

Non-comparable Biotherapeutic Products

What is a “non-comparable biotherapeutic product”?

*For the purposes of this paper, we will use the term “**non-comparable biotherapeutic product**”, a new term that is being proposed by IFPMA, to describe those biotherapeutic medicinal products that are intended to “copy” another biotherapeutic product; have not been directly compared and analyzed against an already licensed reference biotherapeutic product (RBP); and have not been approved via a regulatory pathway that is in alignment with World Health Organization Similar Biotherapeutic Product guidelines that ensure quality, safety, and efficacy.*

The World Health Organization (WHO) Guidelines define **similar biotherapeutic products (SBP)**¹ as “a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference product”.² In other regions, like the European Union (EU), the term “**biosimilars**” has been adopted, and the European Medicines Agency (EMA) states that “a biosimilar” is a biological medicinal product that contains a version of the active substance of an already approved original medicinal product (reference medicinal product), where similarity in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise has been demonstrated.³

Non-comparable biotherapeutic products are sometimes referred to as “non-innovative biological products”. Due to the inconsistent use of terminology, non-comparable biotherapeutic products are often incorrectly referred to as “biosimilars”. This mis-attribution is additionally confounded by the use of the same International Nonproprietary Name (INN) as the RBP. However, no single terminology for these types of products has been agreed upon to date.

How does a non-comparable biotherapeutic differ from a SBP?

a) General

As their name implies, SBPs are “similar” but not identical versions of their originator RBP. Whereas producing generic versions of off-patent chemically-synthesized medicines is relatively straightforward, producing a SBP is far more complicated due to the complex molecular structure and the unique manufacturing process required for biotherapeutic medicines. Unlike chemically-synthesized medicines, it is impossible for SBPs to be exact copies of the RBP. The use of similarity exercises is part of the unique pathway needed to appropriately assess SBPs and to ensure they are highly similar to the originator RBP. Medical experts, for example in the fields of rheumatology and oncology, have assessed the impact of

¹ *Similar Biotherapeutic Products (SBPs) are also referred to as biosimilars, follow-on biologics and subsequent entry biologics.*

² *WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), P. 6*

http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

³ *EMA CHMP Guidelines on similar biological medicinal products, 30 October 2005*

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf



biosimilars on patient care, and emphasize the importance of comprehensive development requirements including quality, safety, and efficacy evaluations prior to marketing, and stringent pharmacovigilance post-approval.⁴

Non-comparable biotherapeutic products are medicinal products that are developed without a complete comparability exercise even though a full regulatory data package of quality, safety and efficacy studies is sometimes provided. In contrast to SBPs, non-comparable biotherapeutic products have **not** been shown to be similar in all three of these fundamental areas to a licensed RBP as defined by WHO guidelines. It is this totality of evidence that enables a SBP to establish a relationship to data originally generated for the originator RBP. In some cases, however, the sponsor of a non-comparable biotherapeutic product utilizes the safety and efficacy profile of another product rather than generating independent, substantive clinical evidence. *Table 1* shows the differences with respect to quality, safety and efficacy data requirements between an originator Reference Biotherapeutic Product (RBP), a Similar Biotherapeutic Product (SBP) meeting WHO expectations and associated guidelines, and a Non-comparable Biotherapeutic Product at the time of market authorization application.

Since there is neither substantive stand-alone data nor sufficient evidence of similarity for a non-comparable biotherapeutic product, the basis of approval of such products is likely questionable. On the basis of this data gap, the balance of benefit versus risk is, in most cases, unknown resulting in substantial uncertainty. Consequently, there is little basis for reference to the safety and efficacy profile of another product.

b) Quality

All biotherapeutic medicines, whether they are new, originator products or not, are expected to have complete CMC (Chemistry, Manufacturing and Controls) data including a stable, well-characterized cell line, a validated, and a robust manufacturing process and control strategy, all of which result in a well-characterized biotherapeutic product.⁵ The fact that it is an intended copy of another biotherapeutic product is not a scientific rationale for the waiver of the above required elements. Further, without an extensive and comparative analytical and functional assessment between the non-comparable biotherapeutic product and the RBP, structural and functional similarity cannot be claimed.

