WHO Questions and Answers: similar biotherapeutic products

Complementary document to the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs)\(^1\)

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<tr>
<td>ADA</td>
<td>anti-drug antibody</td>
</tr>
<tr>
<td>ADCC</td>
<td>antibody-dependent cellular cytotoxicity</td>
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<tr>
<td>ADCP</td>
<td>antibody-dependent cellular phagocytosis</td>
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<tr>
<td>CDC</td>
<td>complement-dependent cytotoxicity</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>ECBS</td>
<td>Expert Committee on Biological Standardization</td>
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<tr>
<td>Ig</td>
<td>immunoglobulin</td>
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<tr>
<td>IU</td>
<td>International Unit(s)</td>
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<tr>
<td>NRA</td>
<td>national regulatory authority</td>
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<tr>
<td>PD</td>
<td>pharmacodynamics</td>
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<tr>
<td>PK</td>
<td>pharmacokinetics</td>
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<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
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<tr>
<td>Q&amp;A</td>
<td>questions and answers</td>
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<tr>
<td>RBP</td>
<td>reference biotherapeutic product</td>
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<tr>
<td>SBP</td>
<td>similar biotherapeutic product</td>
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<td>U</td>
<td>Unit(s)</td>
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Background

The WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) were adopted by the WHO Expert Committee on Biological Standardization (ECBS) in 2009, and 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 improving access to biotherapeutic products and ensuring their quality, safety and efficacy. One of the requests made to the Director-General of WHO was to convene 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 convened a series of meetings to identify those parts of the Guidelines which required updating. In April 2015, an informal consultation was organized during which participants from NRAs of both developing and developed countries, as well as from industry, recognized and agreed that the evaluation principles described in the Guidelines were still valid, valuable and applicable in facilitating the harmonization of SBP regulatory requirements globally. It was therefore concluded that there was no need to revise the main body of the existing Guidelines. However, it was also concluded that there was a need for additional guidance on the evaluation of monoclonal antibody products as SBPs. Such guidance was subsequently developed, adopted by the ECBS and published in 2017. In May 2017, WHO held another consultation on improving access to and use of SBPs, following which it was agreed that a questions and answers (Q&A) document to be read in conjunction with the 2009 Guidelines would be an appropriate way of further clarifying and complementing some of the issues and points covered in the Guidelines.

This Q&A document has been produced for guidance only and should be read in conjunction with relevant WHO guidelines. It is intended to provide clarity concerning questions that may arise during the use of such guidelines. The questions in this document have been selected on the basis of those frequently asked by regulators during implementation workshops on the 2009 WHO Guidelines in the past nine years. The intention is to update this document periodically to reflect new developments and issues that arise. Issues relating to intellectual property, interchangeability, switching, substitution, naming, labelling and prescribing information, or to product shortages, are all outside the scope of the original WHO Guidelines and are therefore not addressed in the current document.
I. Concept of licensing similar biotherapeutic products

QI-1

What is a similar biotherapeutic product (SBP)?

According to the WHO's 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 “similar biotherapeutic product”, a variety of terms have been used to describe these products, including: “similar biological medicinal products”, “biosimilars”, “follow-on protein products” and “subsequent-entry biologics”. Since the main principles of developing SBPs are the same worldwide, other definitions of SBP are complementary to the WHO definition. For example, in the European Union, an SBP should 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. The United States Food and Drug Administration clarifies that there should be no clinically meaningful differences in the safety, purity and potency of the SBP and its RBP. However, there may be differences between the clinically inactive parts of the SBP and the RBP.

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

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

QI-2

How are SBPs evaluated for licensing?

The development and evaluation principles for SBPs are different to those for products containing new active substances, such as RBPs. An RBP is licensed on the basis of a full stand-alone registration dossier on its pharmaceutical quality, pharmacology and toxicology, as well as on its human safety and efficacy in each of its therapeutic indications.

The clinical experience and established safety profile of RBPs facilitates the development of SBPs. 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. Such high similarity allows subsequent abbreviation of nonclinical and clinical development because the regulatory approval of an SBP can then rely on the safety and efficacy data and knowledge gained during the development, licensing and clinical use of its RBP. High similarity is demonstrated 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 registration dossier 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 programmes is to confirm similarity between the SBP and the RBP and not to demonstrate the safety and efficacy of the SBP per se.
The extent of the nonclinical and clinical programmes depends on the ability to demonstrate structural and functional similarity between the SBP and its RBP. Thus, product development should be a stepwise approach in which the results of the previous tests and studies will guide the next steps. Extensive analytical comparisons are the foundation of demonstrating similarity but may not address all residual uncertainties. 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 the “totality of evidence”).

