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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 29 October to 2 November 2018

WHO Questions and Answers: Similar Biotherapeutic Products

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

NOTE:

This draft document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the WHO Expert Committee on Biological Standardization (ECBS). The distribution of this document is intended to bring the proposed WHO document on *Questions and Answers on similar biotherapeutic products* to the attention of a broad audience and to improve the 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 20 September 2018 using the Comment Form available separately and should be addressed to: Department of Essential Medicines and Health Products (EMP), 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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WHO Questions and Answers: Similar Biotherapeutic Products

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Authors and acknowledgements

Other recommended reading

Guidance documents published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRA) and for manufacturers of biological products.

Abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
CDC	complement-dependent cytotoxicity
ECBS	Expert Committee on Biological Standardization
EU	European Union
FDA	(United States) Food and Drug Administration
NRA	national regulatory authority
PD	pharmacodynamics
PK	pharmacokinetics
Q&A	questions and answers
RBP	reference biotherapeutic product
SBP	similar biotherapeutic product
WHO	World Health Organization

Background

WHO's *Guidelines on evaluation of similar biotherapeutic products (SBPs)* (also called "biosimilars"), adopted by the WHO Expert Committee on Biological Standardization (ECBS) in 2009, have raised awareness of the complex scientific issues related to the licensing of SBPs. However, in some countries and for a variety of reasons, biotherapeutic products have been licensed as generics or as small molecule drugs using data which do not now meet current WHO regulatory expectations. Very little is known about the safety and efficacy of these individual products. Consequently, these products need to be reassessed by national regulatory authorities (NRAs), as described in the WHO guidance document on *Regulatory assessment of approved rDNA-derived biotherapeutics*.

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

In response, WHO has convened meetings to identify the needs, as well as the parts of the guidelines which should be updated. In April 2015, an informal consultation was organized on the possible amendment of the guidelines. All participants from NRAs from both developing and developed countries, as well as those from industry, recognized and agreed that the evaluation principles described in WHO's 2009 *Guidelines on evaluation of similar biotherapeutic products (SBPs)* were still valid, valuable and applicable in facilitating the harmonization of SBP requirements globally. It was therefore concluded that there was no need to revise the main body of the existing guidelines on SBPs. However, it was also agreed that there was a need for additional guidance on the evaluation of monoclonal antibody products as biosimilars, and this guidance was subsequently developed and was adopted by the ECBS 2016. In May 2017, WHO held another consultation on improving access to and use of similar biotherapeutic products. From the outcome of this consultation, WHO noted that developing a questions and answers (Q&As) document is more appropriate than revision of the guidance content for further clarifying and complementing some areas and points written in the guidelines.

These Q&As are produced for guidance only and should be read in conjunction with relevant WHO guidelines. The Q&As are intended to provide clarity to questions that may arise in the use of WHO guidelines. The questions in this document have been selected on the basis of those frequently asked by regulators during the implementation workshops on WHO's *Guidelines on evaluation of similar biotherapeutic products (SBPs)* in the past 8 years. The intention is to update the Q&As regularly to reflect new developments and issues that arise, but not to address issues of interchangeability, switching, substitution, naming or shortages which are out of the scope of the original guidelines.

I. Concept for licensing similar biotherapeutic products:

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

According to WHOs *Guidelines on evaluation of similar biotherapeutic products (SBPs),* an SBP is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (RBP).

In addition to "SBP", a variety of terms – such as "similar biological medicinal products", "biosimilar products", "follow-on protein products" and "subsequent-entry biologics" – have been used to describe these products. Since the main principles of developing SBPs are the same, definitions of the SBP are complementary to the WHO definition. For example, in the European Union (EU), a biosimilar must be highly similar to its RBP. High similarity means that the characteristics of quality, biological activity, safety and efficacy of the SBP and its RBP have been shown to be comparable to the degree that the drug substance of the SBP can be called a version of the drug substance of the RBP.

According to the definition of the United States Food and Drug Administration (FDA), there may be differences between the clinically inactive parts of the SBP and the RBP. However, there should be no clinically meaningful differences in the safety, purity and potency of the product.

Based on the above definitions, an SBP is highly similar to an original biotherapeutic product (i.e. RBP) and has been developed and assessed according to the regulatory guidelines that ensure an adequate comparison of the SBP to its RBP.

A medicinal product that has not been compared and shown to be similar to a reference product as indicated in the WHO SBP guidelines should not be called "similar" or SBP (see also the WHO guidance document on *Regulatory assessment of approved rDNA-derived biotherapeutics.*

QI-2 How are SBPs evaluated?

The development and evaluation principles for SBPs and products containing new active substances, such as RBPs, are different. The RBP of an SBP has been licensed on the basis of a full registration dossier of the pharmaceutical quality, pharmacology and toxicology, as well as of human safety and efficacy, in its therapeutic indications.

The development of SBPs relies not only on producing a product that meets the same quality requirements as any other biotherapeutic, but also on generating additional comparative analytical and functional data showing high similarity to the RBP and allowing subsequent abbreviation of the nonclinical and clinical development. This is possible when the manufacturer can demonstrate that the active substances of the SBP and the RBP are highly similar and, thus, can be expected to have the same quality, safety and efficacy. This is achieved by a comprehensive head-to-head analytical comparison of the SBP and the RBP;

these data have to be included and submitted in addition to the pharmaceutical quality part of the SBP. Once the analytical similarity has been established, the nonclinical and clinical studies may be abbreviated and/or refined. The role of the nonclinical and clinical study programme is only confirmatory because the aim of the nonclinical and clinical studies is to demonstrate comparability between the SBP and RBP and not to demonstrate efficacy per se.

The extent of the (non)clinical programme depends on the ability to demonstrate structural and functional similarity between the SBP and its RBP. Thus, the development should be a stepwise approach in which the results of the previous tests and studies will guide the next steps. Extensive comparisons will inevitably reveal some differences that may be real, or may just reflect limitations of the analytical/assay methods used. Therefore, the overall assessment of similarity is based on the evaluation of the whole comparability data package consisting of quality, nonclinical and clinical data (also called "totality of evidence").

