International Advance Journal of Engineering, Science and Management (IAJESM)
ISSN -2393-8048, July-December 2022, Submitted in December 2022, iajesm2014@gmail.com

Challenges Involved in Biosimilar Development

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Abstract

Biosimilars represent, potentially, an attractive market, although there are significant regulatory and commercial hurdles to overcome. Because of the large and complex nature of biological molecules, biosimilars cannot be guaranteed to be identical to innovator biologics. Establishing a high degree of similarity in quality between the biosimilar product and the original product is a crucial key in the regulatory approval process, because biologicals vary greatly in properties and where even small alterations can lead to unacceptable changes in safety and efficacy. Even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences. Protein modifications and higher order structure can be affected by environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems, and delivery device materials. Specific safety or effectiveness concerns regarding the reference product and its class (including history of manufacturing- or source-related adverse events) may warrant more comparative clinical safety and effectiveness data. Assessment of immunogenicity and interchangeability are other important criteria to fulfil the Biosimilar requirements. The rapidly evolving regulatory science in the biosimilar area would benefit from better cooperation, information exchange and collaboration from regulators. It is recommended that the sponsors need to discuss the development strategy with regulators at appropriate stage of development and get their concurrence on the strategy. This will help to ease the regulatory review process and early product approvals.

Key words: Biosimilar, Similar biotherapeutic product, Registration

According to EMA, a biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

Biosimilars can be less expensive than the originator biologics and can potentially provide increased access to biologic therapies including monoclonal antibodies and therapeutic proteins that treat life threatening cancers, anemia and immunological diseases. The changing outlook for biosimilars comes at a time when the global pharmaceutical market is feeling the combined impact of two key events: a period of unprecedented patent expirations on many of the world's largest pharmaceutical brands, and a financial crisis that has required healthcare systems to make significant and sustained cost reductions.

Because of the large and complex nature of biological molecules, biosimilars cannot be guaranteed to be identical to innovator biologics. Therefore, regulators have been concerned that undetected differences in biosimilars may result in reduced efficacy or different adverse reactions. Regulators have been working towards abbreviated licensing pathways to speed up the availability of biosimilars, but efforts have been slowed by complex issues related to demonstrate comparability of biosimilar with the safety and effectiveness of innovator biologics. The biggest challenges facing biosimilar drug developers is proving the equivalence or similarity of their biological drug to the reference product because of great variation in properties and even small alterations can lead to unacceptable changes in safety and efficacy. The key challenges of the biosimilar development program are discussed below;

Nature of Protein Products and Related Scientific Considerations

As per FDA's definition, "Protein means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size". Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. Many potential differences in protein structure can arise. Because even minor structural differences (including certain changes in glycosylation patterns) can

significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences. In general, proteins can differ in at least three ways:

(1) Primary amino acid sequence

(2) Modification to amino acids, such as sugar moieties (glycosylation) or other side chains

(3) Higher order structure (protein folding and protein-protein interactions).

Modifications to amino acids may lead to heterogeneity and can be difficult to control. Protein modifications and higher order structure can be affected by environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems, and delivery device materials. Additionally, process-related impurities may increase the likelihood and/or the severity of an immune response to a protein product, and certain excipients may limit the ability to characterize the drug substance. Hence it is important that appropriate advance analytical techniques should be used for extensive characterization of test product with respect to their physico-chemical and biological properties, such as higher order structures and functional characteristics.

Expression system

Therapeutic protein products can be produced by microbial cells (prokaryotic, eukaryotic), cell lines of human or animal origin (e.g., mammalian, avian, insect), or tissues derived from animals or plants. It is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product.

However, minor modifications, such as N or C terminal truncations that will not have an effect on safety, purity, or potency, may be justified by the applicant. Differences between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered because the type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities (including potential adventitious agents) that may be present in the protein product. Minimizing differences between the proposed and reference expression systems to the extent possible can enhance the likelihood of producing a highly similar protein product.

The characterization of the expression construct, including its genetic stability, should be demonstrated in accordance with principles recommended in ICH Q5B.

