines and plasma derived products are excluded from the scope of this document because
they are highly complex and generally less well characterized entities.

4 Glossary

The definitions given below apply to the terms used in this guideline. They may have different
meanings in other contexts.
Comparable
Absence of any relevant differences at the level of quality, safety or efficacy between two biotherapeutics.

Comparability exercise
Comparison of a biotherapeutic product with a licensed originator product with the goal to establish similar quality, efficacy and safety.

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

Drug substance
The active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components such as buffers.

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

Generic medicine
A generic medicine contains the same active ingredient as and is bioequivalent to an originator prescription medicine, and is subject to all applicable data protection periods and/or intellectual property rights of the originator product. Since generic medicines are identical in the active substance, dose, strength, route of administration, safety, efficacy, and intended use, they can be substituted for the originator product.

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

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

Refers to the medical practice of switching one medicine for another that is equivalent, in a given clinical setting.

Non-inferior

Not inferior to a comparator in the parameter of interest. Non-inferiority trial is a trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparator.

Originator product

A medicine which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e., the approved indication(s) for use were granted based on own quality, efficacy and safety data.

Pharmacovigilance

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

Reference biotherapeutic product (RBP)

A reference biotherapeutic product is used as the comparator for head-to-head studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP.

Similar biotherapeutic product (SBP)

A biotherapeutic product claimed to be “similar” in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product, which is an originator product marketed by an independent manufacturer.

Substitutability

Refers to the practice of automatically substituting one medicine for another equivalent medicine at the pharmacy.

Well-established biotherapeutic product

Well-established biotherapeutic product is the one that has been marketed for a suitable period of time with a proven efficacy and safety.
5 Key principles for the licensing of SBPs

a. The basis for a product being licensed as a SBP hinges on its demonstrated similarity to a suitable RBP, which will then provide a basis for a reduction in the non-clinical and clinical information needed to support the market authorization of the SBP.

b. The development of a SBP involves a stepwise approach of comparability exercise starting with comparison of the quality characteristics of the SBP and RBP followed by non-clinical and clinical studies. Demonstration of similarity of a SBP to a RBP in terms of quality is a prerequisite for the reduction of the non-clinical and clinical data set required for licensure. If major differences are found in the quality, non-clinical, or clinical studies, the product will not be likely to qualify as a SBP and a more extensive non-clinical and clinical data set will likely be required to support the application for licensure.

c. SBPs are not “generic medicines” and many characteristics associated with the authorization process and marketed use of generic medicines generally do not apply.

d. SBPs, like other biotherapeutic products, require effective regulatory oversight for the management of their potential risks and in order to maximize their benefits. Hence, only NRAs with experience and expertise in biotherapeutic products should license SBPs. The NRA is responsible for determining a suitable regulatory framework for licensing SBPs. The NRA may choose to utilize or amend existing pathways or develop a new pathway for this purpose. The licensing of SBPs should be consistent with the laws and regulations for patents, intellectual property, and data protection (where they exist).

e. The decision to allow automatic substitution of a SBP for a RBP should be made on a national level taking into account potential safety issues with the product or class of products. Decisions on interchangeability should be based on appropriate scientific and clinical data and is beyond the scope of this document.
6 Reference biotherapeutic product

To support licensure of a SBP, the SBP is studied in head-to-head comparison with a licensed originator product that is used as the comparator to establish similarity of the SBP. This comparator is the RBP.

Comprehensive information on the RBP provides the basis for establishing the safety, quality, and effectiveness profile to which the SBP is compared. The RBP also provides the basis for dose selection and route of administration, and is utilized in the comparability studies required to support the licensing application. The demonstration of an acceptable level of similarity between the SBP and RBP provides the rationale for utilizing a reduced non-clinical and clinical data set to support the application for market authorization of the SBP. Hence the RBP is central to the licensing of a SBP.

The choice of a RBP is of critical importance for the evaluation of SBP. The rationale for the choice of the RBP should be provided by the manufacturer of the SBP in the submission to the NRA. Considerations by a NRA on its policy on RBPs should include the nature of the biologics industry in the country, the availability of nationally licensed RBPs, and may include, as appropriate, the laws or regulations for patents, intellectual property, and/or data protection. The latter tends to be intrinsically linked with policies for innovative drug development. Traditionally, NRAs have required the use of a nationally licensed reference product for licensing of generic medicines. This practice may not be feasible for countries lacking nationally-licensed RBPs. NRAs may need to consider establishing additional criteria to guide the acceptability of using a RBP licensed or resourced in other countries.
Considerations for choice of reference biotherapeutic product

Since the choice of a RBP is essential to the development of a SBP, the following should be considered.

- The RBP should have been marketed for a suitable duration and have a volume of marketed use such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy.
- The manufacturer needs to demonstrate that the chosen RBP is suitable to support the application for marketing authorization.
- The RBP should be licensed based on a full quality, safety, and efficacy data. Therefore a SBP should not be considered as a choice for RBP.
- The same RBP should be used throughout the development of the SBP (i.e., for the comparative quality, non-clinical, and clinical studies).
- The active substance of the RBP and the SBP must be shown to be similar.
- The dosage form and route of administration of the SBP should be the same as that of the RBP.
- The following factors should be considered in the choice of a RBP that is marketed in another jurisdiction;
  - The RBP should be widely marketed in another jurisdiction which has regulatory standards and principles for evaluation of biotherapeutic products, post-market surveillance activities, and approaches to establishing comparability that are consistent with those of the NRA.
  - The laws and regulations for patents, data protection and intellectual property should be consistent between the different jurisdictions.
  - The acceptance of a RBP for evaluation of a SBP in a country does not imply approval for use of the RBP by the NRA of that country.
7 Regulatory Considerations

One of the responsibilities of a NRA is to set up appropriate regulatory oversight for the licensing of SBPs that are developed and/or authorized for sale in their country. As development of biotherapeutic products is a rapidly evolving area, regular review of the NRAs for their licensing, the adequacy of the regulations for providing oversight, and the processes and policies that constitute the regulatory framework is an essential component of a well-functioning and up-to-date regulatory oversight for biotherapeutics.