c) Clinical safety and efficacy

In some cases, non-comparable biotherapeutic products may have little or no available safety, efficacy or immunogenicity data, since they may have been brought to market using regulatory pathways designed for chemically-synthesized drugs, generic medicines or similarly abbreviated approval processes which do not require such data for licensure. Given that no or only very limited head-to-head comparisons have occurred between the non-comparable biotherapeutic product and the RBP, the pharmacokinetics (PK) and pharmacodynamics (PD) of each product may differ thus nullifying the adaptation of the RBP's posology to that of the non-comparable biotherapeutic product. Other attributes of the non-comparable biotherapeutic

⁴ Dörner T, et al (2013) *The role of biosimilars in the treatment of rheumatic diseases: Ann Rheum Dis* 72:322-328

Mellstedt H (2013) *Anti-neoplastic biosimilars – the same rules as for cytotoxic generics cannot be applied: Annals of Oncology* 24 (Supplement 5): v23-v28

⁵ WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs).

http://www.who.int/biologicals/areas/biological_therapeutics/BIOOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

WHO Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA Technology

http://www.who.int/biologicals/biotherapeutics/rDNA_DB_final_19_Nov_2013.pdf



product critical to its safety and efficacy profile may either be different from the RBP or largely unknown. This uncertainty, coupled with the absence of sensitive pharmacovigilance systems, suggests that such a product in the market place would have unknown efficacy and safety profile, and in the worst case could pose an increased risk to patient safety.

Table 1: Data Requirements at Time of Marketing Authorization

Data category	Reference Biotherapeutic Product (RBP)⁶	Similar Biotherapeutic Product (SBP)⁷	Non-comparable Biotherapeutic Product
Quality	Full stand-alone quality data set.	Full stand-alone quality data set <i>plus</i> comprehensive side-by-side testing showing similarity to an originator RBP. Clinically meaningful differences not identified. Evidence of high degree of similarity is the basis for reduced non-clinical and clinical requirements for licensing.	Scope of quality data unknown. May not include any side-by-side assessment showing similarity to the originator RBP.
Safety	Full stand-alone non-clinical and clinical safety data, including immunogenicity assessment.	Side-by-side non-clinical and clinical safety data, including immunogenicity assessment, supporting claim of biosimilarity. Data generated in a comparative fashion on both SBP and RBP.	Scope of safety data unknown. May not include any side-by-side assessment showing similarity to the originator RBP. May only include very limited (or no) immunogenicity data.
Efficacy	Full stand-alone data set from pivotal efficacy trials.	Targeted clinical program comprising of comparative pharmacokinetic, pharmacodynamic, and efficacy trials, statistically powered to establish non-inferiority or equivalence to the RBP, which is included in the trials.	May include no or only very limited clinical data. Studies may not be powered to establish non-inferiority or equivalence to the originator RBP. Originator RBP may not be included in the clinical trial(s).

⁶ Developed in accordance with WHO rDNA guidelines.

⁷ As defined by and developed in accordance with WHO SBP guidelines.



Global Situation

As science-based pathways specific to the development, registration and surveillance of SBPs come into existence, some national regulatory agencies (NRAs) are still in the process of adapting their regulatory frameworks for biotherapeutic products. As a result, there are some countries where intended copy biotechnological products have been licensed under regulatory pathways that are not appropriate for biotherapeutic medicines, such as (a) those that were intended for generic, chemically-synthesized pharmaceuticals, (b) abbreviated pathways requiring very minimal data due, or (c) pathways where standards for approval are not well-defined (see *Table 2*). In these instances, the lack of specific guidance based on science-based assessment that is in line with the WHO Guidelines on the Evaluation of Similar Biotherapeutic Products (2009) means that biotherapeutic products not shown to be comparable to a suitable RBP have been approved in certain markets. These biotherapeutic products belong to such classes as: interferons, erythropoiesis stimulating agents (ESAs), colony stimulating growth factors (CSF) and somatotropins. Monoclonal antibodies and fusion protein products have also been approved.