Manufacturing Process Considerations

Different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product. The differences in biological systems used to manufacture a protein product may cause different post-translational modifications, which in turn may affect the safety or effectiveness of the product. Thus, when the manufacturing process for a marketed protein product is changed, the application holder must assess the effects of the change and demonstrate through appropriate analytical testing, functional assays, and/or in some cases animal and/or clinical studies, that the change does not have an adverse effect on the identity, strength, quality, purity, or potency of the product as they relate to the safety or effectiveness of the product. Hence it is important that a comprehensive understanding of all steps in the manufacturing process for the proposed biosimilar product should be established during product development. Characterization tests, process controls, and specifications that will emerge from information gained during process development must be specific for the proposed biosimilar product and manufacturing process. The use of Quality-by-Design approaches to pharmaceutical development, along with quality risk management and effective quality systems, will facilitate the consistent manufacturing of a high-quality product.

Assessment of Physiochemical properties - Structural Analysis

Physicochemical assessment of the proposed biosimilar product and the reference product should consider all relevant characteristics of the protein product (e.g., the primary, secondary, tertiary, and quaternary structure, post-translational modifications, and functional activities). It is important to understand the heterogeneity of the proposed biosimilar product and the reference product (e.g., the nature, location, and levels of glycosylation) and the ranges of variability of different isoforms, including those that result from post-translational

modifications. It is expected that appropriate analytical test methods should be selected based on the nature of the protein being characterized and knowledge regarding the structure and heterogeneity of the reference and the proposed biosimilar product, as well as those characteristics that are critical to product performance. To address the full range of physicochemical properties or biological activities adequately, it is often necessary to apply more than one analytical procedure to evaluate the same quality attribute.

In selecting these tests, it is important to consider the characteristics of the protein product, including known and potential impurities. Information regarding the ability of a method to discern relevant differences between a proposed biosimilar product and a reference product should be submitted as part of the comparison. Tests chosen to detect and characterize these post-translational protein modifications should be demonstrated to be of appropriate sensitivity and specificity to provide meaningful information as to whether the proposed biosimilar product and the reference product are highly similar.

Functional Assays/Biological Assays

Functional assays serve multiple purposes in the characterization of protein products. These tests act to complement physicochemical analyses and are a quality measure of the function of the protein product. The pharmacologic activity of protein products can be evaluated by in vitro and/or in vivo functional assays. These assays may include, but are not limited to, bioassays, biological assays, binding assays, and enzyme kinetics.

A functional evaluation comparing a proposed product to the reference product using these types of assays is also an important part of the foundation that supports a demonstration of biosimilarity and may be used to scientifically justify a selective and targeted approach to animal and/or clinical testing. Functional assays are useful to provide additional evidence that the biologic activity and potency of the proposed product are highly similar to those of the reference product and/or to demonstrate that there are no clinically meaningful differences between the proposed product and the reference product. Also provides an additional data to support results from structural analysis, investigate the consequences of observed structural differences, and explore structure activity relationships. The available information about these assays, including sensitivity, specificity, and extent of validation, can affect the amount and type of additional animal or clinical data that may be needed to establish biosimilarity.

If a reference product exhibits multiple functional activities, manufacturers should perform a set of relevant assays designed to evaluate the range of activities. The manufacturer should recognize the potential limitations of some types of functional assays, such as high variability, that might preclude detection of small but significant differences between the proposed biosimilar product and the reference product. As a highly variable assay may not provide a meaningful assessment as to whether the proposed biosimilar product is highly similar to the reference product. Thus, these limitations should be taken into account when assessing the robustness of the quality of data supporting biosimilarity and the need for additional information. Finally, functional assays are critical in assessing the occurrence of neutralizing antibodies in nonclinical and clinical studies.

Receptor Binding and Immunochemical Properties

Binding or immunochemical properties are part of the activity attributed to the protein product, analytical tests should be performed to characterize the product in terms of these specific properties (e.g., if binding to a receptor is inherent in protein function, this property should be measured and used in comparative studies as per ICH Q6B). Various methods such as surface plasmon resonance, microcalorimetry, or classical Scatchard analysis can provide information on the kinetics and thermodynamics of binding. This information can be related to the functional activity and characterization of the proposed biosimilar product's higher order structure. Hence it is important that during biosimilar product development, applicant should study these specific properties with appropriate analytical tools to prove the biosimilarity with reference product.

Impurities

The applicant should characterize, identify, and quantify impurities (product- and process-related as defined in ICH Q6B) in the proposed biosimilar product and the reference product.