A NRA may possess the regulatory authority for authorization of all new drugs and as such may not need to amend its regulations to authorize SBPs. However, the EU has specifically amended its regulations to provide an abbreviated pathway for SBPs (biosimilars)\(^5,6,7,8\). This issue is subject of discussion in a number of other countries where development of SBPs is ongoing. For instance, Health Canada has recently developed their guideline. National guidelines in some other countries are also being developed. Although US FDA did not issue guidelines, their perspective on the assessment of Follow-on Protein Products was published\(^9\). In most instances, NRAs will need to provide guidance to manufacturers on the information needed and regulatory requirements for the authorization of SBPs. A majority of countries will either be using their existing legislation and applicable regulations or they will amend or develop entirely novel frameworks for the authorization of SBPs. In most jurisdictions, regulations for licensing subsequent entry versions of biotherapeutic products are intricately linked with policies for innovation. Hence a NRA will need to coordinate with other stakeholders for consistency.

Scientific considerations and concept for licensing of SBPs

For the licensing of generic medicines, the regulatory framework is well-established in most countries. Demonstration of bioequivalence of the generic medicine with the reference product is usually appropriate to infer (conclude) therapeutic equivalence between the generic and the reference product. However, the generic approach is not suitable for the licensing of SBPs since
biotherapeutic products usually consist of relatively large and complex entities that are difficult
to characterize. In addition, SBPs are manufactured and controlled according to their own
development since the manufacturer of a SBP normally does not have access to all the necessary
manufacturing information on the originator product. However, even minor differences in the
manufacturing process may affect the pharmacokinetics, pharmacodynamics, efficacy and/or
safety of biotherapeutic products. As a result, it has been agreed that the normal method for
licensing generic medicines through bioequivalence studies alone is not scientifically appropriate
for SBPs. Decision making regarding the licensing of SBPs should be based on scientific
evidence. The onus is on a manufacturer of a SBP to provide the necessary evidence to support
all aspects of an application for licensing.

As with any drug development program, the development of a SBP involves a stepwise approach
starting with characterization and evaluation of quality attributes of the product and followed by
non-clinical and clinical studies. Comprehensive characterization and comparison at the quality
level are the basis for possible data reduction in the non-clinical and clinical development. If
differences between the SBP and the RBP are found at any step, the underlying reasons for the
differences should be investigated. Differences should always be explained and justified and may
lead to the requirement of additional data (e.g., safety data).

In addition to the quality data, SBPs require non-clinical and clinical data generated with the
product itself. The amount of additional data considered necessary will depend on the product or
class of products, the extent of characterization possible by state-of-the-art analytical methods,
on observed or potential differences between the SBP and the RBP, and on the clinical
experience with the product class (e.g., safety/immunogenicity concerns in a specific indication).

A case by case approach is clearly needed for each class of products.

A SBP is intended to be similar to a licensed biotherapeutic product for which there is a
substantial public record of safety and efficacy. The ability for the SBP to be authorized based on
reduced non-clinical and clinical data depends on its demonstrated similarity to an appropriate
RBP. Manufacturers should demonstrate a full understanding of their product, consistent and
robust manufacture of their product, and submit a full quality dossier that includes a complete
characterization of the product. The comparability exercise in the quality part represents an
additional element to the ‘traditional’ full quality dossier. The reduction in data requirements is
therefore only possible for the non-clinical and/or clinical parts of the development program. The dosage form and route of administration of the SBP should be the same as for the RBP.  
Studies must be comparative in nature employing analytical strategies (methods) that are sensitive to detect potential differences between the SBP and the RBP. Main clinical studies should use the final formulation derived from the final process material of the SBP. Otherwise, additional evidence of comparability will be required to demonstrate that the SBP to be marketed is comparable to that used in the main clinical studies.  
If similarity between the SBP and the RBP has been convincingly demonstrated, the SBP may be approved for use in other clinical indications of the RBP that have not directly been tested in clinical trials if appropriate scientific justification for such extrapolation is provided by the manufacturer (see section 10.7). Significant differences between the SBP and the chosen RBP detected during the comparability exercise would be an indication that the products are not similar and full non-clinical and clinical data may be required to support the application for licensing.

**Comparability exercise**

The comparability exercise for a SBP is designed to show that the SBP has highly similar quality attributes when compared to the RBP. However, it also includes the non-clinical and clinical studies to provide an integrated set of comparative data. The comparability data at the level of quality can be considered to be an additional set of data over that which is normally required for an originator product developed as a new and independent product. This is the basis for reducing the non-clinical and clinical data requirements.  
Although the quality comparisons are undertaken at various points throughout the quality dossier, a distinction should be made between usual data requirements and those presented as part of the comparability exercises. It may be useful to present these as a separate section in the quality module. The quality expert acting on behalf of the SBP manufacturer should provide a specific review of the quality comparability data.
8 Quality

The quality comparison showing molecular similarity between the SBP and the RBP provides the underlying rationale for predicting that the clinical safety and efficacy profile of the RBP should also apply to the SBP so that the extent of the non-clinical and clinical data required with the SBP can be reduced. Development of an SBP involves thorough characterization of a number of representative lots of the RBP and then engineering a manufacturing process that will reproduce a product that is highly similar to the RBP in all critical product quality attributes; \textit{i.e.}, those product attributes that may impact clinical performance. The quality comparison between the SBP and the RBP is the basis for allowing extrapolation of clinical safety and efficacy data for the RBP to the SBP. A SBP is generally derived from a separate and independent master cell bank using independent manufacturing processes and control. These should be selected and designed to meet the required comparability criteria. A full quality dossier for both drug substance and drug product is always required, which complies with the standards as required by NRAs for originator products.

Increased knowledge of the relationship between biochemical, physicochemical, and biological properties of the product and clinical outcomes will facilitate development of a SBP. Due to the heterogeneous nature of proteins (especially those with extensive post-translational modifications such as glycoprotein), the limitations of some analytical techniques, and the sometimes unpredictable nature of the clinical consequences of differences in protein structural/physico-chemical properties, the evaluation of comparability will have to be carried out independently for each product. For example, oxidation of certain methionine residues in one protein may have no impact on clinical activity whereas in another protein it may significantly decrease the intrinsic biological activity of the protein, or may increase its immunogenicity. Thus, differences in the levels of Met oxidation in the RBP and SBP would need to be evaluated differently for different proteins.