The quality and function of a biotherapeutic product are highly dependent on its manufacturing process. The manufacturing process of a biotherapeutic product, both SBPs and RBPs, is changed several times during its life cycle. Significant changes may have an impact on the product. Therefore, regulatory authorities will require the manufacturer to demonstrate with appropriate tests that the safety and efficacy of the product has not been changed. The requirements of these comparability studies after a manufacturing change are described in WHO's *Guidelines on procedures and data requirements for changes to approved biotherapeutic products*.

Comparability studies may include physico-chemical and structural analyses as well as in vitro functional, often cell-based, tests. For more extensive changes and changes that may have a potential clinical impact, additional nonclinical and clinical studies may be required. Regulators have gained experience over many years of assessing manufacturer changes made to the manufacturing process for numerous biotherapeutics to ensure that the safety and efficacy of the product pre- and post-change is comparable. This experience has enabled the development of the concept of biosimilarity.

The general scientific principles of comparability assessment for manufacturing changes are applicable to an assessment of similarity for SBPs. The demonstration of high similarity is based on an extensive head-to-head comparability exercise consisting of comparative state-of-the-art physico-chemical, structural and in vitro functional tests, as well as nonclinical and clinical studies. The clinical experience and established safety profile of the originator products facilitates the development of SBPs.

QI-3 What are the differences between SBPs and generic products?

The term "generic" medicine is used to describe chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product of which the patent and/or data protection period has expired. In contrast, SBPs refer to relatively large and complex molecules of biological origin which are difficult to characterize. The abbreviated development of both generics and SBPs depends on the data of their reference products.

The demonstration of structural identity and bioequivalence of a generic medicine to the reference product is usually sufficient for the licensing of the generic medicine. However, the approach established for licensing generic medicines through bioequivalent studies alone is not scientifically appropriate for licensing an SBP which requires much more extensive studies. Additional analytical and functional, as well as nonclinical and clinical, studies are needed to demonstrate similarity between an SBP and the RBP. SBPs and RBPs are usually produced in cells that generate a product with some microheterogeneity that is unique to each cell type and manufacturing process. Therefore, SBPs and RBPs, or any other therapeutic protein and their versions after a change in manufacturing process, cannot be shown to be identical.

In some countries, for various reasons, biotherapeutic products were licensed as generics or as small molecule drugs using data that do not meet current WHO regulatory expectations. Often little is known about the safety and efficacy of the individual products. These products need to be reassessed by NRAs) as described in the WHO guidance document on *Regulatory assessment of approved rDNA-derived biotherapeutics.*

QI-4 Which products can be approved as SBPs?

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

The development of an SBP to a licensed original biotherapeutic product (i.e. RBP) depends on the ability to characterize and compare their structure and function. To date, SBPs have been developed for well-established and well-characterized biotherapeutic products, such as recombinant DNA-derived therapeutic proteins with a proven record of clinical safety and efficacy. Vaccines, plasma-derived products and their recombinant analogues are beyond the scope of the WHO guidelines on SBPs as recommended the WHO ECBS in 2008. However, biosimilar versions of low-molecular-weight heparins, although not proteins, have been licensed in some jurisdictions as SBPs.

II. Reference biotherapeutic products:

QII-1 What is the reference biotherapeutic product (RBP) referred to in the biosimilar regulatory framework?

An RBP is the comparator for head-to-head comparability studies with the SBP in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed in accordance with WHO's *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* on the basis of a stand-alone registration dossier can serve as an RBP. The term does not refer to measurement standards such as international, pharmacopoeial or national standards or reference standards. A manufacturer developing an SBP may be allowed to reduce the nonclinical and clinical data set required for licensure if the similarity of the SBP to the chosen RBP in terms of quality is demonstrated by appropriate comparability studies.

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

The main criteria for the selection of the RBP are mentioned in WHO's *Guidelines on evaluation of similar biotherapeutic products (SBPs).* The RBP should have been approved on the basis of a complete registration dossier, including safety and efficacy studies in each therapeutic indication. It should be fully identifiable (e.g. brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, numbers and age of batches). The RBP should have been marketed for a suitable duration and should have a volume of marketed use in a jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of biotherapeutic products and post-marketing surveillance activities.

In general, NRAs require the use of a nationally licensed RBP for the evaluation of the SBP. However, this practice may not be feasible for countries that lack nationally licensed RBPs. In case the RBP is not licensed in a given country, the NRA may set additional criteria for the selection of the RBP licensed or resourced in another country. The RBP should be licensed in another country with a complete dossier according to WHO's *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* or corresponding guidelines. The RBP should also have market experience that takes into account a significant duration and magnitude of exposure on the market. The manufacturer of the SBP should justify the use of an RBP that is not licensed locally and the same RBP should be used in all comparability studies of a given SBP.

QII-3 Under what circumstances would it be acceptable to use a foreign-sourced RBP?

In general, the analytical and in vitro functional comparability of the SBP and the RBP should be demonstrated by using the locally-licensed and sourced product. The use of a foreign-sourced RBP may be feasible when the manufacturer plans a global development. By using this approach, unnecessary repetition of nonclinical and clinical studies can be avoided.

The use of a foreign-sourced RBP in nonclinical and clinical studies is possible if justified by information on the relationship of the manufacturers of locally-sourced and foreign-sourced RBP. For instance, the manufacturer may demonstrate that the locally-licensed RBP and the foreign-sourced RBP are versions of the same RBP, based on the same development data, including the same clinical data set. In some jurisdictions, comparability studies, such as analytical or even clinical pharmacokinetic (PK) data, are required to support the use of a foreign-sourced product.

In smaller jurisdictions, or in cases where there is no locally-licensed RBP, a foreign-sourced RBP may be used throughout the whole comparability exercise to demonstrate similarity to the SBP. The regulatory requirements in such a situation are described in the response to **QII-2.**

QII-4 Can the SBP be approved when compared with an RBP which is not available on the domestic market?

Yes, but it has to be justified. The manufacturers must take advice from the relevant NRA.

QII-5 The guidelines state that "the same RBP should be used throughout the entire comparability exercise". Can an RBP from another manufacturing site be used?