If comparative physicochemical analysis reveals comparable product-related impurities at similar levels between the two products, pharmacological/toxicological studies to characterize potential biological effects of specific impurities may not be necessary. However, if the manufacturing process used to produce the proposed biosimilar product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary.

Process-related impurities arising from cell substrates (e.g., host cell DNA, host cell proteins), cell culture components (e.g., antibiotics, media components), and downstream processing steps (e.g., reagents, residual solvents, leachables, endotoxin, bioburden) should be evaluated. The potential impact of differences in the impurity profile upon safety should be addressed and supported by appropriate data. In all cases, the chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities (see ICH Q2B). In particular, the results of the immunological methods used to detect host cell proteins depend on the assay reagents and the cell substrate used. Such assays should be validated using the product cell substrate and orthogonal methodologies to ensure accuracy and sensitivity. This should be done across both products to the extent relevant and feasible. Also adventitious agents or endogenous viral contamination should be ensured by screening critical raw materials and confirmation of robust virus removal and inactivation achieved by the manufacturing process.

Reference Product and Reference Standards

A thorough physicochemical and biological assessment of the reference product should provide a base of information from which to develop the proposed biosimilar product and justify reliance on certain existing scientific knowledge about the reference product. Sufficient evidence that the proposed biosimilar product is highly similar to the reference product must be demonstrated in an appropriate time frame to support a selective and targeted approach in early product development. An analytical similarity assessment should support the use of lots that demonstrate the biosimilarity of the proposed biosimilar product used in the principal clinical trial to the reference product and the proposed commercial product. The biosimilar application should include a thorough analytical comparison between the proposed biosimilar product and the reference product.

If the drug substance has been extracted from the reference product in order to assess analytical similarity, the applicant should describe the extraction procedure and provide support that the procedure itself does not alter product quality. This undertaking would include consideration for alteration or loss of the desired products and impurities and relevant product-related substances, and it should include appropriate controls that ensure the relevant product characteristics of the reference product are not significantly altered by the extraction procedure.

If there is a suitable, publicly available and well-established reference standard for the protein, then a physicochemical and/or functional comparison of the proposed biosimilar product with this standard should also be performed. For example, if an international standard for calibration of potency is available, a comparison of the relative potency of the proposed biosimilar product with this potency standard should be performed. Overall, analytical studies carried out to support the approval of a proposed biosimilar product should not focus solely on the characterization of the proposed biosimilar product in isolation. Rather, these studies should be part of a broad comparison that includes, but is not limited to, the proposed biosimilar product, the reference product, applicable reference standards, and consideration of relevant publicly available information.

Stability

An appropriate physicochemical and functional comparison of the stability of the proposed biosimilar product with that of the reference product should be initiated. Accelerated and stress stability studies, or forced degradation studies, should be used to establish degradation profiles and provide direct comparison of the proposed biosimilar product with the reference product. These comparative studies should be conducted under multiple stress conditions

(e.g., high temperature, freeze thaw, light exposure, and agitation) that can cause incremental product degradation over a defined time period. Results of these studies may reveal product differences that warrant additional evaluation and also identify conditions under which additional controls should be employed in manufacturing and storage. Sufficient real time, real condition stability data should be provided to support the proposed shelf life.

Animal Data

Animal Toxicity Studies

The scope and extent of any animal toxicity studies will depend on the body of information available on the reference product, the proposed product, and the extent of known similarities or differences between the two. If animal toxicity studies are not warranted, additional comparative in vitro testing, using human cells or tissues when appropriate, may be warranted. In general, nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies are not warranted when the proposed product and reference product have been demonstrated to be highly similar through extensive structural and functional characterization and animal toxicity studies. If there are specific safety concerns based on the clinical use of the reference product, some of or all such additional animal studies with the proposed product may be warranted.

Inclusion of Animal PK and PD Measures

A single-dose study in animals comparing the proposed product and reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity. Specifically, applicant can use results from animal studies to support the degree of similarity based on PK and PD profiles of the proposed product and the reference product. PK and PD measures also can be incorporated into a single animal toxicity study, where appropriate. Animal PK and PD assessment will not negate the need for human PK and PD studies.