To evaluate comparability, the manufacturer should carry out a comprehensive physicochemical and biological characterization of the SBP in head-to-head comparisons with the RBP. All aspects of product quality and heterogeneity should be assessed (see characterization below). A high degree of similarity between the SBP and the RBP is the basis for reducing non-clinical and clinical requirements for licensing. However, some differences are likely to be found, \textit{e.g.},
due to differences in impurities or excipients. Such differences should be assessed for their potential impact on clinical safety and efficacy of the SBP and a justification, e.g., own study results or literature data, for allowing such differences provided. Differences of unknown clinical relevance, particularly regarding safety, may have to be addressed in additional studies pre- or post-marketing. Differences in critical product quality attributes (i.e., those that are known to have potential impact on clinical activity) will add to the clinical testing required for the SBP. For example, if differences are found in glycosylation patterns that alter the biodistribution of the product and thereby change the dosing scheme, then dose-finding studies for the product would likely be required. Similarly, since differences in fucosylation of the Fc portion of monoclonal antibodies are known to impact receptor binding and biological activity in vivo, the impact on clinical efficacy and/or safety of differences between the SBP and RBP would likely need to be evaluated with appropriate clinical studies. Other differences between the SBP and RBP may be acceptable, and would not trigger the need for extra clinical evaluation. For example, a therapeutic protein that has lower levels of protein aggregates would, in most cases, be predicted to have a better safety profile than the RBP and would not need added clinical evaluation. Along the same lines, if heterogeneity in the N-terminal amino acids is known, with sufficient documentation, not to affect the bioactivity, biodistribution, or immunogenicity of the RBP or similar products in its class, then there may be no need for added clinical safety or efficacy studies based upon differences in this portion of the RPB and SBP.

Due to the unavailability of drug substance for the RBP, the SBP manufacturer will usually be using commercial drug product for the comparability exercise. The commercial drug product will, by definition, be in the final dosage form containing the active substance(s) formulated with excipients. It should be verified that these do not interfere with analytical methods and thereby impact the test results. If the active substance in the RBP needs to be purified from a formulated reference drug product in order to be suitable for characterization, studies must be carried out to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process. The approach employed to isolate and compare the SBP to the RBP should be justified and demonstrated, with data, to be appropriate for the intended purpose. Where possible, the product should be tested with and without manipulation.
8.1 Manufacturing process

Manufacture of a SBP should be based on a comprehensively designed production process taking all relevant guidelines into account. The manufacturer needs to demonstrate the consistency and robustness of the manufacturing process by implementing Good Manufacturing Practices\textsuperscript{10}, modern quality control and assurance procedures, in-process controls, and process validation. The manufacturing process should meet the same standards as required by the NRA for originator products. The manufacturing process should be optimized to minimize differences between the SBP and RBP in order to (a) maximize the ability to reduce the clinical testing requirements for the SBP based upon the clinical history of the RBP, and (b) minimize any predictable impact on the clinical safety and efficacy of the product. Some differences between the SBP and RBP are expected and may be acceptable, provided, appropriate justification with regard to lack of impact on clinical performance is given.

It is understood that a manufacturer developing a SBP does not have access to confidential details of the manufacturing process of the RBP such that the process will differ from the licensed process for the RBP (unless there is a contractual arrangement with the manufacturer of the RBP). The manufacturing process for a SBP should employ state-of-the-art science and technology to achieve a high quality SBP that is as similar as possible to the RBP. This will involve evaluating the RBP extensively prior to developing the manufacturing process for the SBP. The SBP manufacturer should assemble all available knowledge of the RBP concerning the type of host cell and expression system, formulation, stability profile, and container closure system used for marketing the RBP. The SBP manufacturer should then determine the potential impact of changing any one of these elements on product quality, safety and efficacy and apply this knowledge to the design of the manufacturing process. The rationale for accepting these differences needs to be justified based upon sound science and clinical experience, either with the SBP, or the RBP.

As a general rule, the product should be expressed and produced in the same host cell type as the RBP (e.g., \textit{E.coli}, CHO cells, etc) in order to minimize the potential for important changes to critical quality attributes of the protein and to avoid introduction of certain types of process-related impurities (e.g., host cell proteins, endotoxins, yeast mannans) that could impact clinical outcomes and immunogenicity. The host cell type for manufacture of the SBP should only be
changed if the manufacturer can demonstrate convincingly that the structure of the molecule is not affected or that the clinical profile of the product will not change. For example, somatropin produced in yeast cells appears to have similar characteristics to somatropin expressed in *E. coli*. In most cases, however, the use of a different host cell type will not be feasible for glycoproteins because glycosylation patterns vary significantly between different host cell types. Novel host cell production systems should not be used for the SBP.

A complete description and data package should be provided that delineates the manufacturing process, starting with development of expression vectors and cell banks, cell culture/fermentation, harvest, purification and modification reactions, filling into bulk or final containers, and storage. The development studies conducted to establish and validate the dosage form, formulation, and container closure system (including integrity to prevent microbial contamination) and usage instructions should be also documented (see relevant guidelines such as ICH).

### 8.2 Characterization

Characterization should start with the RBP to set the target for the SBP. The manufacturing process should then be optimized, and the characterization of the SBP carried out using appropriate, state-of-the-art biochemical, biophysical, and biological analytical techniques. For the active ingredient(s) (*i.e.*, the desired product), details should be provided on primary and higher-order structure, post-translational modifications (including but not limited to glycoforms), biological activity, purity, impurities, product-related (active) substances (variants), and immunochemical properties, where relevant.

When conducting a comparability exercise, head-to-head characterization studies are required to compare the SBP and the RBP. If any differences between the SBP and the RBP are found, they should be evaluated for their potential impact on safety and efficacy of the SBP. The acceptance limit for allowable differences should be set in advance by the manufacturer and a justification for allowing such differences should be provided. This determination will be based upon knowledge of the relationship between product quality attributes and clinical activity of the RBP and related products, the clinical history of the RBP, and lot-to-lot differences for commercial lots of the RBP. For example, quality attributes such as composition and profile of glycosylation,
biological activity which known to be related to clinical activity (e.g., insulin), and receptor binding activity should determine the acceptance limit for differences before performing comparability exercise.

Knowledge of the analytical limitations of each technique used to characterize the product (e.g., limits of sensitivity, resolving power) should be applied when making a determination of similarity. Representative raw data should be provided for all complex analytical methods (e.g., high quality reproductions of gels, chromatograms, etc) in addition to tabular data summarizing the complete data set and showing the results of all release and characterization analyses carried out on the SBP and the RBP.

The following criteria should be considered when conducting the comparability exercise:

8.2.1 Physicochemical Properties
The physicochemical characterization should include the determination of primary and higher order structure (secondary/tertiary/quaternary) and other biophysical properties. An inherent degree of structural heterogeneity occurs in proteins due to the biosynthesis process such that the RBP and the SBP are likely to contain a mixture of post-translationally modified forms. Appropriate efforts should be made to investigate, identify and quantify these forms.