Yes. Production batches from different manufacturing sites can be used provided that products from all manufacturing sites are approved by the relevant regulatory authority and that all RBP production batches used in the comparability exercise conform to the same specifications.

III. Quality:

QIII-1 Should the expression system used in producing an SBP be the same as the one used to produce the RBP?

Not necessarily. The expression system (i.e. expression vector and production cells) need not be the same as for the RBP if the expressed protein has the same amino-acid sequence as well as a comparable higher-order structure and post-translational modifications. It is recommended that the manufacturers of SBPs use an expression system similar to that of the RBP where possible, since the cell type influences the pattern of post-translational modifications such as glycosylation. Differences between the RBP and SBP in the level and type of post-translational modifications need to be justified in terms of the potential to have an impact on the potency, safety and efficacy of the SBP.

The manufacturers of SBPs should also consider expression system-specific process impurities. In general, a manufacturer of an SBP is not able to use the same clone of production cells as the manufacturer of the RBP. The developers of an SBP must develop their own master cell banks for their production cells. If a company wishes to use a novel expression system this might give rise to different glycosylation patterns and new process-related impurities, and typically regulators would ask for more clinical immunogenicity data.

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

Not necessarily, as long as the differences do not have an impact on the quality, safety and efficacy of the SBP, and the SBP and RBP can be demonstrated to be comparable. In addition, the manufacturer should justify potential differences between the formulations of the SBP and the RBP. In general, the formulations should be state-of-the-art with regard to stability, compatibility, integrity and impact on activity and strength of the active substance.

It is important to justify the lack of adverse impact on the relative efficacy and safety of the SBP if a different formulation and/or container/closure system is used – especially any material that is in contact with the medicinal product. The aim of the biosimilar comparability exercise is to demonstrate that the SBP and the RBP chosen by the manufacturer are comparable.

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

No, it is not necessary for an SBP to have the same delivery device or container closure system as the RBP. The lack of any adverse impact of the delivery device/container closure system on quality, safety, efficacy and usability should be demonstrated. The manufacturer of an SBP should demonstrate that the product remains stable over long-term storage when stored in the chosen container closure systems.

Thus it is possible, for instance, to use a different delivery device, such as pre-filled syringe or autoinjector, even if the RBP has only a vial provided that the products are shown to be comparable.

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

Yes. In general, an SBP should have the same concentration of drug substance as the RBP. The total content of the drug substance per dosage form should be defined by the posology of the RBP and should allow the appropriate application. A difference in the total content of SBP and RBP should be justified. If needed, additional data should be provided. Any difference should not compromise safety. The total content and concentration should be expressed by using the same measurement system as the RBP (i.e. mass units or units of activity).

QIII-5 Should the specifications of the SBP be the same as those of the RBP?

The specifications control the most important RBP and SBP quality attributes concerning identity, purity, potency and molecular heterogeneity. Nevertheless, specifications of RBP and SBP are likely to be somewhat different because of different manufacturing processes and analytical methods. Thus, the specifications reflect the experience of the manufacturer's own product. The specifications should be based on WHO's *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology*.

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

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

The analysis of multiple batches of the RBP by the manufacturer is necessary for developing an optimal manufacturing process for a candidate SBP. For this purpose, the manufacturer of an SBP needs to collect a representative set of batches of the RBP over an extended period to justify comparability ranges for critical quality attributes. The relevance of the ranges should be discussed, taking into account the number of RBP batches tested, the quality attributes investigated, the age of the batches at the time of testing, and the evolution of quality attributes over time as well as the test method used. The age of the different batches of the RBP (relative to the expiry dates) should also be considered when establishing the target quality profile.

At the next stage, comprehensive head-to-head physico-chemical, structural and in vitro functional comparisons are performed for multiple representative batches of RBP and SBP to confirm representative and comparable quality profiles. It may not be possible to set a definite number for batches of the comprehensive comparability exercise. The number of batches needed to show similarity of each quality attribute and to establish the range of SBP specifications should be sufficient to allow a meaningful comparison with the RBP. The manufacturers may request advice from the relevant regulatory authority on the appropriate number of batches when preliminary results from the degree of variability have been obtained.

Where several strengths or presentations are available, their selection should be appropriately justified.

QIII-7 What is the role of pharmacopoeial monographs in the evaluation of SBPs?

Pharmacopoeial monographs are public standards which include quality requirements for medicinal products and their constituents. Monographs for biotherapeutic products have been issued in various jurisdictions. An SBP must show the same level of compliance with a pharmacopoeial monograph as the RBP. However, compliance with pharmacopoeial monographs will not be sufficient to demonstrate biosimilarity.

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

WHO provides International Standards and Reference Reagents, which serve as primary reference standards of defined biological activity expressed in an international unit (IU) or unit (U).[1] They are used either to calibrate assays directly or to calibrate secondary standards (e.g. pharmacopoeial and national reference standards) or manufacturers' working standards.

When available, manufacturers can use international/pharmacopoeial reference standards and reagents for qualification and standardization of the tests used to characterize and quantify RBP and SBP. For example, the potency (expressed, for instance, in units or international units [IU]) is the quantitative measure of biological activity based on an attribute of the product. The potency of each batch of the drug substance and the final dosage form should be established by using, wherever possible, an appropriate national or international reference material which is normally calibrated in units of biological activity such as IU. In the absence of such preparations, an approved in-house reference preparation may be used for assay standardization.

Many biological products are labelled and dosed in terms of mass units rather than potency units. For such products, the reference standard (in-house, national or international) may be used to calibrate the working reference standard and the corresponding bioassay used to confirm product quality. In these situations, quality determination of bioactivity is normally expressed in percentage relative terms rather than in units and is not used for product labelling.

[1] See: http://www.who.int/biologicals/reference_preparations/en/ (accessed 19 July 2018).

However, these reference standards are distinct entities and cannot be used instead of the RBP for demonstration of comparability.

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

The expiry date of an SBP is based on the SBP stability data which defines its shelf-life and is independent of the RBP. The shelf-life of the SBP should be justified on the basis of full real-time and real-temperature stability data obtained according to the relevant guidelines, namely WHO's *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* and the ICH Q5C guideline on *Quality of biotechnological products: stability testing of biotechnological/biological products*.