QI-3

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 physicochemical test. Regulators may use their previous experience, gained for example from evaluating changes introduced into the manufacturing processes of other products, to understand the functional and clinical impact of a particular physicochemical difference between the SBP and its RBP. The results of physicochemical tests should always be interpreted in the light of the performance of a particular analytical method and the lot-to-lot variability of the results. When available, orthogonal analytical techniques should always be used to strengthen the evaluation of comparability.

In vitro functional assays (usually cell based) may be helpful in understanding the significance of a difference detected during analytical testing. It is important to understand the factors that have an impact on the functional tests. The sensitivity of some 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 bioanalytical assay. It is also important to consider the use of other tests that may better reflect the physiological situation. Tests using cells from a specific patient population may also be helpful in the interpretation of the observed difference.

In general, in vitro functional tests are more sensitive than clinical studies in detecting differences between the SBP and RBP. The results of physicochemical and functional tests should be considered when planning the clinical comparability programme, especially pharmacokinetics (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 (that is, 90% confidence interval (CI) of ratios of SBP to RBP) of orally administered and chemically synthesized small molecules 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 the 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, may be needed. It is recommended that steady state PK should be measured in the repeat-dose safety and efficacy studies. This may mitigate concerns when PK differences are observed after a single-dose study. The equivalence design is recommended for confirmatory efficacy and safety studies. A 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 outcome should be that the difference is not clinically meaningful.

QI-4

What are the differences between SBPs and generic products?

The term “generic” is used to describe typically chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product for which the patent and/or data protection period has expired. In contrast, “SBP” refers to usually relatively large and complex molecules of biological origin which are more difficult to characterize due to the inherent heterogeneity of biological products. The abbreviated development of both generics and SBPs depends on the data and knowledge gained over time about their reference products.

The demonstration of structural sameness and bioequivalence of a generic medicine to the reference product is often sufficient for its licensing. However, the data requirements for licensing generic medicines are not scientifically appropriate for licensing an SBP – which requires much more extensive studies. Additional analytical and functional studies – as well as nonclinical and clinical studies – are needed to demonstrate similarity between an SBP and the RBP (see also QI-2). 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 cannot be shown to be identical, and the regulatory approach established for generic medicines is not suitable for licensing SBPs.

In some countries, for various reasons, biotherapeutic products were licensed as generics using data that do not 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 NRAs, as described in the WHO guidance document on Regulatory assessment of approved rDNA-derived biotherapeutics.

QI-5

Which products can be approved as SBPs?

SBPs should be developed and evaluated according to the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) and/or relevant national guidelines. The RBP should have been licensed on the basis of full stand-alone data on its quality, safety and efficacy in accordance with the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology.

The development of an SBP to a licensed original biotherapeutic product (that is, 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. In line with a 2008 recommendation made by the WHO ECBS, vaccines, plasma-derived products and their recombinant analogues are beyond the scope of the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs). 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) mentioned in the concept for licensing SBPs?

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 the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology on the basis of a full stand-alone registration dossier can serve as an RBP. Analytical characterization of the RBP is used to understand its lot-to-lot variability over its shelf-life, and to define the target quality profile of the SBP. The term does not refer to measurement standards such as international, pharmacopoeial or national standards or reference standards.

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

The main criteria for the selection of an RBP are provided in the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs). The RBP should have been approved on the basis of a full stand-alone registration dossier, including clinical studies in each therapeutic indication. It should be fully identifiable (for example, brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, numbers of lots and age of lots relative to their expiry dates). The RBP should have been marketed for a suitable duration and should have a history of marketed use in a jurisdiction with a well-established regulatory framework and principles, and with considerable experience in the evaluation of biotherapeutic products and post-marketing surveillance activities.

In general, NRAs require the use of a domestically licensed RBP for the evaluation of the SBP. However, an RBP that is licensed and marketed in another jurisdiction may also be used. In this case, the NRA may set additional criteria for the selection of the RBP licensed and sourced in another country. The RBP should be licensed with a full stand-alone dossier according to the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, or corresponding guidelines. Market experience of the RBP should also be available based on 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 domestically and the same RBP should be used in all comparability studies of a given SBP. The circumstances under which such a scenario would be acceptable are described in QII-4.