8.2.2 Biological Activity
Biological assays serve multiple purposes in the assessment of product quality and are required for characterization, batch analyses, and immunogenicity assessments. Ideally, the bioassay will reflect the understood mechanism of action of the protein and will thus serve as a link to clinical activity. A bioassay is a quality measure of the ‘function’ of the protein product and can be used to determine whether a product variant has the appropriate level of activity (i.e., a product-related substance) or is inactive (and is therefore defined as an impurity). The biological assay also complements the physicochemical analyses by confirming the correct higher order structure of the molecule. Thus, the use of a relevant biological assay(s) with appropriate precision and accuracy provides an important means of confirming that a significant functional difference does not exist between the SBP and the RBP. In addition, a relevant bioassay is essential for determining whether antibodies that develop in response to the product have neutralizing activity that impacts the biological activity of the product and/or endogenous counterparts to the product.
For a product with multiple biological activities, manufacturers should perform, as part of product characterization, a set of relevant functional assays designed to evaluate the range of activities of the product. For example, certain proteins possess multiple functional domains that express enzymatic and receptor-binding activities. In such situations, manufacturers should evaluate and compare all relevant functional activities of the SBP and RBP.

The results of the biological assay(s) should be provided and expressed in units of activity. Where possible (e.g., for in vitro biochemical assays such as enzyme assays or binding assays), the results may be expressed as specific activities (e.g., units/mg protein). Assays should be calibrated against an international or national reference standard, when available and appropriate.

8.2.3 Immunochemical Properties

When immunochemical properties are part of the characterization (e.g., for antibodies or antibody-based products), the manufacturer should confirm that the SBP is comparable to the RBP in terms of specificity, affinity, binding kinetics, and Fc functional activity, where relevant.

8.2.4 Impurities

Process- and product-related impurities should be identified, quantified and compared between the SBP and RBP. Some differences may be expected because the proteins are produced by different manufacturing processes. If differences are observed in the impurity profile of the SBP relative to the RBP, the differences should be evaluated to assess the potential impact on safety and efficacy of the product. This should include evaluation of the potential impact on immunogenicity of the product. It is critical to have suitable assays for process-related impurities, specific to the cell line used for production.

8.3 Specifications

Specifications are employed to verify the routine quality of the drug substance and drug product rather than to fully characterize them. As for any biotherapeutic product, specifications for a SBP should be set as described in established guidelines and monographs, where these exist. It should be noted that pharmacopoeial monographs may only provide a minimum set of requirements for a particular product and additional test parameters may be required. Reference to analytical
methods used and acceptance limits for each test parameter of the SBP should be provided and justified. All analytical methods referenced in the specification should be validated; the corresponding validation should be documented.

Specifications for a SBP will not be the same as for the RBP since different analytical procedures and laboratories will be used for the assays. Nonetheless, the specifications should capture and control key product quality attributes known for the RBP (e.g., correct identity; purity, potency; molecular heterogeneity in terms of size, charge, and hydrophobicity, if relevant; degree of sialylation; inter-molecular disulfide bonding and number of individual polypeptide chains; glycosylation of a functional domain; aggregate levels). The setting of specifications should be based upon the manufacturer’s experience with the SBP (e.g., manufacturing history; assay capability; safety and efficacy profile of the product) and the experimental results obtained by testing and comparing the SBP and RBP. Sufficient lots of SBP should be employed in setting specifications. The manufacturer should demonstrate, whenever possible, that the limits set for a given specification are not significantly wider than the range of variability of the RBP over the shelf-life of the product, unless justified.

8.4 Analytical techniques

Although the power of analytical methods for characterization of proteins has increased dramatically over the past few decades, there are still obstacles to completely characterizing complex biotherapeutic products. A battery of state-of-the-art analyses is needed to determine structure, function, purity, and heterogeneity of the products. The methods employed should separate and analyze different variants of the product based upon different underlying chemical, physical, and biological properties of protein molecules. For example, PAGE, ion exchange chromatography, isoelectric focusing, and capillary electrophoresis all separate proteins based upon charge, but they do so under different conditions and based upon different physicochemical properties. As a result, one method may detect variants that another method does not detect. The goal of the comparability investigation is to be as comprehensive as possible in order to minimize the possibility of undetected differences between the RBP and SBP that may impact clinical activity. The analytical limitations of each technique (e.g., limits of sensitivity, resolving
power) should be considered when making a determination of similarity between a SBP and a RBP.

The measurement of quality attributes in characterization studies (versus in the specifications) does not necessarily require the use of validated assays, but the assays should be scientifically sound and qualified; i.e., they should provide results that are meaningful and reliable. The methods used to measure quality attributes for lot release should be validated in accordance with relevant guidelines, as appropriate. A complete description of the analytical techniques employed for release and characterization of the product should be provided in the license application.

8.5 Stability

The stability studies should be in compliance with relevant guidance as recommended by the NRA. Studies should be carried out to show which release and characterization methods are stability-indicating for the product. Generally, stability studies should be summarized in an appropriate format such as tables, and they should include results from accelerated degradation studies and studies under various stress conditions (e.g., temperature, light, humidity, mechanical agitation). Accelerated stability studies comprise an important element of the determination of similarity between a SBP and a RBP because they can reveal otherwise-hidden properties of a product that warrant additional evaluation. They are also important for identifying the degradation pathways of a protein product. The results obtained from accelerated stability studies may show the additional controls should be employed in the manufacturing process and during shipping and storage of the product in order to ensure the integrity of the product. Head-to-head accelerated stability studies comparing the SBP to the RBP will be of value in determining the similarity of the products by showing comparable degradation profiles. Representative raw data showing the degradation profiles for the product should be provided in the license application.

The stability data should support the conclusions regarding the recommended storage and shipping conditions and the shelf life/storage period for the drug substance, drug product, and process intermediates that may be stored for significant periods of time. Stability studies on drug substance should be carried out using containers and conditions that are representative of the actual storage containers and conditions. Stability studies on drug product should be carried out in the intended drug product container-closure system. Real time/real temperature stability
studies will determine the licensed storage conditions and expiration dating for the product. This may or may not be the same as for the RBP.

9 Non-clinical evaluation

The non-clinical part of the guideline addresses the pharmaco-toxicological assessment of the SBP. The establishment of safety and efficacy of a SBP usually requires the generation of some non-clinical data with the SBP. In general, the demonstration of a high degree of molecular similarity between the SBP and RBP should significantly reduce the need for non-clinical studies since the RBP will already have a significant clinical history. Non-clinical studies, if considered necessary (see below), should be conducted with the final formulation of the SBP intended for clinical use, unless otherwise justified.