Animal Immunogenicity Studies

Animal immunogenicity assessments generally do not predict potential immunogenic responses to protein products in humans. However, when differences in manufacturing (e.g., impurities or excipients) between the proposed product and the reference product may result in differences in immunogenicity, measurement of anti-protein antibody responses in animals may provide useful information relevant to patient safety. Additionally, significant differences in the immune response profile in inbred strains of mice, for example, may indicate that the proposed product and the reference product differ in one or more product attributes not captured by other analytical methods. If available, this information is of value in the design of clinical immunogenicity assessment.

Clinical Studies

Human Pharmacology Data

Human PK and PD studies comparing a proposed product to the reference product generally are fundamental components in supporting a demonstration of biosimilarity. Both PK and PD study (where there is a relevant PD measure) generally will be expected to establish biosimilarity, unless an applicant can scientifically justify that an element is unnecessary. A human PK study that demonstrates similar exposure (e.g., serum concentration over time) with the proposed product and reference product can provide support for a biosimilarity demonstration. A human PD study that demonstrates a similar effect on a clinically relevant PD measure or measures related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) can also provide strong support for a biosimilarity determination.

Applicants should provide a scientific justification for the selection of the human PK and PD study population (e.g., patients versus healthy subjects) and parameters, taking into consideration the relevance of such population and parameters, the population and parameters studied for the licensure for the reference product, as well as the current knowledge of the intra-subject and inter-subject variability of human PK and PD for the reference product. Also applicants should predefine and justify the criteria for PK and PD parameters for studies included in the application to demonstrate biosimilarity. Establishing a similar human PK and

PD profile contributes to the demonstration of biosimilarity and may provide a scientific basis for a selective and targeted approach to subsequent clinical testing.

Immunogenicity assessment

The goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and severity of human immune responses. Hence, establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a key element in the demonstration of biosimilarity. Structural, functional, and animal data are generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product will generally be expected.

The extent and timing (e.g., premarket testing versus pre- and postmarket testing) of a clinical immunogenicity program will vary depending on a range of factors, including the extent of analytical similarity between the proposed product and the reference product, and the incidence and clinical consequences of immune responses for the reference product. If the immune response to the reference product is rare, two separate studies may be sufficient to evaluate immunogenicity: (1) a premarket study powered to detect major differences in immune responses between the two products and (2) a postmarket study designed to detect more subtle differences in immunogenicity. The applicant should develop assays capable of sensitively detecting immune responses, even in the presence of circulating drug product (proposed product and reference product). The proposed product and reference product should be assessed in the same assay with the same patient sera whenever possible.

Clinical safety and effectiveness

For Biosimilar applications, comparative safety and effectiveness data is necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment. Specific safety or effectiveness concerns regarding the reference product and its class (including history of manufacturing- or source-related adverse events) may warrant more comparative clinical safety and effectiveness data.

Alternatively, if the reference product has a long, relatively safe marketing history and there have been multiple versions of the reference product on the market with no apparent differences in clinical safety and effectiveness profiles, there may be a basis for a selective and targeted approach to the clinical program.

Biosimilar Guidelines Road Mapping:[39-45]

The concept of Biosimilar understanding is still evolving globally and the regulatory authorities have requirements across the globe are varying country to country. Hence, it is important to study the requirements stipulated by the regulatory agencies and the biosimilar development program should address all the expectations of regulatory agencies across the globe. The following major countries guidelines are reviewed and key parameters have been summarized in this section.

Table-1: Discussion on list of countries/agencies and key attributes

List of countries/agencies	Key attributes discussed
a) World Health Organization b) US c) EU d) Japan e) India f) South Korea g) Canada	1) Terminology 2) Scope 3) Selection of Reference product 4) Manufacturing process 5) Specifications 6) Comparability studies 7) Stability studies 8) Non-clinical studies 9) Pharmacokinetic studies 10) Pharmacodynamic studies 11) Efficacy studies 12) Safety studies 13) Extrapolation of clinical indication 14) Post marketing surveillance

Table-2: A comparison of requirements for the evaluation of SBPs between different regions

Parameters	Agency/ country	Guidances
Terminology	WHO	Similar Biological products
	US	Biosimilars
	EU	Similar biological medicinal product
	Japan	Follow-on Biologics
	India	Similar Biologics
	South Korea	Biosimilars
	Canada	Subsequent Entry Biologicals
Scope	WHO	Well-established and well-characterized Biotherapeutic products such as recombinant DNA-derived therapeutic proteins
	US	Recombinant protein drugs (except any chemically synthesized polypeptide)
	EU	Any biological medicinal product, e.g.: medicinal products containing biotechnology-derived proteins as active substance, immunologicals such as vaccines, blood-derived products, monoclonal antibodies, etc.
	Japan	Recombinant proteins and polypeptide products, their derivatives, and products of which they are components, e.g., conjugates.
	India	Similar biologics that contain well characterized proteins as their active substance, derived through modern biotechnological methods such as use of recombinant DNA technology
	South Korea	All types of biological products, specifically to biological products that contain well-characterized protein.
	Canada	Biologic drugs that contain well characterized proteins derived through modern biotechnological methods such as use of recombinant DNA and/or cell culture.
Reference Product selection	WHO	The rationale for the choice of a RBP should be provided by the manufacturer of the SBP in the submission to the National Regulatory Authority.
	US	Reference product should be licensed by FDA
	EU	The chosen reference medicinal product, defined on the basis of its marketing authorization in the Community, should be used during the development of a similar biological medicinal product
	Japan	The reference products should be drugs approved in Japan and be the same product throughout the development period of the biosimilar products.

	India	Reference biologic which is authorized using complete dossier is critical for the development of similar biologic. The rationale for the choice of the reference biologic should be provided.
	South Korea	The reference product should be a biological product authorized in Korea. However, if a reference product authorized in Korea is not commercially available or if there are other justifiable reasons, the same biological product as the one authorized in Korea may be purchased from overseas markets and used as the reference product.
	Canada	The reference biologic drug should be authorized and marketed in Canada, and should be used throughout the studies. In appropriate circumstances, a biologic drug that is not authorized for sale in Canada may be used as a reference biologic drug.
Manufacturing process	WHO	• The manufacturing process should be optimized to minimize differences between the SBP and RBP in order to (a) maximize the ability to reduce the clinical testing requirements for the SBP based upon the clinical history of the RBP, and (b) minimize any predictable impact on the clinical safety and efficacy of the product. • Some differences between the SBP and RBP are expected and may be acceptable, provided, appropriate justification with regard to lack of impact on clinical performance is given.
	US	• Different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product. • Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer
	EU	• The formulation of the biosimilar does not need to be identical to that of the reference medicinal product. • The applicant should take into account state-of-the-art technology and, regardless of the formulation selected, the suitability of the proposed formulation with regards to stability, compatibility (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and strength of the active substance should be demonstrated. • If a different formulation and/or container/closure system to the reference medicinal product is selected (including any material that is in contact with the medicinal product), its potential impact on the safety and efficacy should be appropriately justified
	Japan	• A highly consistent and robust manufacturing process should be established. As in new recombinant protein products, the quality attributes of the follow-on biologic under development should be fully characterized and the thus obtained data should be submitted. • The manufacturing process should be suitably optimized based not only on the characteristics of the active ingredient(s) of the follow-on biologic but also the comparison of the relevant quality attributes with those of the original biologic
	India	• The manufacturing process for similar biologic should be highly consistent and robust. If the host cell line used for the production of reference biologic is disclosed, it is desired to use the same cell line as the reference biologic.
Manufacturing process	South Korea	• A complete description of the manufacturing process for the drug substance and drug product should be provided in detail. • The manufacturing process should be reasonable and justifiable taking into account the modern science and technology and the nature of the drug product. • Submissions should include the information on quality control/quality assurance, in-process controls, and process validation