QII-3
Can an SBP be approved when compared with an RBP which is not approved or available on the domestic market?

Yes, as long as it is justified. The manufacturer should take advice from the relevant NRA. It is important to note that the acceptance of an RBP for the evaluation of an SBP in a particular country does not imply that the NRA of that country has approved the RBP for use on the domestic market.
QII-4
Under what circumstances would it be acceptable to use an RBP sourced from another country?

Many NRAs expect that the analytical and in vitro functional comparability of the SBP and its RBP will be demonstrated using the domestically licensed and sourced product. This is because the jurisdiction concerned will already be familiar with the product and its use. Nevertheless, when the manufacturer plans the global development of an SBP, and to avoid unnecessary repetition of nonclinical and clinical studies already undertaken with an RBP licensed and sourced in another country, the use of a domestically licensed RBP for the quality studies and a foreign-sourced RBP in nonclinical and clinical comparability studies may be possible, if justified. For example, the manufacturer may demonstrate that the domestically licensed RBP and the foreign-sourced RBP are versions of the same RBP, licensed on the basis of the same development data, including the same clinical data set. In some jurisdictions, comparability studies (such as analytical or even clinical PK studies) are required to support the use of a foreign-sourced product in this way.

In cases where there is no domestically 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-5
The 2009 WHO Guidelines state that “the same RBP should be used throughout the entire comparability exercise”. Can an RBP from different manufacturing sites be used?

Yes. Production lots from different manufacturing sites can be used provided that products from all manufacturing sites are approved by the relevant regulatory authority.
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 (that is, 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 comparable higher-order structure and post-translational modifications. It is recommended that where possible SBP manufacturers use an expression system similar to that of the RBP since the cell type used influences the pattern of post-translational modifications such as glycosylation. Any differences between the RBP and SBP in the levels and types of post-translational modifications need to be justified considering their potential 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 should develop their own master and working 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 regulators would typically ask for more clinical immunogenicity data.

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

The aim of the comparability exercise is to demonstrate that the SBP is similar to the RBP chosen by the manufacturer. Differences in formulation are acceptable as long as they do not impact on the quality, safety and efficacy of the SBP and where the SBP and RBP can be demonstrated to be comparable. In addition, the manufacturer should justify any potential differences between the formulations of the SBP and the RBP. A new formulation will have to be developed when the formulation of the RBP is patented. In general, the formulation used should be state-of-the-art with regard to stability, compatibility, integrity and impact on the activity and strength of the active substance.

It is important to demonstrate a 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 for any material that is in contact with the medicinal product.

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 also demonstrate that the product remains stable during long-term storage when stored in the chosen container closure system.

Thus it is possible, for example, to use a different delivery device (such as a pre-filled syringe or autoinjector) for the SBP even if the RBP is only provided in 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 or strength of drug substance as the RBP. Deviation from the RBP as regards strength is possible if justified, but the posology and route of administration of the SBP should be the same as those of the RBP. The concentration or strength of the SBP should be expressed using the same measurement system as the RBP (that is, 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, the specifications of the RBP and SBP are likely to be somewhat different because of different manufacturing processes, product-attribute understanding and analytical methods. Thus, the specifications of the RBP reflect the experience with the manufacturer’s own product. The specifications of the SBP should be based on the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology.

It should be noted that pharmacopoeial monographs provide only minimal requirements (see also QIII-7). It is expected that the specifications of an SBP do not allow significantly wider lot-to-lot variation than found for the RBP during the quality comparability exercise.

QIII-6
How many batches (lots) should be analysed in the comprehensive comparability studies?
The analysis of multiple lots of the RBP by the SBP manufacturer is necessary for developing an optimal manufacturing process for a candidate SBP. For this purpose, the SBP manufacturer needs to collect a representative set of lots of the RBP over an extended time period to justify comparability ranges for critical quality attributes. The relevance of the ranges should be considered, taking into account the number of RBP lots tested, the quality attributes investigated, the evolution of quality attributes over time, and the test method used. The ages of the different RBP lots (relative to the expiry dates) should also be considered when establishing the target quality profile.