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

Stability testing of SBPs should comply with the relevant guidelines, namely: WHO's *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* and the ICH Q5C guideline on *Quality of biotechnological products: stability testing of biotechnological/biological products*. Stability studies on the drug product should be carried out in the intended drug product container closure system.

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

Comparative accelerated stability tests not only provide important information on degradation pathways of the active substance and the suitability of the formulation and the container closure system but may also uncover differences between the degradation profiles of the SBP and RBP. Results obtained from the studies may show that additional controls should be used in the manufacturing process and during shipping and storage in order to ensure the integrity of the product.

Stress stability testing is necessary for an SBP in order to further investigate appropriate conditions for shipping and storage unless these conditions are covered by accelerated stability studies. In general, comparative stress testing of SBP and RBP does not provide added value. However, depending on the potential degradation mechanism of the molecule, stress conditions (e.g. high/low pH, humidity, oxidation) may reveal differences between the degradation profiles of the SBP and RBP.

QIII-11 When conducting a comparability exercise, head-to-head characterization studies are required to compare the SBP and its RBP. How much difference or

what kinds of differences can be accepted while ensuring a high degree of similarity between the SBP and its RBP?

The conclusion of high similarity is based on evaluation of the whole data package from quality, nonclinical and clinical parameters and not on an individual variable or physico-chemical test. The regulators may use their previous experience, generated for instance from changes introduced into manufacturing processes for the RBP, to understand the functional and clinical impact of a particular physico-chemical difference between the SBP and its RBP.

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

In vitro, usually cell-based, functional assays may be helpful in understanding the significance of a difference detected in the analytical testing. It is important to understand the factors that have an impact on the functional tests. The sensitivity of some of the functional tests, such as reporter gene-based assays, has been increased to the degree that they do not correspond to the physiological situation. In these situations, the manufacturer needs to consider the significance of the results and understand the difference between a robust assay for release and a bio-analytical assay. It is also important to consider other tests that may better reflect the physiological situation. Tests using cells from a specific patient population may also be helpful for interpretation of the observed difference.

In general, in vitro functional tests are more sensitive than clinical studies at detecting differences between the SBP and RBP. Results of physico-chemical and structural tests should be considered in planning the clinical comparability programme, especially in PK, pharmacodynamics (PD) and immunogenicity studies.

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

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

QIII-12 How comprehensive should the evaluation of glycan structure (i.e. level of details) be?

A glycoform is an isoform of a protein that differs from others only with respect to the number or type of attached glycans. The biotechnological manufacturing process of a given glycoprotein is sensitive to culture conditions, which may lead to production of different glycoforms in spite of the same glycosylation machinery. This glycoform pattern may to some extent vary from batch to batch. In addition, production cells from different species may produce qualitatively different glycans that should be identified and justified, especially if such glycan does not exist in humans.

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

Differences in the glycans and glycan profiles may have an impact on the structure, potency, PK, safety and efficacy of a product. For instance, sialylated, afucosylated and mannose-containing structures may display clinically significant variations.

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

QIII-13 How can statistical analysis support the demonstration of similarity of an SBP to the RBP in quality evaluation?

Statistical methods have a crucial role to play in interpretation of comparative clinical data, especially PK and efficacy. The role of statistics in evaluation of biosimilarity is less clear with regard to the interpretation of results of comparative physico-chemical, structural and in vitro functional tests, and requires a different approach from that applied when analysing clinical data.

Statistical methods usually deal with means. The means may change within the acceptability range. Nevertheless, in some jurisdictions it has been suggested that statistical analyses of comparability data should be conducted in order to evaluate analytical similarity. Using a descriptive statistical approach to establish ranges for quality attributes in the context of comparability is generally more widely accepted.

The establishment of similarity by statistical analysis may be influenced by the number of batches and observations, uncertainty regarding the clinical impact of an attribute and distribution of results, performance of the assays, source and age of the batch etc. In conclusion, the use of statistics in defining comparability is still at an empirical stage in most jurisdictions.

It is important to realize, however, that statistical tools, while helpful in supporting conclusions about similarity, should not be used as the sole basis for decision-making on biosimilarity for marketing authorization approval which should be based on evaluation of the whole data package for each of the quality, nonclinical and clinical parameters.

IV. Nonclinical evaluation:

QIV-1 Which general factors should be considered for the planning/conduct of the nonclinical studies for an SBP?

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

Initially, significant emphasis was put on in vivo comparative nonclinical studies and the original WHO *Guidelines on evaluation of similar biotherapeutic products (SBPs)* required at least a head-to-head repeat-dose toxicity study. WHO's newer *Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)* promote a stepwise nonclinical development starting from demonstration of the physico-chemical and in vitro functional comparability before proceeding to the analysis of remaining uncertainties. If in vivo studies are considered to be indicated, the developer should clarify the availability of relevant animal models. If the drug substance of candidate SBP shows specific pharmacological activity only in great apes, the developer should seriously weigh the need for in vivo studies to avoid pharmaco-toxicological testing in these species. A consultation with the relevant NRA is recommended.

Nonclinical in vitro studies

QIV-2 What kind of in vitro studies should be conducted for the nonclinical evaluation of an SBP?

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

Typically, receptor-binding assays and cell-based functional assays are used to compare the functions of the SBP and RBP. The developer should justify the relevance, sensitivity and discriminatory capability of the tests by submitting qualification and or validation studies using the RBP and SBP. Test results should be given in units of activity calibrated against an international or national reference standard, where available.

For instance, monoclonal antibodies have several functionally active sites. Assays are available to measure the binding affinity and activity of the monoclonal antibodies as well as cell-based functional assays for each active site. The standard assays can be tailored to better reflect the physiological or pathological conditions in a particular therapeutic indication**.** A detailed analysis of the biological activity, including Fab- and/or Fc-mediated functions, such as ability to bind to different isoforms of Fc gamma and neonatal Fc receptors and to complement C1q, should be provided whether or not they are considered essential for the therapeutic mode of action. The absence of a mode of action should be considered by the SBP developer, although this may not require an extensive analytical demonstration and may be assessed via cell-based or binding assays. The corresponding cell-based functional assays, such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) are important as they may play different roles in different therapeutic indications.