	Canada	• A well-defined manufacturing process with its associated process controls assures that an acceptable product is produced on a consistent basis • Where details of the manufacturing process for the reference biologic drug are available to the SEB sponsor and can be compared with those for the SEB, such an analysis may help identify which tests should be performed during the comparability exercise
Specifications	WHO	• The setting of specifications should be based upon the manufacturer's experience with the SBP (e.g. manufacturing history; assay capability; safety and efficacy profile of the product) and the experimental results obtained by testing and comparing the SBP and RBP. Sufficient lots of SBP should be employed in setting specifications. • The manufacturer should demonstrate, whenever possible, that the limits set for a given specification are not significantly wider than the range of variability of the RBP over the shelf-life of the product, unless justified.
Specifications	US	• Not specified
	EU	• The rationale used to establish the proposed range of acceptance criteria should be described. Each acceptance criterion should be established and justified based on data obtained from lots used in non-clinical and/or clinical studies, and by data from lots used for the demonstration of manufacturing consistency, data from stability studies, any other relevant development data and data obtained from the biosimilar comparability exercise (quality, safety and efficacy).
	Japan	• Specifications and test procedures for follow-on biologics should be set based on the results of characterization or lot analysis. • Specifications for the drug substance and drug product should be set, taking into account the results of the comparability exercise versus the original biologic, where necessary
	India	• Specifications of similar biologics are established around critical quality attributes of the product with the intent of ensuring consistency in product quality and comparability to reference biologic. • Acceptance limits should be set based on reference biologic data and data from sufficient number of batches from preclinical or clinical batches.
	South Korea	• Each acceptance criterion should be established and justified based on data obtained from representative lots (such as data obtained from lots used in non-clinical and/or clinical studies, data from lots used for the demonstration of manufacturing consistency, data from stability studies, relevant development data, and data obtained from the comparability studies and justifications for the methods used and the proposed range should be provided
	Canada	• The tests and analytical procedures chosen to define drug substance or drug product specifications alone are not considered adequate to assess product differences since they are chosen to confirm the routine quality of the product rather than to fully characterise it. • The manufacturer should confirm that the specifications chosen for the SEB are appropriate to ensure product quality
	WHO	Comparability study should include the following;
	EU	

Comparability Study	US	• Physicochemical Properties - primary and higher order structure (secondary/tertiary/quaternary) and Post-translational modifications using appropriate analytical methods • Biological activity - the use of a relevant biological assay(s) with appropriate precision and accuracy provides an important means of confirming that a significant functional difference does not exist between the SBP and the RBP • Immunochemical Properties - manufacturer should confirm that the SBP is comparable to the RBP in terms of specificity, affinity, binding kinetics, and Fc functional activity, where relevant • Impurities - Process and product-related impurities should be identified, quantified by state-of-the-art technology and compared between the SBP and RBP. If significant differences are observed in the impurity profile between the SBP and the RBP, their potential impact on efficacy and safety, including immunogenicity, should be evaluated. • Quantity should be determined using an appropriate assay, and should normally be expressed in the same units as the reference medicinal product. • Applicant to demonstrate that the selected methods used in the comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality.
	Japan	• The quality attributes of the follow-on biologic should be characterized and elucidated using the state-of-art scientific technologies, such as (1) structure and composition, (2) physicochemical properties, (3) bioactivity, (4) immunochemical properties and (5) purity, impurities and contaminants.
Comparability study	India	• First three consecutive standardized batches which have been used to demonstrate consistency of the manufacturing process should be used. • Head-to-head characterization studies are required to compare the similar biologic and the reference biologic at both levels of drug substance and drug product • The quality comparison between the similar biologic and the reference biologic should employ state-of-the-art analytical techniques, including the analytical methods that are sensitive enough to detect the possibilities of changes to the product.
	South Korea	• Characterization studies should at least include the physicochemical properties, biological properties, immunological properties, purity (process-related and product-related impurities), contaminants, potency, and strength Characterization studies should be designed to allow direct comparison of the biosimilar product and the reference product at both the drug substance and the drug product levels. • However, if characterization studies result in different patterns, the implications of such differences should be evaluated and additional characterization studies may be required