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

Where several product strengths or presentations are available, their selection for comparability studies 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 should show the same level of compliance with a pharmacopoeial monograph as the RBP. However, since pharmacopoeial monographs provide only minimal requirements, compliance with pharmacopoeial monographs will not be sufficient to demonstrate biosimilarity.

QIII-8
What is the role of reference standards in the evaluation of SBPs?
WHO provides International Standards and International Reference Reagents which serve as primary reference standards of defined biological activity expressed in International Units (IU) or Units (U).2 They are used either to calibrate assays directly or to calibrate secondary standards (for example, pharmacopoeial and national reference standards) or manufacturers’ working standards. These reference standards cannot be used instead of the RBP for the demonstration of biosimilarity.
When available, manufacturers can use international/pharmacopoeial reference standards for the qualification and standardization of tests used to characterize and quantify RBPs and SBPs. For example, potency (expressed, for example, in IU or U) is the quantitative measure of biological activity based on an attribute of the product. The potency of each lot of the drug substance and the final dosage form of the SBP should be established by using, wherever possible, an appropriate national or international reference preparation which is normally calibrated in units of biological activity such as IU. In the absence of such preparations and in cases where the RBP is labelled in U but not IU, an approved in-house reference preparation needs to be used for assigning the potency of the SBP.
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.

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 the WHO 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.

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QIII-10

Are comparability studies in accelerated and stress stability needed?

Stability testing of SBPs should comply with the relevant guidelines, namely the WHO 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 storage conditions and 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. The results of such 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 stability testing of the SBP and RBP does not provide added value.

QIII-11

How comprehensive should the evaluation of glycan structure (that is, level of detail) 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 the production of different glycoforms despite the same glycosylation machinery. This glycoform pattern may to some extent vary from lot to lot. In addition, production cells from different species may produce qualitatively different glycans that should be identified and justified, especially if such a 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 of the glycoform pattern of the RBP and the functional role of different glycoforms. Knowledge regarding variations in the glycoform pattern between lots of the RBP will help in the 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 example, 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 demonstrating the comparability of an SBP and its RBP. Glycans are rarely immunogenic – however, glycans
that are not normally present in humans may be immunogenic. For example, Galactose-
alpha-1,3-galactose (alpha-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-12**

**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 the interpretation of comparative clinical
data, especially PK and efficacy data. The role of statistics in evaluating biosimilarity is less
clear with regard to the interpretation of the results of comparative physicochemical,
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. The use of a descriptive statistical approach to establish ranges for
quality attributes in the context of comparability is widely accepted.

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

It is important to realize therefore that statistical tools, while helpful in supporting
conclusions about similarity, should not be used as the sole basis for decision-making on
biosimilarity for the purpose of marketing authorization approval. Such approval should
instead 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 in planning and conducting 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. The more recent WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) promote a stepwise nonclinical development procedure starting from the demonstration of physicochemical 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 a candidate SBP shows specific pharmacological activity only in great apes, the developer should carefully weigh up the need for in vivo studies to avoid pharmaco-toxicological testing in these species. Consultation with the relevant NRA is recommended.

Nonclinical in vitro studies

QIV-2
What kind of in vitro studies should be conducted in 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 evaluate to what extent the in vitro assays used are representative and or 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 example, monoclonal antibodies have several functionally active sites. Assays are available to measure the binding affinity and activity of the monoclonal antibodies, along with 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 each 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 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 these functions 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 considered when planning and conducting the nonclinical in vitro studies?

It is important to understand what is known about the mechanism of action of the molecule when selecting the relevant tests for biological activity. The quality comparability studies may reveal differences that might 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 that could, according to current scientific knowledge, be of 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 the SBP and its RBP than studies in animals, such assays can be considered to be of paramount importance for the nonclinical comparability exercise.

Nonclinical in vivo studies

QIV-4
Which factors should be considered when deciding whether in vivo animal studies are required for the 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 the 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 are identified that would prevent direct entrance into humans then in vivo animal studies may be considered unnecessary.

In some jurisdictions, legislation requires the application of the 3Rs principles (Replacement, Reduction and Refinement of animal experiments) during product development in order to reduce animal suffering. 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 physicochemical, structural and in vitro functional tests have demonstrated their similarity.

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 of the clinical safety profile of the RBP and the outcome of the physicochemical, 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 relevant 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 when planning and conducting in vivo animal studies on the PD and/or PK of an SBP?