There are an increasing number of publications suggesting quality differences and lack of similarity between different non-comparable biotherapeutic medicines and the RBP.⁸ More recently safety signals have been associated with their use, such as the pure red blood cell aplasia (PRCA) cases detected in Thailand.⁹

Table 2: Global Situation for Existing Regulatory Pathways

Countries where SBP guidelines have been adopted		Countries where SBP guidelines have not been adopted
<p>Non-comparable biotherapeutic products that were approved before the implementation of country-specific SBP guidelines, and the product is currently in the market as approved by NRAs according to prior local regulations (e.g. generic or abbreviated pathway).</p>	<p>Non-comparable biotherapeutic products that are approved after the implementation of country-specific SBP guidelines based on an alternate or abbreviated pathway that has been adopted by the NRA.</p>	<p>Non-comparable biotherapeutic medicinal products are approved as stand-alone products and the data meet neither the WHO SBP Guidelines nor the standard for newly developed innovative biotherapeutic products¹⁰. Clinical equivalence trials are not performed.</p>

Naming

As the global market is experiencing a considerable rise in the number of approved originator biotherapeutic and biosimilar products, IFPMA strongly supports the development of a coding system that includes a 'biologic qualifier' to be used with the INN for all biotherapeutic products, whether they are originator products or not, to ensure the best possible traceability and tracking of potential adverse events in all pharmacovigilance systems and effective world-wide identification. The ability to uniquely identify biotherapeutic products is even more urgent in the context of non-comparable biotherapeutic products,

⁸ Shellekens H (2009) *Biosimilar therapeutics – what do we need to consider?*: NDT Plus 2 [Suppl 1]: i27–i36

⁹ Praditpornsilpa K, et al (2011) *Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies*: *Kidney International* 80, 88–92

¹⁰ WHO Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA Technology http://www.who.int/biologicals/biotherapeutics/rDNA_DB_final_19_Nov_2013.pdf



which typically enter the market using the same INN as the RBP without appropriate scientific justification and comprehensive evidence of structural similarity.

Potential issues connected to non-comparable biotherapeutic products and the need for action

The clinical profile of non-comparable biotherapeutic products cannot be expected to be the same as the RBP and remains unknown due to lack of quality side-by-side assessment showing similarity to the originator RBP and/or lack of comparative clinical data. These potentially significant differences may put patients at risk of a poor health outcome. The patient may, for instance, experience reduced or no response, adverse events, toxicity reactions or even a fatal outcome. Taken together, promotion of products of unknown quality and clinical profile can pose a public health burden to patients and generate high costs to society and the entire healthcare system.

Addressing non-comparable biotherapeutics already in the market

IFPMA believes that the risk to patients and public health posed by non-comparable biotherapeutic products must be minimized or eliminated through an appropriate comparative evaluation of quality, efficacy and safety in a manner consistent with WHO Guidelines. It is recognized that there must be a transitional period in which this evaluation can occur. This transition period would require an appropriate timeline for each non-comparable biotherapeutic product to remain on the market and then, to apply in each case, the stepwise approach set forth in the WHO Guidelines. This approach would minimize disruptions of supply, while enhancing internationally accepted standards of quality, safety and efficacy.