Where available, international reference standards can be used to support bioassay, characterization, calibration and performance. See also **QIII-8**.

QIV-3 Which specific factors should be observed in the planning/conduct of the nonclinical in vitro studies?

It is important to understand what is known about the mechanism of action of the molecule for the selection of the relevant tests for the biological activity. The quality comparability studies may reveal differences that may have an impact on clinical performance, such as PK or efficacy. The nonclinical in vitro studies should be sensitive, specific and sufficiently discriminatory to show any potential differences which, according to current scientific knowledge, could be of potential clinical relevance. Some assays used in the quality assessment may be utilized to inform nonclinical studies. In these cases, the clinical relevance of these assays should be justified. Since in vitro assays may often be more specific and sensitive for detecting differences between SBP and RBP than studies in animals, such assays can be considered paramount for the nonclinical biosimilar comparability exercise.

<u>Nonclinical in vivo studies</u>

QIV-4 Which factors should be considered when deciding whether in vivo animal studies are required for nonclinical evaluation of a specific SBP?

On the basis of the totality of available quality and nonclinical in vitro data and the extent of residual uncertainty about the similarity of SBP and RBP, nonclinical in vivo studies may not be required. If the quality-comparability exercise and nonclinical in vitro studies are considered satisfactory and no issues that would prevent direct entrance into humans are identified, in vivo animal studies may be considered unnecessary.

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

A number of factors reduce the need for in vivo studies in the development of an SBP:

- The risk of first-in-man use of an SBP can usually be estimated on the basis of knowledge about the clinical safety profile of the RBP and the outcome of the physico-chemical, structural and in vitro functional tests with the SBP.
- Most toxic effects of therapeutic proteins are related to an exaggeration of their known pharmacological effects.
- The functional activity of a biotherapeutic drug substance is often species-specific, making it difficult to identify a suitable animal species.
- Human drug substances are often immunogenic in conventional animal models due to species-specificity, which prevents or hampers the interpretation of repeat-dose animal studies
- Conventional animal models are often not sensitive enough to detect small differences.

QIV-5 Which specific factors should be considered in the planning/conduct of in vivo animal studies on pharmacodynamics and/or pharmacokinetics of an SBP?

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

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

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

In vivo assays, if warranted (see **QIV-4**), may include the use of animal models of disease to evaluate functional effects on PD markers or efficacy measures. PK measurements may need to be performed in parallel in order to interpret the study results.

QIV-6 Which specific factors should be considered in the planning/conduct of in vivo animal toxicity studies for an SBP?

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

If a toxicity study is considered, the suitability of conventional toxicology models needs to be evaluated. In vivo toxicological studies should be conducted only in an animal species in which the SBP is pharmacologically active. However, many biological products may not be pharmacologically/toxicologically active in the species used in conventional toxicology tests. In addition, human proteins are often immunogenic in other species, thus restricting the duration of toxicology studies and hampering the interpretation of study results. Also, the discriminatory ability of the in vivo model in a reasonably-sized study, especially in multiple dose studies, should be evaluated realistically.

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

Local tolerance may be evaluated in the context of a repeat-dose toxicity study, if one is performed. Safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies are not needed.

QIV-7 Where no suitable animal model is available, how can the nonclinical comparability exercise be extended?

First, the developer needs to consider whether in vivo nonclinical studies are necessary (see **QIV-4**). If the risk analysis based on data from the physico-chemical, structural and in vitro functional comparability studies raises concerns about the transition to clinical studies, the developer may consider the following options:

- optimization of the manufacturing process to remove factors that raise concerns (e.g. reduction of impurities or modification of the formulation);
- performance of additional tailored quality or nonclinical studies designed to reduce residual uncertainty;
- application of specific risk mitigation measures upon entry to clinical studies.

QIV-8 Under what circumstances/conditions would additional in vivo nonclinical comparability studies be required?

In vivo nonclinical studies should be considered if there is one or more of the following:

- a significant functional difference suggested by nonclinical in vitro studies;
- a novel excipient in the formulation of the SBP which may justify a more thorough nonclinical programme to assure the safety of the excipient in its intended route of administration;
- a new expression system or purification process in the manufacturing process, leading to a significant change in the process-related impurities;
- a narrow therapeutic window for the drug substance.

Although these factors may not necessarily always warrant in vivo testing, the factors should be considered when assessing the level of concern and when determining whether there is a need for in vivo testing.

V. Clinical evaluation:

QV-1 What is the role of clinical evaluation in SBP development?

The purpose of the clinical comparability programme for an SBP is to confirm similarity to the RBP rather than independently to establish its own efficacy and safety profile. An SBP relies on safety/efficacy data and knowledge gained from the RBP. The SBP clinical study programme should be designed with the use of sensitive models (e.g. disease indications/populations) to detect clinically meaningful differences. Clinical trials aim to resolve uncertainties regarding the similarity of the candidate SBP with the RBP.

QV-2 What is immunogenicity and which factors should be considered in terms of immunogenicity for an SBP?

The purpose of the immune system is to recognize and eliminate foreign substances and denatured structures of the body itself. Immunogenicity of a therapeutic protein means that the immune system is capable of recognizing the protein as non-self and is able to generate an immune response against it. Unfortunately, this immune response can sometimes recognize therapeutic proteins as foreign invaders and react against them. This reaction may abolish the therapeutic effect and cause hypersensitivity and autoimmune reactions.

The human immune system has evolved to recognize proteins, including therapeutic proteins. If a protein is deemed foreign, non-self, the immune system will mount an immune response against the protein. If the protein is classified as a normal body constituent – i.e. “self” – no reaction is triggered. Thus, there is an immunological tolerance to the protein. The immunological tolerance varies between individuals as it is partly genetically determined.