Nonclinical PK studies with the SBP, if warranted, should be justified on the basis of RBP data and the potential interference of anti-drug antibodies (ADAs) in the interpretation of such a study.

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 whether 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 generally have little added value.

The 2009 WHO Guidelines indicate that, if an in vivo PK/PD study is conducted, the PK and/or PD of the SBP and 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 also 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 when planning and conducting 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 using receptor-binding assays and in vitro nonclinical functional tests, including cell-based assays. Therefore, with regard to the conducting of toxicological studies, the developer should focus on other types of adverse effects known to occur following treatment with the RBP and on adverse effects that could potentially be caused by differences observed between the SBP and RBP 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 toxicity 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 (for example, in accordance with the 3Rs principles). The conducting of repeat-dose toxicity studies in non-human primates is usually not recommended (see also 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 euthanase 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 also QIV-4). If the risk analysis based on data from the physicochemical, 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 (for example, 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;
- an excipient used 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 process-related impurities;
- a narrow therapeutic window for the drug substance.

Although these factors may not necessarily always warrant in vivo testing they 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 its similarity to the RBP rather than to independently 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 using sensitive models (for example, disease indications/populations) to detect clinically meaningful differences.

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

The purpose of the immune system is to recognize and eliminate foreign substances and denatured structures of the body itself. Immunogenicity in relation to a therapeutic protein means that the immune system is capable of recognizing the protein as foreign (“non-self”) and is able to generate an immune response against it. Unfortunately, this immune response may abolish the therapeutic effect and cause hypersensitivity and autoimmune reactions. If the protein is considered by the immune system to be a normal body constituent (“self”) then no such reactions are triggered. Thus, there is an immunological tolerance to the protein. This immunological tolerance varies between individuals as it is partly genetically determined.

An immune response to a therapeutic protein is usually detected by measuring 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 immunoglobin (Ig) 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 pathogenic immune complexes (therapeutic protein + ADA) are formed. Another type of 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 therapeutic proteins (including SBPs and RBPs) should be tested for ADAs in clinical trials. The additional challenge for SBPs is the need to investigate immunogenicity relative 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 (for example, small subvisible and visible aggregates, non-human glycans and host-cell proteins) need to be controlled at sufficiently low levels. For final confirmation, SBP immunogenicity is always compared head to head with its RBP in pre-marketing clinical trials. The scope and extent of comparative immunogenicity evaluations should take into account prior knowledge concerning the 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 usually tested on only 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 developed according to WHO and other corresponding guidelines and assessed by regulatory
agencies with the necessary scientific expertise and experience has caused more adverse immune reactions than its RBP.

**QV-3**

What is the required duration of immunogenicity studies?

The immune response to a biotherapeutic product evolves over time. Immunogenicity studies aim to characterize the immune response in terms of 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 timing of immunogenicity sample collection should be determined on a case-by-case basis, taking into account product-specific factors such as half-life and washout period.

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

**QV-4**

How are differences in immunogenicity addressed?

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 SBP 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, the ADA assay should be re-evaluated for possible bias. The most common problem with ADA assays is drug interference. This means that the residual product in the blood sample causes false negative results in the ADA assay. In this case, the drug tolerance of the assay(s) should be recalculated in order to demonstrate that it exceeds the drug concentrations in the blood samples.

If no technical problem is discovered, the manufacturer should review all differences observed in the analytical, structural and functional comparisons, and evaluate 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 evaluate the safety implications of the increased exposure.
The burden of proof is on the manufacturer of the SBP to demonstrate to regulators 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 ADAs 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 an RBP 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 into the clinical comparability studies because their 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 for 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 the investigation of immunogenicity if a surrogate PD marker is used.

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

**QV-7**

**How can SBPs be approved for indications for which no clinical studies have been conducted?**

In general, if biosimilarity has been demonstrated based on analytical, functional, nonclinical and clinical studies (that is, based on the totality of evidence), and appropriate justification is provided, indications for which the RBP is authorized can be granted without conducting clinical studies to support that indication. Extrapolation cannot be claimed automatically for all indications of the RBP and requires sound scientific justification (see also QV-8).

**QV-8**

**What are the most important “points to consider” in extrapolating safety and efficacy demonstrated 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 also QI-2). If a close similarity has been demonstrated, extrapolation is possible. Nevertheless, as described in the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) and WHO Guidelines on evaluation
of monoclonal antibodies as similar biotherapeutic products (SBPs), a scientific justification should be presented taking into account the following points:

▪ **What is the sensitivity of the studied clinical model (therapeutic indication and patient population) in detecting differences?**

The therapeutic effect should be significant and consistent across the historical clinical trials performed on the RBP with sensitive clinical end-points used 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 (for example, epoetin alfa).

For monoclonal antibodies, extrapolation is more complicated since there are several receptorsfunctional sites that can mediate or modify therapeutic effects and the relative importance of individual receptorsactive sites may vary between the approved therapeutic indications of the RBP. Therefore, the binding and function of the relevant receptorsfunctional 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 (for example, from autoimmune disease to cancer) where the PK and posology may be different. In these cases, additional PK/PD or other clinical studies 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 in accordance with the same principles used for extrapolation before approval of the SBP.

QV-10

**Why are different regulatory decisions on extrapolation reached by different NRAs 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 were 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. There could also be additional non-scientific reasons for differences – for example if the applicant did not seek authorization of an indication or if the national patent situation precludes authorization of the indication. Moreover, some regulatory
bodies may have a lot of experience with extrapolation whereas some regulators may have only recently been exposed to it. In some areas, SBP approval, including extrapolation, has been controversial among stakeholders. Additionally, the estimation of the 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 and when more post-marketing safety data and new clinical data become available.

**QV-11**

**How should less experienced NRAs deal with the differing regulatory decisions made by 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. In addition, differences in the judgement and/or interpretation of scientific data exist across regulatory agencies (see also QV-10). In order to understand the reasons for such different interpretations, it is helpful to read the 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 an NRA that made a positive decision.

**QV-12**

**Is there always a need to conduct a clinical study for an SBP?**

As noted in the WHO 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. Analytical methodology has developed rapidly during the SBP era. As a result, even complex biotechnology-derived products such as monoclonal antibodies can be characterized to a degree that may allow for their abbreviated clinical development (see the WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)).

For less-complex proteins or polypeptides (such as insulin and filgrastim) 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/immunogenicity studies in the target population.

Very simple peptides may be licensed with only a small PK/PD bioequivalence study. For example, 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 in WHO guidelines for SBPs.
VI. Pharmacovigilance

QVI-1
Are SBPs as safe as originator products?
Yes, if they are developed according to WHO 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 million doses of SBPs authorized in the European Union had been administered by 2016. In spite of this 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 similar safety of an SBP and its RBP is based on the physicochemical and structural similarity 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-extensive or less-extensive clinical testing for efficacy and safety data may be necessary in addition to the PK data. The safety of SBPs is monitored by pharmacovigilance systems, and often by additional post-marketing risk-detection and risk-minimization measures.

QVI-2
After an SBP has been approved is it a requirement 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 the WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products). Every significant change in the manufacturing process of biotherapeutic products should be supported by a comparability exercise comparing the pre- and post-change versions of the product to demonstrate that its safety and efficacy have not been altered.

Both RBP manufacturers and SBP manufacturers are responsible for ensuring that their products remain safe and efficacious throughout their life-cycle by preventing significant changes to individual products. Experience from hundreds of manufacturing changes introduced for RBPs over several decades demonstrates that clinically relevant changes to individual products over time are very rare. Currently there are no data to suggest that any SBP has lost its similarity to the RBP following manufacturing changes. However, if new safety information is added in the product information of the RBP after the original approval of the SBP, the labelling information of the SBP should follow the changes made for the RBP unless it can be demonstrated that the new information is not relevant to the SBP. In this context, it is important to emphasize that the required data can be obtained only by having robust pharmacovigilance systems that allow for the collection of product-specific data.

QVI-3
Would it be beneficial to review and 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 the 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 the pooling of data to facilitate safety signal detection.

**QVI-4**

If safety information on the RBP is amended (that is, as the result of adverse events) 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 the SBP product information given that the approval of an SBP is based on the comparable safety and efficacy of the 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 has not previously been established. This depends, however, on the regulations of the specific NRA. The manufacturer of the SBP should consult with 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 for the SBP should be in line with that for the RBP except for product-specific differences. For reasons of public health (for example, possible off-label use) cautions for the use of all therapeutic indications for the RBP should be included in the product information for the SBP even when the cautions are related to a therapeutic indication that was not applied for.
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