	Canada	• Determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity. • When conducting a comparability study, a complete side-by-side characterization is generally warranted to directly compare the SEB and the reference biologic drug. • When immunochemical properties are part of the characterization (e.g., for antibodies or antibody-based products), the manufacturer should confirm that the SEB is comparable to the reference biologic drug in terms of the specific properties • Differences observed in the purity and impurity profiles of the SEB relative to the reference biologic drug should be evaluated to assess their potential impact on safety and efficacy
Stability studies	WHO	• Accelerated degradation studies • Studies under various stress conditions (e.g. temperature, light, humidity, mechanical agitation)
	US	• Comparison of Accelerated degradation studies • Studies under various stress conditions
	EU	• Comparison of Accelerated degradation studies • Studies under various stress conditions
	Japan	• A comparison of stability with reference product will not necessarily be required • Studies under various stress conditions
	India	• Side-by-side accelerated and stressed studies comparing the similar biologic to the reference biologics
Stability studies	South Korea	• A comparison of stability with reference product will not necessarily be required • Impurity profile studies under various stress conditions at drug substance and drug product levels
	Canada	• Comparison of Accelerated degradation studies or Studies under various stress conditions
Non-clinical studies	WHO	• In vitro (e.g., receptor-binding, cell-based assays) • In vivo (pharmacodynamic activity, at least one repeat dose toxicity study, antibody measurements, local tolerance)
	US	
	EU	
	Japan	• Comparative non-clinical PK studies • Comparative non-clinical PD studies • Repeated dose-toxicity studies
	India	• In vitro (e.g., receptor-binding, cell-based assays) • In vivo (pharmacodynamic activity, at least one repeat dose toxicity study, antibody measurements, local tolerance)
	South Korea	
	Canada	
Clinical – PK studies	WHO	• The PK profile should always be investigated. • PK studies must be comparative in nature
	US	• Human PK and PD studies comparing a proposed product to the reference product generally are fundamental components in supporting a demonstration of biosimilarity.
	EU	• Comparative PK studies are an essential part of the comparability exercise.
	Japan	• The sponsor should conduct the comparability exercise of PK studies
	India	• Comparative pharmacokinetic (PK) studies should be performed in healthy volunteers or patients to demonstrate the similarities in pharmacokinetic characteristics
	South Korea	• The PK profile should always be investigated. • PK studies must be comparative in nature

	Canada	Comparative PK studies should be conducted.
Clinical – PD studies	WHO	• It may be advisable for the manufacturer to ensure similar PD profiles before proceeding to clinical trials
	US	• Human PK and PD studies comparing a proposed product to the reference product generally are fundamental components in supporting a demonstration of biosimilarity.
	EU	• The PD markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product.
	Japan	• If possible, it is necessary to select PD markers for clinical efficacy & to conduct the comparability studies using the appropriate PD marker.
	India	• PK studies in the similar biologic clinical development program, the pharmacodynamic (PD) studies should also be comparative in nature
	South Korea	• In general, the PD studies may be performed in combination with PK studies and the PD parameters should be selected on the basis of their relevance to demonstrate clinical efficacy.
	Canada	• PD studies may be combined with PK studies. • The PD studies should be comparative in nature
Efficacy studies	WHO	• Clinical trials are required to demonstrate similar efficacy. • In certain cases, comparative PK/PD studies may be appropriate
	US	• Comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment
	EU	• Comparative clinical trials are required for the demonstration of clinical comparability. In certain cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability
	Japan	• The comparability of biosimilar products should be evaluated through the clinical studies. • In case PK/PD studies are sufficient to assure comparability in clinical endpoint of interest, additional clinical studies might be omitted
Efficacy studies	India	• Comparative safety and efficacy in relevant patient population is mandatory for all similar biologics • The confirmatory clinical safety and efficacy study can be waived if all the below mentioned conditions….
	South Korea	• Clinical trials are required to demonstrate similar efficacy • Comparative PK/PD studies may be appropriate for the following cases….
	Canada	• Comparative clinical trials are critically important to demonstrate the similarity in efficacy and safety profiles
	WHO	• Pre-licensing safety data should be obtained • The frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared
	US	• Comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment
	EU	• Pre-licensing safety data should be obtained. • The immunogenicity of SBP must always be investigated

Safety (Immunogenicity) studies	Japan	• Clinical safety studies, including a study on immunogenicity should be considered. • At an appropriate stage of the clinical development, studies should be conducted to evaluate antibody formation & other immunogenicity
	India	• Comparative safety and efficacy in relevant patient population is mandatory for all similar biologics • The confirmatory clinical safety and efficacy study can be waived if all the below mentioned conditions….
	South Korea	• Pre-authorization safety data should be obtained • The frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared before authorization
	Canada	• Pre-authorization safety data should be obtained • The frequency and type of antibodies induced as well as possible clinical consequences of the immune response should be compared before authorization
Extrapolation (multiple indication)	WHO	• Extrapolation of these data to other indications of the RBP (not studied using independent clinical studies with the SBP) may be possible
	US	• Data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for the proposed product to be licensed for one or more additional conditions of use for which the reference product is licensed. • However, the sponsor will need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought
	EU	• Demonstration of the clinical comparability in one indication will allow the extrapolation of the other indications of the RMP if the mechanism of action is the same
Extrapolation (multiple indication)	Japan	• In certain cases it may be possible to extrapolate from one indication to other indications of the reference product • Where each relevant indication has different mechanism of action, the comparability of efficacy should be demonstrated for each indication without extrapolation
	India	• Extrapolation of the safety and efficacy data of a particular clinical indication (for which clinical studies has been done) of a similar biologic to other clinical indications may be possible if following conditions are met…..
	South Korea	• Extrapolation of these data to other indications of the reference products for which post-marketing survey was completed may be possible
	Canada	• In some situations, proposals for additional indications held by the reference biologic drug may be granted to the SEB in the absence of such clinical data
Post-marketing surveillance	WHO	• Further close monitoring of the clinical safety of these products in all approved indications and a continued benefit-risk assessment is necessary in the post-marketing phase
	US	• Robust post marketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar therapeutic protein products. • Because some aspects of post marketing safety monitoring are product-specific, FDA encourages sponsors to consult with appropriate FDA divisions to discuss the sponsors' proposed approach to post marketing safety monitoring