Proposed approach for the assessment of the non-comparable biotherapeutic products to an appropriate RBP

IFPMA supports such an approach that provides a framework for evaluating products licensed prior to the establishment of a proper biotherapeutic and/or SBP pathway in a manner consistent with the WHO rDNA product & SBP guidelines¹¹, while simultaneously ensuring that treatment of patients in the market is not interrupted. Importantly, the WHO SBP guideline states that the traditional “generics” pathway is not appropriate for development of SBPs, but instead that a distinct regulatory pathway specific to SBP medicinal products should be used. Thus, until such time that NRAs are able to implement a science-based pathway consistent with WHO guidelines, IFPMA envisions a process whereby NRAs would first weigh some important general considerations against which products should be evaluated.¹²

NRAs should evaluate each product approved in their specific market against several important factors in order to determine a sufficient time for the non-comparable biotherapeutic product to remain on the market during assessment, in some cases urgency will be required. The time allocated should be scientifically justified and sufficient to allow adequate time for the applicant to submit appropriate data for regulatory evaluation in agreement with the regulatory authority to support the continuation of the license. Therefore the appropriate time to leave a non-comparable biotherapeutic product in a particular market should be

¹¹ *Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology*

http://www.who.int/biologicals/biotherapeutics/rDNA_DB_final_19_Nov_2013.pdf?ua=1

Guidelines on evaluation of Similar Biotherapeutic Products (SBPs), WHO 2009.

http://www.who.int/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_22APRIL2010.pdf

¹² *The WHO has issued a draft document on the “Regulatory Expectations and Risk Assessment for Biotherapeutic Products”*

http://www.who.int/biologicals/WHO_Risk_Assessment_for_Biotherapeutics_1st_PC_24_Jan_2014.pdf



determined on a case-by-case basis according to consideration of several factors. The factors to be weighed by the regulatory authority should include:

- The extent of use of the product (e.g., number of patients impacted);
- The existence of an appropriately licensed RBP in the market;
- The availability of a licensed, suitable alternative product/products on the market approved for those indications of the non-comparable biotherapeutic product ;
- The volume and type of data provided to support the registration of the non-comparable biotherapeutic product and how closely it is harmonized to the WHO Guidelines;
- The demographic of the patient population (pediatric or adult);
- The strength and ability of the pharmacovigilance system in the market to monitor and determine adverse events and efficacy of the non-comparable biotherapeutic product; and
- The extent and nature of any existing efficacy and adverse event data directly attributable to the product (clinical studies and market experience).

The consideration of these factors will permit an assessment of both the risks posed by the particular product as well as the need for the product to be on the market for uninterrupted treatment of patients. The weighing of these factors will determine the time needed for adaptation. Once an appropriate pre-defined time period has been determined utilizing the above factors, then a stepwise approach to the assessment of the non-comparable biotherapeutic product to an appropriate RBP should be undertaken in accordance with the country's SBP regulatory pathway. As mentioned in the beginning, the standard for the assessment of the non-comparable biotherapeutic product should be the same as for the initial registration of a SBP in the country, including quality, nonclinical and clinical data in a stepwise fashion and taking into consideration, as the "totality of the evidence" to demonstrate high similarity.

In line with this approach, once the NRA has established a secondary review timeframe for each non-comparable biotherapeutic product, the license holder should be informed of the data needed. It is accepted that provision of comparative non-clinical and clinical efficacy/safety data will require a longer period of time to assimilate and may need to be submitted on a rolling basis, however, it should be possible for comprehensive comparative analytical data with sensitive assays to be provided within 1 year of notification. The data provided should document the physicochemical and biological attributes of the locally licensed biotherapeutic product, recognizing all relevant mechanisms of action, and also demonstrate high similarity with an approved RBP. If no locally approved RBP is available, then a RBP approved in one of the ICH countries should be used as a comparator. The robustness of the analytical data will enable the NRA to determine if the locally approved biotherapeutic product is highly similar to the RBP. This analysis will subsequently inform the amount of additional clinical safety and efficacy data that will be required to support on-going marketing.