The design of an appropriate non-clinical study program requires a clear understanding of the product characteristics. Results from the physico-chemical and biological characterization studies should be reviewed from the point-of-view of potential impact on efficacy and safety. When developing a SBP some existing guidelines may be relevant and should therefore be taken into account; e.g., the ´Note for preclinical safety evaluation of biotechnology-derived pharmaceuticals` (ICH S6)\textsuperscript{11}.

Problems in the non-clinical evaluation of SBPs containing biotechnology-derived recombinant proteins as active substance are often related to the fact that these products - may show species-specific pharmacodynamic activity such that it is sometimes difficult to identify a relevant species for pharmacodynamic and toxicological evaluation - will, as ´foreign proteins`, usually elicit an antibody response in long-term animal studies. Thus, the results of subchronic or chronic repeat dose studies may be difficult to interpret due to the formation of antibody complexes with the active substance.
9.1 Special considerations

Non-clinical evaluation of a new biotherapeutics normally encompasses a broad spectrum of pharmacodynamic, pharmacokinetic and toxicological studies\textsuperscript{11}. For SBPs, however, as long as the quality (including bioactivity) of the SBP is sufficiently similar to an appropriate RBP, the minimum requirements for non-clinical studies are head-to-head comparative toxicology studies. The amount of additional non-clinical data required to establish safety and efficacy of a SBP is considered to be highly dependent on the product and substance-class related factors. Factors that often elicit the need for additional non-clinical studies include, but are not restricted to:

- Quality-related factors:
  - Significant differences in the cell expression system compared with the RBP,
  - The presence of a complex mixture of less well characterized product- and/or process-related impurities
  - International reference standards unavailable

- Factors related to pharmaco-toxicological properties of the active substance
  - Mechanism(s) of drug action are unknown or poorly understood
  - The active substance is associated with significant toxicity and/or has a narrow therapeutic index

Depending on these factors, the spectrum of studies required to establish safety and efficacy of the SBP may vary considerably and should be defined on a case-by-case basis. In the case of a highly complex active substance that is difficult to characterize by analytical techniques and which possesses a narrow therapeutic index, the non-clinical development program may encompass a significant portion of the spectrum of studies described in relevant guidelines such as ICH S6\textsuperscript{11}. On the other hand, for products for which the active substance and the impurity profile are well characterized by analytical means and which possess a wide therapeutic index, the non-clinical development program will likely be more limited. Most SBPs will meet this latter criterion since, at present, only well-characterized proteins with a good benefit:risk ratio should be developed as SBPs.
The non-clinical studies constitute a part of the overall comparability exercise. Therefore, the studies should be comparative in nature and designed to detect differences in response between the SBP and the RBP and not just the response to the SBP alone.

**In vitro studies:**
Assays like receptor-binding studies or cell-based assays (e.g., cell-proliferation or cytotoxicity assays) should normally be undertaken in order to establish comparability of the biological/pharmacodynamic activity of the SBP and RBP. Such data are already available from the biological assays described in the quality part of the dossier. Reference to these studies can be made in the non-clinical part of the dossier.

**In vivo studies:**
Animal studies should be designed to maximize the information obtained. Such studies should be comparative in nature (see above), should be performed in (a) species known to be relevant (i.e., a species in which the RBP has been shown to possess pharmacodynamic and/or toxicological activity) and employ state-of-the-art technology. Where the model allows, consideration should be given to monitoring a number of endpoints such as:
- Biological/pharmacodynamic activity relevant to the clinical application. These data should be available from biological assays described in the quality part of the dossier and reference to these studies can be made in the non-clinical part of the dossier.
- Non-clinical toxicity as determined in at least one repeat dose toxicity study with a relevant species and including toxicokinetic measurements. These measurements should include determination and characterization of antibody responses, including anti-product antibody titres, cross reactivity with homologous endogenous proteins, and product neutralizing capacity. The duration of the studies should be sufficiently long to allow detection of relevant differences in toxicity and antibody responses between the SBP and RBP.

Besides being a part of the overall comparability exercise, the comparative repeat-dose toxicity study is considered to provide reassurance that no ‘unexpected’ toxicity will occur during clinical use of the SBP. If performed with the final formulation intended for clinical use, the
repeat-dose toxicity study will, in principle, allow for detection of potential toxicity associated with both the active substance and product- and process-related impurities.

Although the predictive value of animal models for immunogenicity in humans is considered low, antibody measurements, if applicable, should be included in the repeat-dose toxicity study to aid in the interpretation of the toxicokinetic data and to help assess, as part of the overall comparability exercise, whether important differences in structure or immunogenic impurities exist between the SBP and RBP (i.e., the immunological response may be sensitive to differences not detected by laboratory analytical procedures).

Depending on the route of administration, local tolerance may need to be evaluated. If feasible, this evaluation may be performed as part of the described repeat-dose toxicity study.

On the basis of the demonstration of similarity between the SBP and RBP by the additional comparability exercise performed as part of the quality evaluation, normally other routine toxicological studies such as safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies are not generally requirements for the non-clinical testing of a SBP, unless triggered by results of the repeat-dose toxicity study or the local tolerance study and/or by other known toxicological properties of the RBP (e.g., known adverse effects of the RBP on reproductive function).

10 Clinical evaluation

The main/pivotal clinical data should be generated using the product derived from the final manufacturing process and therefore reflecting the product for which marketing authorization is being sought. Any deviation from this recommendation needs to be justified and additional bridging data may be required, such as from PK studies comparing the PK profiles of the products from the previous and final formulations.

Clinical studies should be designed to demonstrate comparable safety and efficacy of the SBP to the RBP and therefore need to employ testing strategies that are sensitive enough to detect relevant differences between the products, if present (see below).

The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic and pharmacodynamic studies followed by the pivotal clinical trials.
10.1 Pharmacokinetic (PK) studies

The PK profile is an essential part of the basic description of a medicinal product and should always be investigated. PK studies should generally be performed for the routes of administration applied for and using doses within the therapeutic dosing range recommended for the RBP.

PK studies must be comparative in nature and should be designed to enable detection of potential differences between the SBP and the chosen RBP. This is usually best achieved by performing single-dose, cross-over PK studies in a homogenous study population and by using a dose where the sensitivity to detect differences is largest. For example, for a medicinal product with saturable absorption (saturation kinetics), the lowest therapeutic dose would be most appropriate, provided that the employed assay can measure the resulting drug plasma levels with sufficient accuracy and precision. In order to reduce variability not related to differences between products, PK studies should normally be performed in healthy volunteers. If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to perform the PK studies in the proposed patient population.

In general, single dose PK studies will suffice. However, in cases of dose or time-dependent pharmacokinetics, resulting in markedly higher concentrations at steady-state than expected from single dose data, a potential difference in the extent of absorption of the SBP and RBP may be larger at steady-state than after single dose administration. In such cases, it may be advisable for the manufacturer to perform an additional comparative multiple dose study to ensure similar PK profiles also at steady-state before commencing the confirmatory clinical trial(s). In steady-state PK studies, the administration scheme should preferably use the highest customary dosage recommended for the RBP.

The choice of single-dose studies, steady-state studies, or repeated determination of PK parameters and the study population should be justified by the manufacturer. The cross-over design reduces inter-subject variability and therefore, compared to the parallel design, reduces the sample size necessary to show equivalent PK profiles of the SBP and RBP. The treatment phases should be separated by an adequate wash-out phase to avoid carry-over effects. The
cross-over design may not appropriate for biological medicinal products with a long half-life or for proteins for which formation of anti-product antibodies is likely. In parallel designs, care should be taken to avoid relevant imbalances in all prognostic variables between treatment groups that may affect the pharmacokinetics of the active substance (e.g., ethnic origin, smoking status, extensive/poor metabolic status of the study population).

PK comparison of the SBP and the RBP should not only include absorption/bioavailability but should also include elimination characteristics; i.e., clearance and/or elimination half-life, since differences in elimination rate of the SBP and the RBP may exist.

Acceptance criteria for the demonstration of similar PK between the SBP and the RBP should be pre-defined and appropriately justified. It is noted that the criteria used in standard clinical PK comparability studies (bioequivalence studies) were developed for chemically-derived, orally administered products and may not necessarily be applicable for biological medicinal products. Due to the lack of established acceptance criteria designed for biologicals, the traditional 80-125% equivalence range is often used. However, if the 90% confidence intervals of the ratio of the population geometric means (test/reference) for the main parameters under consideration (usually rate and extent of absorption) fall outside that range, the SBP may still be considered similar to the RBP based on similar PD, efficacy and safety data.

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

Historically, the PK evaluation of peptide or protein products has suffered from limitations in the assay methodology thus limiting the usefulness of such studies. Special emphasis should therefore be given to the analytical method selected and its capability to detect and follow the time course of the protein (the parent molecule and/or degradation products) in a complex biological matrix that contains many other proteins. The method should be optimized to have satisfactory specificity, sensitivity and a range of quantification with adequate accuracy and precision.

In some cases, the presence of measurable concentrations of endogenous protein may substantially affect the measurement of the concentration-time profile of the administered exogenous protein. In such cases, the manufacturer should describe and justify the approach to minimize the influence of the endogenous protein on the results.
10.2 Pharmacodynamic (PD) studies

Although comparative clinical trials are usually required for demonstration of similar efficacy and safety of the SBP and RBP, it may be advisable for the manufacturer to ensure similar PD profiles before proceeding to clinical trials, particularly if a difference in PK profiles of unknown clinical relevance has been detected. In many cases, PD parameters are investigated in the context of combined PK/PD studies. Such studies may provide useful information on the relationship between dose/exposure and effect, particularly if performed at different dose levels. In the comparative PD studies, PD effects should be investigated in a suitable patient population using a dose/doses within the steep part of the dose-response curve in order to best detect potential differences between the SBPs and the RBP. PD markers should be selected based on their clinical relevance.

10.3 Confirmatory pharmacokinetic/pharmacodynamic (PK/PD) studies

Usually, clinical trials are required to demonstrate similar efficacy between the SBP and the RBP. In certain cases, however, comparative PK/PD studies may suffice, provided that 1) the PK and PD properties of the RBP are well characterized, 2) at least one PD marker is an accepted surrogate marker for efficacy, and 3) the relationship between dose/exposure, the relevant PD marker(s) and response/efficacy of the RBP is established. Euglycaemic clamp studies would be an example for acceptable confirmatory PK/PD studies for the comparison of efficacy of two insulins. In addition, absolute neutrophil count is the relevant PD marker for the activity of granulocyte colony stimulating factor (G-CSF) and could be used in PK/PD studies in healthy volunteers to demonstrate similar efficacy of two G-CSF-containing medicinal products.

The study population and dosage should represent a test system that is known to be sensitive to detect potential differences between the SBP and the RBP. For example, in the case of insulin, the study population should consist of non-obese healthy volunteers or patients with type 1 diabetes rather than insulin-resistant patients with type 2 diabetes. Otherwise, it will be necessary to investigate a relevant dose range to demonstrate that the test system is discriminatory. In
addition, the acceptance ranges for demonstration of similarity in confirmatory PK and PD
parameters should be pre-defined and appropriately justified.

10.4 Efficacy studies

Dose finding studies are not required for a SBP. Demonstration of comparable potency, PK and
PD profiles provide the basis for the use of the posology of the RBP in the confirmatory clinical
trial(s).

Similar efficacy of the SBP and the chosen RBP will usually have to be demonstrated in
adequately powered, randomized, and parallel group clinical trial(s). The principles of such trials
are laid down in relevant ICH guidelines\(^{12,13}\). Clinical studies should preferably be double-blind
or at a minimum observer-blind. In the absence of any blinding, careful justification will be
required to prove that the trial results are free from significant bias\(^6\).

Potential differences between the SBP and the RBP should be investigated in a sensitive and
preferably well-established model. For example, in the case of growth hormone (GH), treatment-
naïve children with GH deficiency usually represent the most appropriate study population as
opposed to children with non GH-deficient short stature that are usually less sensitive to the
effects of GH. Although adult patients with GH deficiency could also be considered a “sensitive”
population, the endpoint used to measure effects of GH treatment (\(i.e.,\) body composition) is less
sensitive than the one used in children (\(i.e.,\) longitudinal growth) and an equivalence/non-
inferiority margin is difficult to define.

In principle, equivalence or non-inferiority studies may be acceptable for the comparison of
efficacy and safety of the SBP with the RBP. Equivalence/non-inferiority margins have to be
pre-specified and justified based on clinical relevance; \(i.e.,\) the selected margin should represent
the largest difference in efficacy that would not matter in clinical practice. Treatment differences
within this margin would thus be acceptable because they have no clinical relevance. For
example, for Silapo (epoetin zeta) the EMEA accepted equivalence margins of 80-125% for the
treatment difference in epoetin dose because such differences within this range were shown to
have no major impact on hemoglobin concentrations and were within the batch-to-batch
variability of the reference product (epoetin alfa).
Similar efficacy implies that similar treatment effects can be achieved with similar dosages. Therefore, in cases for which the medicinal product is titrated according to treatment response (e.g., epoetin, insulin) rather than given at a fixed dosage (e.g., somatropin in GH-deficient children), equivalence/non-inferiority should be demonstrated not only with regard to treatment response but also with regard to dosage. This is best achieved by defining a combined primary endpoint that also includes the dosage.

Equivalence trials are strongly recommended for medicinal products with a narrow safety margin (therapeutic index), such as insulin, to ensure that the SBP is not less and not more effective than the RBP when used at the same dosage. For medicinal products with a wide safety margin, a non-inferiority trial may also be appropriate for demonstration of similar efficacy of the SBP and RBP. It should, however, be considered that non-inferior efficacy does not exclude the possibility of superior efficacy of the SBP compared to the RBP. In such cases, sufficient reassurance should be provided by the manufacturer that superior efficacy of the SBP would not be associated with additional adverse events if used at the same dosage as the RBP, particularly if the SBP and the RBP are considered interchangeable. This could be achieved, for example, by including a key safety variable as a co-primary endpoint with a well-defined non-inferiority margin.

Whereas several examples exist for licensing of SBPs based on equivalence trials (e.g., recombinant human GH, epoetin and G-CSF in the EU), experience with non-inferiority trials for this purpose is limited and mainly based on theoretical considerations. An additional advantage of demonstration of equivalent efficacy (rather than non-inferior efficacy) is that this would provide a stronger rationale for the possibility of extrapolation of efficacy data to other indications of the RBP, particularly if these include different dosages than the one(s) tested in the clinical trial (see section 10.7). However, if there is no disadvantage to increased efficacy in any indication (e.g., for a cancer treatment or an anti-infective), then non-inferiority trials may still support extrapolation to other indications.

**Special statistic consideration about sample size**

Equivalence trials should not require a larger sample size compared to non-inferiority trials if the efficacy of the SBP and RBP is reasonably expected to be similar based on the quality
comparison of the products. In clinical research, the type 1 error for a wrong or false positive conclusion (e.g., erroneously accepting the test drug as an alternative to the reference drug in a non-inferiority trial) is usually set at 2.5%. The type 1 error is set at 5% for the two-sided procedure and is designed to prevent the wrong conclusion that the test drug is either better or worse than a placebo or the active comparator. Since a drug will not be acceptable if it is inferior to a placebo or the active comparator, the error of a false positive conclusion is still limited to 2.5%.

For products that are demonstrated to be highly similar at the molecular level and for which no important clinical differences are expected, there is no formal difference between equivalence and non-inferiority designs, where the non-inferiority (irrelevance) margin would be specified on one side (i.e., to exclude the possibility that the efficacy of the SBP is worse than the efficacy of the RBP) and the equivalence margin would be specified on two sides (i.e., to exclude that the possibility that the efficacy of the SBP is either worse or better than that of the RBP). In case both drugs are equally effective (as they should be), the chosen approach would be irrelevant. A larger sample-size would only be required, if the SBP would be known or suspected to be less effective than the RBP. In a non-inferiority study, the sample-size could be reduced if the SBP is suspected of being more efficacious than the RBP. This, however, may be seen as a contradiction to the concept that the amount of clinical data required for evaluation of a SBP can be reduced based upon similarity to the RBP, and to justify the treatment recommendation based on similarity arguments. On the other hand, this approach would be acceptable if the manufacturer can provide reassurance that better efficacy will not come at the price of lessened or lowered tolerability.

10.5 Safety

Pre-licensing safety data should be obtained in a sufficient number of patients to characterize the safety profile of the SBP. Usually, safety data obtained from the efficacy trial(s) will suffice (i.e., trials that are powered for their primary efficacy endpoint(s)). Comparison with the RBP should include type, frequency and severity of adverse events/reactions. For cases in which similar efficacy is demonstrated in confirmatory PK/PD studies but safety data relevant for the target population cannot be deduced from these studies, safety data in the target population are still
needed. For example, for two soluble insulins, the euglycaemic clamp study is considered the most sensitive method to detect differences in efficacy. However, immunogenicity and local tolerance of subcutaneously administered SBP cannot be assessed in such studies and should therefore preferably be evaluated in the target population.

Safety data should preferably be comparative. Comparison with an external control group is usually hampered by differences in the investigated patient population and concomitant therapy, observation period and/or reporting.

Safety data obtained from the clinical trials can be expected to mainly detect frequent and short-term adverse events/reactions. Such data are usually sufficient pre-licensing, but further close monitoring of clinical safety of the SBP may be necessary in the post-marketing phase (see section 11).

10.6 Immunogenicity

Immunogenicity of biotherapeutic products should always be investigated pre-authorization. Even if efficacy and safety of a SBP and RBP have been shown to be similar, immunogenicity may still be different.

The immune response against a biotherapeutic is influenced by many factors such as the nature of the active substance, product- and process-related impurities, excipients and stability of the product, route of administration, dosing regimen, and patient-, disease- and/or therapy-related factors. The consequences of unwanted immunogenicity may vary considerably, ranging from clinically irrelevant to serious and life-threatening. Although neutralizing antibodies directly alter the pharmacodynamic effect of a product (i.e., by directly blocking the bioactivity of the protein), binding antibodies often affect pharmacokinetics and thereby also influence pharmacodynamics. Thus, an altered effect of the product due to anti-product antibody formation might be a composite of pharmacokinetic, pharmacodynamic and safety effects.

Immunogenicity of a biotherapeutic should always be investigated in humans since animal data are usually not predictive of the immune response in human. The frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared for the SBP and the RBP. Comparison with an external control group is not considered
appropriate because this is usually hampered by differences in the investigated patient population, observation period, sampling time points, assays employed, and interpretation of results.

Generally, the amount of immunogenicity data obtained from the comparative efficacy trial(s) \((i.e.,\) trials that are powered for their primary efficacy endpoint) will allow detection of a marked increase in immunogenicity of the SBP compared to the RBP and will be sufficient pre-licensing. Where clinically meaningful or even serious antibody development has been encountered with the RBP or the substance class but is too rare to be captured pre-licensing (\(e.g.,\) cross-reacting neutralizing anti-epoetin antibodies causing pure red cell aplasia), a specific risk management plan (RMP) for the SBP may be necessary to assess this specific risk post-marketing (see section 11). In case similar efficacy is demonstrated in confirmatory PK/PD study(ies), immunogenicity data in the target population are still needed (see section 10.5). If the manufacturer intends to extrapolate efficacy and safety data to other approved indications of the RBP (see section 10.7), care should be taken to ensure that immunogenicity is investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events.

The manufacturer will need to justify their antibody testing strategy including the selection, assessment, and characterization of assays, identification of appropriate sampling time points including baseline, sample volumes and sample processing/storage as well as selection of statistical methods for analysis of data. Antibody assays need to be validated for their intended purpose. A screening assay of sufficient sensitivity should be used for antibody detection and a neutralization assay should be available for further characterization of antibodies, if present. Possible interference of the circulating antigen with the antibody assay(s) should be taken into account. Detected antibodies need to be further characterized and their potential clinical implications regarding safety, efficacy and pharmacokinetics evaluated. For example, the isotype of the antibodies should be determined if they may be predictive of safety \((i.e.,\) development of IgE antibodies correlates with the development of allergic and anaphylactic responses. If the antibody incidence is higher with the use of the SBP compared to the RBP, the reason for the difference needs to be investigated. Special attention should be paid to the possibility that the immune response seriously affects the endogenous protein and its unique biological function.

The required observation period for immunogenicity testing will depend on the intended duration of therapy and the expected time of antibody development and should be justified by the manufacturer. In the case of chronic administration, one-year data will usually be appropriate
pre-licensing to assess antibody incidence and possible clinical implications. This is, for example, the case for somatropin-containing products, where antibody development usually occurs within the first 6-9 months of treatment but potential effects on growth are only seen later. In some cases, shorter observation periods may be sufficient; e.g., for insulins, where most susceptible patients will develop antibodies within the first 6 months of treatment and clinical consequences, if any, would usually be at around the same time as antibody development. If considered clinically relevant, development of antibody titers, their persistence over time, potential changes in the character of the antibody response and the possible clinical implications should be assessed pre- and post-marketing. Since pre-licensing immunogenicity data are often limited, further characterization of the immunogenicity profile may be necessary post-marketing, particularly, if rare antibody-related serious adverse events may occur that are not likely to be detected in the pre-marketing phase.

10.7 Extrapolation of efficacy and safety data to other clinical indications

If similar efficacy and safety of the SBP and RBP have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the RBP (not studied using independent clinical studies with the SBP) may be possible if all of the following conditions are fulfilled:

- A sensitive clinical test model has been used that is able to detect potential differences between the SBP and the RBP
- The mechanism of action and/or involved receptor(s) are the same; e.g., GH action in different conditions of short stature in children; erythropoiesis-stimulating action of epoetins in different conditions associated with anaemia or for the purpose of autologous blood donation
- Safety and immunogenicity have been sufficiently characterized and there are no unique/additional safety issues expected for the indication(s) for which clinical data on the SBP are not being provided
• If the efficacy trial used a non-inferiority study design and demonstrated that relevant
inferiority with regard to efficacy and safety can be excluded, the manufacturer should
provide a convincing argument that this finding can be applied to the extrapolated indications
If these prerequisites for extrapolation of efficacy and safety data to other indication(s) of the
RBP are not fulfilled, the manufacturer will need to submit own clinical data to support the
desired indication(s).

11 Pharmacovigilance

As for most biological medicines, data from pre-authorization clinical studies are usually too
limited to identify all potential unwanted effects of a SBP. In particular, rare adverse events are
unlikely to be encountered in the limited clinical trial populations being tested with the SBP.
Therefore, further close monitoring of the clinical safety of these products in all approved
indications and a continued benefit-risk assessment is necessary in the post-marketing phase.

The manufacturer should submit a safety specification and pharmacovigilance plan at the time of
submission of the marketing authorization application. The principles of pharmacovigilance
planning can be found in relevant guidelines such as ICH E2E\(^{15}\). The safety specification should
describe important identified or potential safety issues for the RBP, the substance class and/or
any that are specific for the SBP. The pharmacovigilance plan should describe the planned post-
marketing activities and methods based on the safety specification\(^{16}\). In some cases, risk
minimization measures such as educational material for patients and/or treating physicians may
enhance the safe use of the SBP.

Any specific safety monitoring imposed on the RBP or product class should be incorporated into
the pharmacovigilance plan for the SBP, unless a compelling justification can be provided to
show that this is not necessary. Moreover, potential additional risks identified during the review
of the data obtained with the SBP should be subject to further safety monitoring (e.g., increased
immunogenicity that might result from a difference in the glycosylation profile). The NRAs
should closely monitor the compliance with the marketing commitments, where appropriate, and
pharmacovigilance obligations.
Post-marketing safety reports should include all information on product tolerability received by the marketing authorization holder. The safety information must be evaluated in a scientific manner and should include evaluation of the frequency and causality of adverse events. Manufacturers should ensure that, at the time of the marketing authorization, they have in place an appropriate pharmacovigilance system including the services of a qualified person responsible for monitoring pharmacovigilance and the necessary means for the notification of adverse reactions that occur in any of the countries where the product is marketed.

In addition, as for all biotherapeutics, an adequate system is necessary to ensure specific identification of the SBPs. The NRA shall ensure the ability to identify any biotherapeutics marketed in their territory which is the subject of adverse reaction reports. This implies that an adverse reaction report for any biotherapeutic should include, in addition to the International Nonproprietary Names (INN)\textsuperscript{16}, other indicators such as proprietary (brand) name, manufacturer’s name, lot number and country of origin.

### 12 Other Considerations

**Prescribing information**

The prescribing information for the SBP should be as similar as possible to that of the RBP except for product-specific aspects, such as different excipient(s). This is particularly important for posology and safety-related information, including contraindications, warnings and adverse events. However, if the SBP has fewer indications than the RBP, the related text in various sections may be omitted unless it is considered important to inform doctors and patients about certain risks; e.g., because of potential or likely off-label use. In such cases it should be clearly stated in the prescribing information that the SBP is not indicated for use in the specific indication(s). If applicable, study results should be presented in a way that enables readers to clearly distinguish the data obtained from studies with the SBP from those obtained with the RBP.
Authors and acknowledgements

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Further revision of the draft guidelines, undertaken by the drafting group, led to this draft of the guidelines which is posted on WHO Biologics website (http://www.who.int/biologicals/en/) for public consultation.

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