Post-marketing surveillance	EU	• Clinical safety of similar biological medicinal products must be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.
	Japan	• The clinical safety of biosimilar products should be followed and monitored on an ongoing basis during post-marketing surveillance
	India	• The clinical studies done on similar biologics prior to market authorization are limited in nature so post marketing studies should be conducted and the reports be submitted to DCGI.
	South Korea	• Further characterization of the immunogenicity profile may be necessary post-marketing
	Canada	• It is important that a Risk Management Plan be presented prior to issuance of marketing authorization

Summary and Conclusion

Way forward: global consensus and national solutions:

Although the debate on how best to license copy biological products using reduced non-clinical and clinical data packages continues, there is increasing alignment between jurisdictions. However, there will be inevitably some differences due to national regulations and needs. There will also be differences in the scope of which type of products are included under the umbrella of biosimilars. Biologicals are mostly protein based although polysaccharide and DNA molecules may be considered for SBP status in some cases. The guiding principles in the WHO Guidelines on SBPs do not provide a sufficient level of detail regarding the evaluation of the quality, safety and efficacy of vaccines. Therefore, WHO recommendations on the quality, safety and efficacy of specific vaccines will continue to be provided in vaccine specific documents.

Since the publication of the WHO Guidelines, several activities at the global and regional level have been conducted by WHO. An issue of critical importance for the appropriate evaluation of copy and similar biological products is the expertise of the regulators responsible for the licensing of biotherapeutic products. Much investment in the development of biosimilar and copy products is now going on in many countries, including those with emerging economies and it is recognized that the regulatory agencies of many of these countries need also to be strengthened with respect to their regulatory oversight of biotechnology products as well as biosimilars. In 2010, the first WHO implementation workshop was held and a survey in 13 countries was conducted. Significant improvement in the understanding of the need for clinical trials and of the importance of having an appropriate design of comparability studies, and of the clinical part in particular, were noted.

It is expected that WHO will assist many countries to establish appropriate approaches for evaluating these products properly or for phasing them out in a reasonable period of time. WHO's role in building the technical expertise in NRAs worldwide is recognized as an important contribution towards better regulation of biotherapeutics as a whole. One of the specific tasks in coming years will be the provision of appropriate scientific principles for the evaluation of biotherapeutics as standalone products.

This will involve updating existing WHO documents to include the numerous issues that have emerged over time. It is expected that implementation workshops will continue and be devoted to specific aspects, such as the comparability exercise in terms of quality parameters. Increasing knowledge in assessing SBPs, exchange of information among regulators, regular update regarding the licensure of SBPs and key issues that have been raised by evaluators and the development of training curricula are some of the activities that could be organized through WHO collaborating centres. In spite of the initiatives at the global level, it is expected that national solutions will make a real difference in terms of the use of SBPs.

The involvement of all relevant parties at the country level is a key prerequisite for the success in increasing patients' access to the biotherapeutic products that are most needed. In addition to the regulators and manufacturers, public health authorities, health care providers, general practitioners, pharmacists and patients' organizations all need to be consulted during

the decision-making process regarding the actual use of SBPs at the country and/or provincial level.

Conclusion:

Overall, the rapidly evolving regulatory science in the biosimilar area would benefit from better cooperation, information exchange and collaboration from regulators. The sponsor should adopt a robust development strategy and it is recommended that the sponsors need to discuss the development strategy with regulators at appropriate stage of development and get their concurrence on the strategy. This will help to ease the regulatory review process and early product approvals.

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