An immune response to a therapeutic protein is usually detected by measuring anti-drug antibodies (ADAs). An ADA response may be transient and may not have any clinical consequences. However, ADAs may neutralize the effect of a biotherapeutic product and lead to a loss of efficacy. Safety problems may arise if the ADA-response continues to evolve by immunoglobulin class switch, antibody affinity maturation and epitope-spreading. Life-threatening hypersensitive reactions may occur if the ADAs undergo a class switch to IgE or if pathogenetic immune complexes (therapeutic protein + ADA) are formed. Another type of a serious reaction is possible if the therapeutic protein has an endogenous counterpart. In this situation, ADAs may cross-react with the endogenous protein and cause serious complications, as noted in the case of anti-erythropoietin antibodies which cause pure red cell aplasia.

According to WHO guidelines, all new therapeutic proteins, including SBPs and RBPs, should be tested for ADAs in clinical trials. The additional challenge for SBPs is the need to demonstrate comparable immunogenicity to the RBP. This is done first at the quality level by demonstrating that the amino acid sequence, and therefore the backbone epitopes, is identical between SBP and RBP. In addition, potential immunogenic impurities (e.g. aggregates, non-human glycans, host-cell proteins) need to be controlled at sufficiently low amounts. For final confirmation, an SBP is always compared head-to-head to its RBP in pre-marketing clinical trials to demonstrate comparable PK, immunogenicity, efficacy and immune-mediated adverse effects. The scope and extent of comparative immunogenicity evaluations should take into account prior knowledge concerning immunogenicity of the RBP, the route of administration, and product- and patient-specific factors. An SBP cannot have more immune-mediated adverse effects than its RBP. An RBP may have several therapeutic indications but an SBP is tested usually only on one of them. Therefore, it is important to study a therapeutic indication and patient population that provides a sensitive model for detecting differences in immunogenicity. To date, no SBP has caused more adverse immune reactions than its RBP, so long as it was developed according to WHO and other corresponding guidelines and assessed by regulatory agencies with the necessary scientific expertise and experience.

QV-3 What duration of immunogenicity is required in the clinical studies?

The immune response to a biotherapeutic product evolves over time. Immunogenicity studies aim to characterize the immune response for the incidence, titre, neutralizing activity and persistence of ADAs. Sampling for ADAs in the comparative clinical PD, efficacy and safety studies is important for investigating the relative clinical impact of a potential immune response.

The duration on pre-licensing immunogenicity studies depends on the duration of treatment and the nature of the observed immune response and should be justified. In chronic treatment, the minimum follow-up of immunogenicity is 6 months. A longer follow-up is often necessary to determine the persistence and clinical impact of the immune response. This is also important for biosimilars in order to demonstrate a comparable evolution of the immune responses to SBP and RBP.

QV-4 How are differences in immunogenicity handled?

The purpose of immunological studies is to detect harmful immunogenicity in the clinically relevant population. The first step is to compare the incidence, titre, persistence over time and neutralizing capacity of the induced ADAs. Secondly, the possible clinical correlations should be investigated. Differences in efficacy and safety arising from differences in immunogenicity are not tolerated.

The ADA assays should preferably be capable of detecting antibodies against both the biosimilar and the reference molecule but should at least be able to detect all antibodies developed against the biosimilar molecule.

The root cause of a difference in immunogenicity should always be investigated, even if the SBP appears to be less immunogenic. First of all, the ADA assay should be re-evaluated for possible bias. The most common problem in the ADA assays is drug interference in which the residual product in the blood sample for ADA analysis causes false negative results.

Therefore, the drug tolerance of the assay(s) should be revisited and the drug concentrations in the samples compared.

If no technical problem is discovered, the manufacturer should review all differences observed in the analytical, structural and functional comparisons and discuss their possible role in immunogenicity.

If differences in ADA incidences or titres, including neutralizing ADAs, are observed, the persistence of the ADA responses and possible clinical correlations should be explored by comparing PK, recording relevant symptom complexes such as hypersensitivity or autoimmunity, and comparing cumulative drug doses of the SBP and RBP in relevant clinical studies.

If the SBP is indeed less immunogenic on the basis of ADA-assays, the manufacturer should ensure that there is no impact on exposure. If exposure is increased as a result of reduced immunogenicity, the manufacturer should discuss the safety implications of the increased exposure.

The burden of evidence is on the manufacturer of the SBP who must convince regulators of the lack of clinical impact of a difference in immunogenicity. If no harmful effects are observed, the manufacturer may have to commit to post-marketing studies to exclude potential rare immunological complications of the SBP and to ensure a positive benefit–risk balance.

QV-5 If the RBP shows a higher rate of anti-drug antibodies than the historical data, what would be the data requirement for the SBP?

It is not uncommon for the incidence of ADAs to be lower in older studies of the RBPs than in newer ones. This can be explained by the higher sensitivity of current ADA assays. For this reason, head-to-head comparisons using validated state-of-the-art assays are the only way to demonstrate comparable immunogenicity. Deviations from this rule may be allowable in low-risk situations after consultation with local competent authorities on a case-by-case basis.

QV-6 If the comparability study of efficacy is waived, is a separate immunogenicity study required or could immunogenicity assessment be conducted in a comparative PK/PD study?

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

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

If other kinds of PD studies are conducted, additional specific immunogenicity studies may be needed pre- or post-marketing unless the product is expected to have a low risk of immunogenicity. A consultation with the local regulatory authorities is warranted (see **QV-12**).

QV-7 How can SBPs be approved for indications for which no clinical studies have been conducted?

The aim of the biosimilar comparability studies is to demonstrate a high similarity between the SBP and RBP. If this is achieved, it can be expected that the function of the products is also similar. Additional studies are needed if the therapeutic indication that was investigated in the clinical comparability study is not representative of other requested therapeutic indications in terms of safety and efficacy (see **QV-8**).

QV-8 What are the most important "points to consider" in extrapolating clinical data showing biosimilarity in one indication to other licensed indications of the RBP?

Clinical studies of an SBP are part of the overall comparability exercise. The ability to extrapolate is based on the totality of evidence (see **QI-2**). If a close similarity has been demonstrated, extrapolation is possible. Nevertheless, as described in WHO's *Guidelines on evaluation of similar biotherapeutic products (SBPs)* and *Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)*, a scientific justification should be presented with consideration of the following points:

- **What is the sensitivity of the studied clinical model (therapeutic indication and patient population) in detecting differences?**
  This means that the therapeutic effect should be significant and consistent across the clinical trials and that there are sensitive clinical endpoints for comparing the outcomes.

- **Are the same receptors or binding sites involved in the effects of the drug substance in all therapeutic indications claimed for the SBP?**
  Extrapolation may be straightforward if the same receptors or active sites are involved in the therapeutic indications (e.g. epoetin alfa).
  For monoclonal antibodies, extrapolation is more complicated since there are several receptors/functional sites that can mediate or modify therapeutic effects and the relative importance of individual receptors/active sites may vary between the approved therapeutic indications of the RBP. Therefore, the binding and function of the relevant receptors/functional sites should be examined. In some cases, functional tests need to be modified by using different target and effector cells to better simulate the pathology of the target disease. Additional PD or clinical efficacy and safety studies may be considered although they may not be as sensitive as in vitro functional tests.

- **Are there specific concerns in the therapeutic indications that were not investigated or cannot be addressed by data obtained from the clinical trial(s)?** Immunogenicity may vary between therapeutic indications as a result of differences in the state of the immune system. Another concern is extrapolation from one disease group to another (e.g. from autoimmune disease to cancer) where the PK and posology may be different. In these cases, additional PK/PD or clinical trials may be needed to address the residual uncertainty. Potential rare adverse effects should also be monitored post-marketing.

QV-9 After an SBP has been approved, can a new indication added to the RBP be shared with the SBP?

In principle, a new therapeutic indication added to the RBP may be shared with the SBP. However, an appropriate scientific justification should be provided along the same principles as extrapolation before approval of the SBP.

QV-10 Why are different regulatory decisions on extrapolation reached by different national regulatory authorities when using the same regulatory data package?

There may be some differences in the marketing authorization conditions granted by different regulatory authorities. In addition, it is not usually known whether the same data to support extrapolation was submitted to different authorities, especially when the submissions took place at different times. The regulatory history of the RBP, including manufacturing changes and labelled therapeutic indication as well as local guidelines and regulatory policies, may also vary in different jurisdictions. Moreover, some regulatory bodies may have a lot of experience with extrapolation whereas some regulators have only recently been exposed to it. In some areas, SBPs, including extrapolation, have been controversial among stakeholders. Additionally, the estimation of benefit–risk balance involves values and uncertainties that may be judged differently.

However, differences in the initial regulatory decisions on extrapolation are expected to diminish over time as when more post-marketing safety data and new clinical data become available. For instance, there were initially differences between regulatory bodies concerning the extrapolation of efficacy and safety of the first infliximab SBP from rheumatic diseases to inflammatory bowel diseases. Nevertheless, within a few years all major regulatory bodies reached the same conclusion on the basis of increased experience.

QV-11 How should inexperienced NRAs deal with differing regulatory decisions of major experienced NRAs?

In general, the major experienced regulatory bodies have reached similar conclusions and decisions on SBPs. However, national legislations may introduce some differences in the regulatory approach. For instance, legislation in the USA provides additional approval criteria for interchangeable SBPs whereas European legislation prohibits the European Medicines Agency from taking a position on interchangeability. The same is true in Canada where interchangeability decisions are in the hands of the provincial health authorities. Consequently, it is important to understand the background to regulatory decisions.

Differences in judgement/interpretation of scientific data exist across regulatory agencies (see **QV-10**). In such cases, in order to understand the reasons for the different interpretations, it is helpful to read publicly available assessment reports of regulatory agencies that have reached different conclusions. In addition, it may be useful to review post-marketing data on safety and efficacy from the NRA that made the positive decision.

QV-12 Is there always a need to conduct a clinical study for an SBP?

As noted in WHO's *Guidelines on evaluation of similar biotherapeutic products (SBPs)*, the demonstration of comparability of an SBP to its RBP in terms of quality is a prerequisite for the reduction of the nonclinical and clinical data set required for licensure. Thus, the WHO guidelines mention the reduction but not the complete omission of clinical data.

The complexity of biotherapeutic products varies enormously from simple linear peptides to large macromolecules with secondary, tertiary and quaternary structures and extensive post-translational modifications. The analytical methodology has developed rapidly during the era of SBPs. As a result, even complex biotechnology-derived products such as monoclonal antibodies can be characterized to a degree that may allow an abbreviated clinical development (see WHO's *Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)*).

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

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

In conclusion, some pre-licensing clinical data are always required for an SBP but the clinical development can be abbreviated, as outlined by the WHO guidelines for SBPs.

VI. Pharmacovigilance:

QVI-1 Will SBPs be as safe as originator products?

Yes, if they are developed according to WHO's and other corresponding guidelines and assessed by regulatory agencies that have the necessary scientific expertise and experience. For example, it is estimated that approximately 700 000 000 doses of SBPs authorized in the EU had been administered by 2016. In spite of the large exposure, no SBPs have been withdrawn for safety reasons and no new adverse effects have been reported that have not been reported for the reference products as well. The equal safety of the SBP and its RBP is based on the physico-chemical and structural similarity that is demonstrated by the extensive comparability exercise comprising analytical, structural and functional tests, as well as clinical data. Depending on the nature of the SBP, more or less extensive clinical testing with efficacy and safety data may be necessary in addition to PK data. The safety of SBPs is monitored by pharmacovigilance systems and often by additional post-marketing risk detection and minimization measures.

QVI-2 After an SBP has been approved, is the SBP required to show the maintenance of biosimilarity with its RBP?

No. Following approval, many NRAs consider that an SBP has its own life cycle and there is no formal requirement to re-establish similarity to the reference product when comparability exercises are conducted upon manufacturing changes (see WHO's *Guidelines on procedures and data requirements changes to approved biotherapeutic products*). Every significant change in the manufacturing process of biotherapeutic products must be supported by a comparability exercise comparing the pre- and post-change versions of the product to demonstrate that the safety and efficacy have not been altered.

The manufacturers of both SBP and RBP are responsible for ensuring that their products remain safe and efficacious throughout their life cycle by preventing significant changes to the product. Experience from hundreds of manufacturing changes introduced for RBPs over several decades demonstrates that significant changes to individual products over time are very rare. At this point in time, there are no data to suggest that an SBP lost its similarity to the RBP following manufacturing changes. However, when new safety information is added in the product information of the RBP after the original approval of the SBP, labelling information of the SBP should follow the changes made in the RBP unless it can be demonstrated that the new information on the RBP is not relevant to the SBP. In that context, it is important to emphasize that these data could be obtained only by having robust pharmacovigilance systems in place, including unique product identification that allows the collection of product-specific data.

QVI-3 Would it be beneficial to review/discuss post-marketing commitments from each NRA after extrapolation of indications?

Yes. It is always appropriate to discuss post-marketing commitments prior to initial approval. NRAs may ask for specific risk detection measures to address possible safety concerns in the "extrapolated therapeutic indications" after licensure. Risk detection measures may range from the monitoring of specific adverse events to patient registries and specific clinical trials. Risk minimization measures may include strengthening of product labelling to highlight new safety information or the provision of educational materials for health-care providers and/or patients. These measures are determined by each NRA and may differ across different jurisdictions. Where possible, it would be beneficial to harmonize the post-marketing commitments of NRAs to allow for pooling data to facilitate safety signal detection.

QVI-4 If safety information on the RBP (i.e. as the result of adverse events) is amended, how would it be applied to SBPs that are already approved?

This is a national regulatory decision. In principle, new safety information should be added to SBP in view of the fact that the approval of an SBP is based on comparable safety and efficacy of SBP and RBP. The manufacturer of the SBP should submit a variation to update its safety information to the relevant regulatory agencies unless it can be demonstrated that the new information on the RBP is not relevant to the SBP.

QVI-5 Can the SBP marketing authorization holder seek approval for a new indication, dosage form or route of administration that is different from the RBP?

In principle yes, if the marketing authorization holder submits relevant data to support the application. The requirements may follow the data requirements applicable to a stand-alone application – such as the efficacy, safety and immunogenicity profile of the SBP in the new indication or at the new dosage and route of administration that have not previously been established. This depends, however, on the regulations of the specific NRA. The manufacturer of the SBP should consult the local NRA when planning studies for the new indication, dosage form or route of administration.

QVI-6 Should cautions for the use of an SBP be the same as those for the licensed RBP?

Yes. In general, the product information (PI) of the SBP should be in line with the PI of the RBP except for product-specific differences. For reasons of public health (e.g. possible off-label use), cautions for use of all therapeutic indications for the RBP should be included in the PI of the SBP even when the cautions are related to a therapeutic indication that was not applied for.

Authors and acknowledgements

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The document **WHO/BS/2018.2352** is now being posted on the WHO Biologicals website for a second round of public consultation from xx July to 20 September 2018.

Other recommended reading

1. Guidelines on evaluation of similar biotherapeutic products (SBPs). In: WHO Expert Committee on Biological Standardization: sixtieth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 977; http://www.who.int/biologicals/expert_committee/TRS_977_60th_report.pdf?ua=1, accessed 19 July 2018).

2. Regulatory assessment of approved rDNA-derived biotherapeutics. In: WHO Expert Committee on Biological Standardization: sixty-sixth report. Geneva: World Health Organization; 2016: Annex 3 (WHO Technical Report Series, No. 999; http://www.who.int/biologicals/areas/biological_therapeutics/Annex_3_Regulatory_assessment_of_approved_rDNA-derived_biotherapeutics.pdf?ua=1, accessed 19 July 2018).

3. Resolution WHA67.21. Access to biotherapeutic products including similar biotherapeutics products and ensuring their quality, safety and efficacy. Sixty-seventh World Health Assembly, Geneva, 18–26 May 2014. Geneva: World Health Organization; 2014 (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R21-en.pdf, accessed 19 July 2018).

4. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs). In: WHO Expert Committee on Biological Standardization: sixty-seventh report. Geneva: World Health Organization; 2017: Annex 2 (WHO Technical Report Series, No. 1004; http://who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1, accessed 19 July 2018).

5. Guidelines on procedures and data requirements for changes to approved biotherapeutic products. Adopted by the sixty-eighth WHO Expert Committee on Biological Standardization; 2017 (http://who.int/biologicals/expert_committee/PAC_highlighted_20_Oct_2017.HK.IK.pdf?ua=1, accessed 19 July 2018).

6. Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology. In: WHO Expert Committee on Biological Standardization: sixty-fourth report. Geneva: World Health Organization; 2014: Annex 4 (WHO Technical Report Series, No. 987; http://who.int/biologicals/biotherapeutics/TRS_987_Annex4.pdf?ua=1, accessed 19 July 2018).

7. Quality of biotechnological products. Stability testing of biotechnological/biological products. ICH Guideline Q5C. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 1995.

8. Abbreviated licensing pathways for biological therapeutic products. In: WHO Expert Committee on Biological Standardization: fifty-ninth report. Geneva: World Health Organization; 2012 (WHO Technical Report Series, No. 964:14–15; http://www.who.int/biologicals/WHO_TRS_964_web.pdf?ua=1, accessed 19 July 2018).

9. Vaccines and biotherapeutics: recent and planned activities in biological standardization. In: WHO Expert Committee on Biological Standardization: sixty-sixth

report. Geneva: World Health Organization; 2016 (WHO Technical Report Series, No. 999:7–8 http://www.who.int/biologicals/expert_committee/WHO_TRS_999_corrigenda_web.pdf?ua=1, accessed 17 May 2018).

10. Report on the expert consultation on improving access to and use of similar biotherapeutic products, Geneva, Switzerland, 2–3 May 2017. Geneva: World Health Organization; 2017 (http://www.who.int/medicines/access/biotherapeutics/FINAL_Report-improving-access-to-and-use-of-biotherapeutics_October2017.pdf , accessed 19 July 2018).

11. IPRF Biosimilars Working Group. Reflection paper on extrapolation of indications in authorization of biosimilar products. International Pharmaceutical Regulators Forum; 2017 (https://www.i-p-r-f.org/files/6715/1012/3262/Final_BWG_Reflection_paper_Biosimilar__Extrapolation_Final_clean_version_17.9.25.pdf, accessed 10 May 2018).

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