In cases where significant analytical disparities which may be linked to safety or efficacy concerns exist, the regulatory authority could give the non-comparable biotherapeutic product sponsor the opportunity to resubmit its registration application as a stand-alone product and update its labeling claim accordingly, i.e. based on the risk/benefit demonstrated in clinical trial(s) with that product in specific indications. If a withdrawal would precipitate a security of supply issue (e.g. no other product is available for treatment) then the NRA should consider exceptional circumstances such as prescription on a named-patient basis only until the product has been re-assessed and licensed under an appropriate submission route based on its own quality, non-clinical and clinical data.



Need for enhanced pharmacovigilance

The WHO describes “pharmacovigilance” as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”.¹³ As a result, pharmacovigilance systems are widely recognized as important tools in the regulatory process for all medicines, for protecting public health and are an integral component of patient healthcare.

One driver for establishing a national pharmacovigilance system is that it is impossible to completely characterize the safety profile of a new medicine through clinical investigation before the marketing authorization is first granted. Consequently, post-marketing surveillance (pharmacovigilance) is an important tool that allows health authorities to continue to assess benefit/risk throughout the life-cycle of a medicine and potentially detect rare and serious adverse events that were not detected before the initial marketing authorization. Pharmacovigilance can also identify new safety signals related to product quality and/or changes in use and prescription patterns.

Implicit in the above guidance is the recommendation to the NRA to strengthen their pharmacovigilance system while the non-comparable biotherapeutic product is being evaluated. If the market does not have sufficient pharmacovigilance surveillance to detect adverse events, then this gap warrants an earlier removal from the market. Establishing a robust pharmacovigilance system includes routinely gathering post-marketing data from many sources including spontaneous reports, published literature or case studies, clinical studies and regulatory reports.

To ensure clear identification of the medicinal product that has been used for treatment, the adverse event reports should always contain different identifiers, for example the INN, the brand name, manufacturer’s name and the batch number. WHO is currently considering/exploring the use of biological qualifiers for further use in distinguishing all biotherapeutic products.¹⁴

Adequacy of labeling requirements

Effective labeling provides directions that inform the safe and effective use of the product. NRAs should implement labeling policies for non-comparable biotherapeutic products that are consistent with the accepted standards for labeling, including providing all information necessary for a health professional to make prescribing decisions. Non-comparable biotherapeutic products have not demonstrated similarity to the RBP according to the WHO requirements for SBPs, therefore, the label of non-comparable biotherapeutic products should contain information only on the product’s own clinical data that support the registered indications, and should not directly “cut and paste” the RBP’s label. In addition, regulatory authorities could consider including a symbol that makes clear to healthcare professionals that the particular non-comparable biotherapeutic product has not demonstrated similarity to an originator product based on WHO SBP Guidelines.

¹³ http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/; accessed 29 April 2014

¹⁴ 57th Consultation on International Nonproprietary Names for Pharmaceutical Substances
http://www.who.int/medicines/services/inn/57th_Executive_Summary.pdf?ua=1



Key message

Any approved product intended to be a copy of an already licensed RBP that does not meet or is not consistent with WHO regulatory criteria for SBPs - i.e. has not been demonstrated to be similar with regard to quality and non-clinical properties, as well as, clinical safety and efficacy in head-to-head comparative studies - should not be labeled or referred to as a “biosimilar”. Unless a sponsor provides all the necessary scientific evidence qualifying its product as a SBP, any approval should be reassessed by the NRA. It is recognized that a reassessment process may, in some countries, require concomitant changes to the regulatory framework to create an approval process on the basis of WHO expectations for SBP and rDNA products. An opportunity for less experienced NRAs to seek guidance from well-established NRAs and/or WHO to achieve convergence of regulatory and scientific data interpretation could be highly beneficial.

Glossary¹⁵

Comparability Exercise: Head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal to establish similarity in quality, safety, and efficacy. Products should be compared in the same study using the same procedures.

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

Head-to-Head Comparison: Direct comparison of the properties of the SBP with the RBP in the same study.

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

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

Reference Biotherapeutic Product (RBP): A reference biotherapeutic product is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

Similar Biotherapeutic Product (SBP): A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

¹⁵All definitions are taken from the WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), 2009. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf