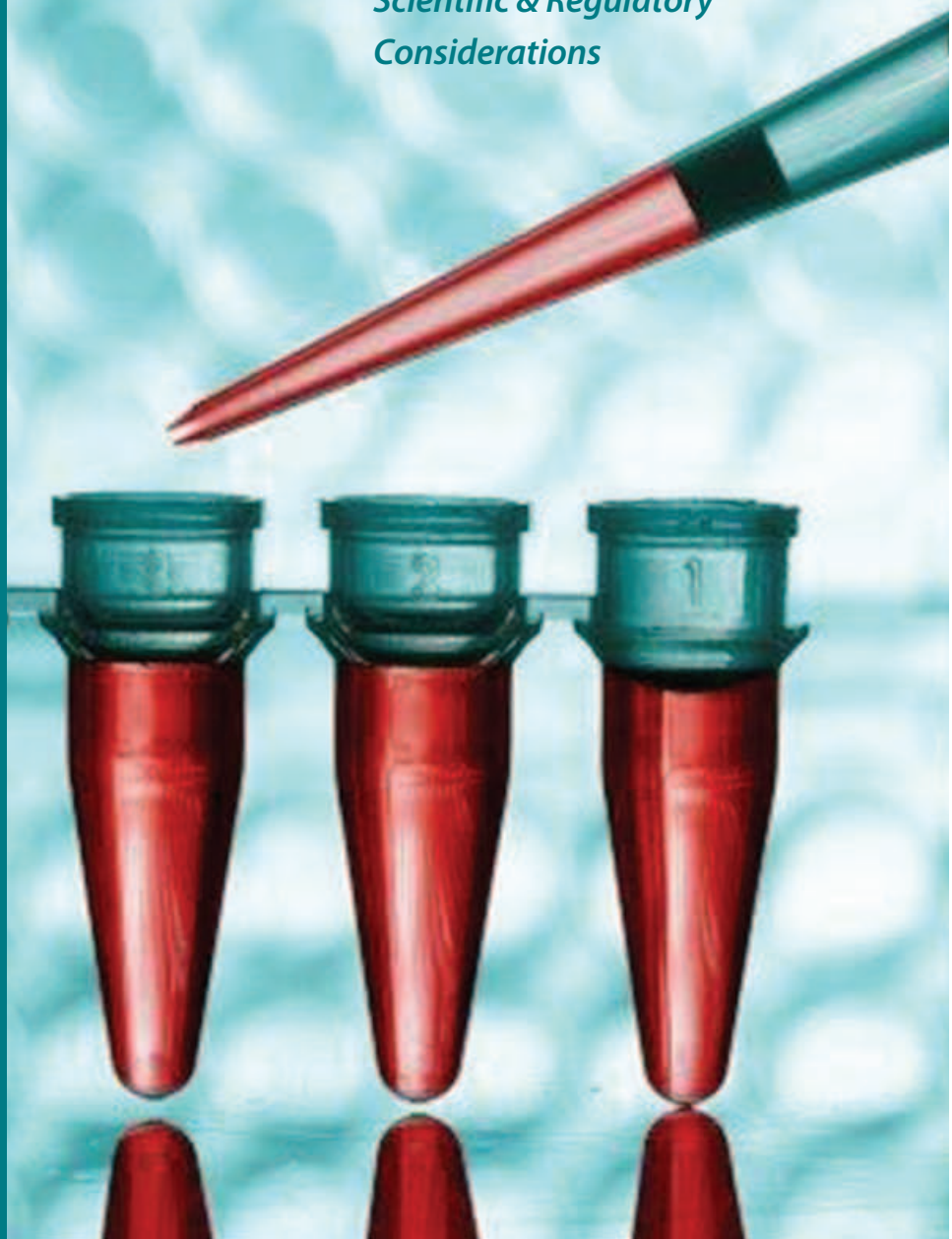
International Federation
of Pharmaceutical
Manufacturers & Associations

Similar Biotherapeutic Products

Scientific & Regulatory Considerations



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Contents

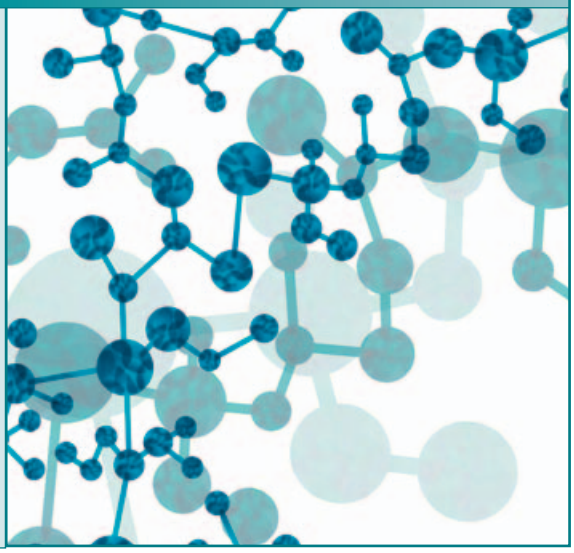
Introducing biotherapeutic medicines

Biotherapeutic medicines[1] are drugs produced by living organisms through highly complex processes, and whose active ingredients are mainly proteins such as hormones, antibodies, cytokines, and insulin[2]. They are predominantly larger and more complex than chemically-synthesized small molecule medicines, are manufactured using living organisms, and their characteristics and properties are influenced by the manufacturing process. Biotherapeutic medicines are a very diverse class of medicines – they include innovative products for the treatment of chronic diseases such as cancer, diabetes, and rheumatoid arthritis, as well as for acute conditions such as myocardial infarction and stroke.

In contrast, small molecule medicines are produced through a step-by-step chemical synthesis process, and their far smaller size and simpler structure allow these products to be well characterized and more easily reproduced. Generally, chemically-synthesized small molecule medicines have much lower molecular weight and are structurally less complex than biotherapeutic medicines. On the contrary, biotherapeutics are large, complex molecules (e.g. monoclonal antibodies generally contain tens of thousands of atoms), with less well characterized structures.

Manufacturing biotherapeutic medicines – protein synthesis

Biotherapeutic medicines are made using living systems, usually by producing a recombinant protein in living cells (such as bacterial or mammalian cells). The first step in the production of a protein is assembling its basic components, amino acids. Twenty different amino acids exist and are encoded by specific sequences of DNA. The chemical building blocks that make up DNA are known as nucleotides and are represented by the letters A, C, G, and T. This code was first deciphered in 1961, when it was discovered that the genetic sequences that encode proteins are organized in triplets of letters, known as codons.



What is an immune response?

The immune system is the sum of the body's mechanisms that help it in protecting itself against foreign agents, including those causing diseases. This system consists of different types of cells (such as white blood cells, also known as leukocytes and soluble substances produced by them, known as cytokines), each of which have a specific task assigned to them in the defense of the body, by identifying and attacking foreign substances (such as viruses and bacteria).

An immune response is the way in which the body actually recognizes and defends itself from these substances. An important concern with all biotherapeutic medicines is the risk of an unwanted immune response – such as an allergic reaction or anaphylactic shock – where the patient shows an immune reaction against proteins in the medicine, limiting its efficacy or affecting its safety.

The complexity of biotherapeutic medicines

Producing biotherapeutic medicines is a complex process. While chemically-synthesized small molecule medicines can be produced with a near-absolute level of uniformity, biotherapeutics, being produced by living cell systems, are subject to micro-heterogeneity – meaning that the final product is understood to be a mixture of protein molecules. The nature of this heterogeneity is highly dependent on the production process – small changes in this process can lead to changes in the final product composition and, consequently, to clinical implications. The phrase "the process defines the product" is often used with biotherapeutic medicines to indicate the importance of the process in defining the identity of the final product.

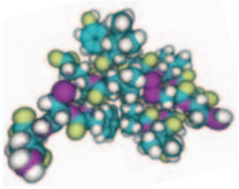
Because of their structural complexity, and impurity profile, biotherapeutic medicines may induce the formation of antibodies and trigger immune responses. Immunogenicity – the ability of a substance to trigger an unwanted or unanticipated immune response or reaction – is a concern in the use of biotherapeutic medicines and must be addressed, to the extent possible, during the development of the medicine.

How do biotherapeutic medicines actually work?

Biotherapeutic medicines are large molecules often designed to specifically disrupt, trigger or replace complex protein-protein, cell-cell, or protein-cell interactions in a patient's body. For example in the case of diabetes, human insulin produced by recombinant DNA technology – the world's first biotechnologically manufactured medicine – acts to replace the missing protein in the patient.

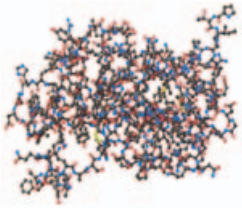
Biotherapeutic medicines are developed based on a very deep understanding of disease biology, and can be targeted to the specific cause, or debilitating symptoms of a disease.

Insulin



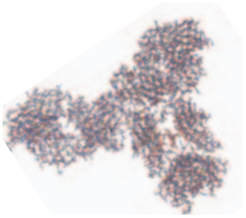
Human insulin is a relatively small protein; it contains 51 amino acids arranged in two chains, and is absolutely essential for the metabolism of carbohydrates. For many years, insulin-dependent diabetic patients could use only insulin extracted from the pancreas of animals. It was efficacious, but susceptible to a higher incidence of immunogenic reactions, which, among other consequences, reduced the effectiveness of treatment. In 1980, came the first human insulin produced by recombinant DNA technique in a culture of E. coli bacteria, superior in quality to the animal-derived products and in sufficient quantities to meet demand. Intentional changes in the amino acid sequence of the natural hormone gave rise to second-generation insulins, the so-called insulin analogs, which include faster-acting as well as slow, prolonged-acting products.

Growth Hormone



Human growth hormone is a non-glycosylated protein (solely composed of a specific sequence of amino acids) containing 191 amino acids and is produced in the anterior pituitary. It regulates important metabolic functions, has effects on almost all organs of the body, and is essential for the development of the body. Insufficient secretion leads to dwarfism and other forms of short stature in children. For many years, patients who needed to take growth hormone had access to only the product extracted from cadavers. However, production was not sufficient to meet demand, and prices were very high. In 1982, with the discovery of the prion that transmits the degenerative brain disease known as Creutzfeldt-Jacob Disease (the bovine version was called "mad cow disease"), justified suspicions were raised that cadaveric material could be associated with the transmission of the disease. In April 1985, the U.S. Food and Drug Administration (FDA) reported three cases of Creutzfeldt-Jacob disease in patients treated with growth hormone, and other cases were reported later. In September of that year, the pharmaceutical industry launched the first recombinant human growth hormone produced in E. coli cultures. This is one of many great examples of how molecular biotechnology was used to address an unmet medical need through the production of a safer medicine.

Monoclonal Antibodies



Antibodies are glycoproteins (proteins with attached sugar units) produced by B cells (a type of white blood cell or lymphocyte) of the immune system. Antibodies have the remarkable ability to specifically detect, recognize, bind, and inactivate molecules assumed to be foreign to the body, called antigens. It is possible to induce the formation of antibodies against a single antigenic component by a single clone of B cells, which are highly specific and are called monoclonal antibodies. Currently, it is possible to develop monoclonal antibodies directed to a vast range of molecular targets. Using monoclonal antibodies it has been possible to develop innovative treatments for various cancers, cardiovascular diseases, autoimmune diseases, transplant rejection, and sophisticated reagents for diagnostic tests. The first commercially produced monoclonal antibody was made available in 1986, for the prevention of transplant rejection. They were initially produced from mouse cells and, therefore, known as murine. Later, mixed molecules were created with murine and human fragments (known as chimeric) with minimized murine components (known as humanized), and, finally, fully human, hoping to reduce immunogenicity problems for patients. Several dozen monoclonal antibodies are now available for the prevention, diagnosis, treatment and cure of various diseases.

The WHO Guidelines define similar biotherapeutic products as "a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference product."

Similar biotherapeutic products or biosimilars

Once the exclusivity and patent protection on a specific originator biotherapeutic medicine expire, the registration and marketing of similar biotherapeutic products (SBPs), or biosimilars, e.g. subsequent versions of an existing biotherapeutic product, becomes possible[3]. As their name implies, biosimilars are similar, but not the same as their originator biotherapeutic medicine of reference. Indeed, biosimilars are not the same as generics, which have simpler active ingredients that can be shown to be identical to their reference molecule[4].

Due to the complex nature of biotherapeutic medicines, the licensing of biosimilars requires specialized regulatory pathways and specific development and evaluation standards to address their unique nature. Several regional and national regulatory authorities have already begun applying legislation and guidelines suited to these products.

For example, in 2005 the European Medicines Agency (EMA) implemented the first regulatory framework exclusively for the authorization of biosimilars[5]. A few years later, in 2009, the World Health Organization (WHO) developed Guidelines that served as a blueprint for countries in the development and evaluation of similar biotherapeutic products[6].

In their definitions these regulations and guidelines provide a useful foundation to understand the unique characteristics of biosimilar medicines, and how they significantly differ from chemically-synthesized small molecule generic medicines.

- The WHO Guidelines define similar biotherapeutic products as "a biotherapeutic product which is **similar** in terms of quality, safety and efficacy to an already licensed reference product".
- The EMA[7] states that "a biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized 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".
- The US FDA[8] describes a biosimilar as "a biological product that is **highly similar** to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency".
- Japan's PMDA[9] states that a "follow-on" biologic is a biotechnological drug product developed to be **comparable** in regard to quality, safety and efficacy to an already approved (in Japan) biotechnology-derived product of a different company".

The WHO "Guidelines on evaluation of similar biotherapeutic products" define an originator as "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".

Assessing biosimilarity

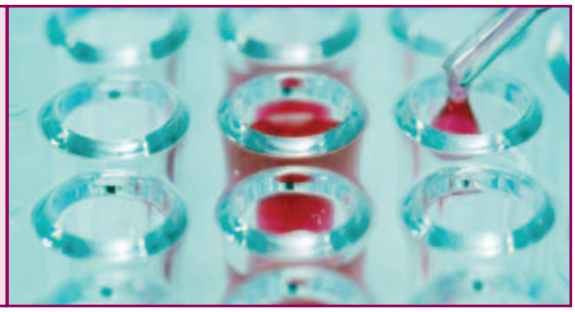
Unlike chemically-synthesized small molecule generic medicines, it is impossible for biosimilars to be exact copies of their reference biotherapeutic product (RBP)[10]. Given their complex nature, they require distinct regulatory pathways from those applied to generic medicines. This need has been recognized by the WHO and by several regional and national regulatory authorities that have acted accordingly in order to safeguard, and protect, patient safety.

An integral part of these distinct pathways is the determination of high similarity, which is needed to ensure that biosimilars can actually achieve the expected results without compromising patient safety. High similarity is determined through specific comparability exercises, defined by the WHO as "the head-to-head comparison of a biotherapeutic product with a licensed originator product, with the goal to establish similarity in quality, safety, and efficacy[11]".

The aim of this biosimilarity exercise is to demonstrate that the biosimilar under development and the RBP are similar at the level of the finished product, meaning that the patient can expect a comparable clinical profile between the two medicines. If it has been demonstrated that there is no impact on the clinical profile, minor differences between the two products may be scientifically justified. To this end, the WHO Guidelines define similarity as "the absence of a relevant difference in the parameter of interest that is studied"[12]. The US FDA defines this concept as "the absence of clinically meaningful differences in terms of quality, safety, and efficacy".

Structural or process related differences between a biosimilar and the RBP could potentially lead to clinical impacts on the effectiveness and safety of the biosimilar. This is especially the case for more complex biotherapeutics – such as monoclonal antibodies – since the mechanisms that make these medicines so successful may not be fully known. Similarly, different patient groups may respond differently to the same biotherapeutic, due to differences in age, gender, sex, co-morbidities, or other medications taken. Thus, appropriate evaluations of similarity of efficacy, safety and immunogenicity should be conducted in the patient population(s) that are most sensitive to differences in these parameters[13]. The patient population most sensitive to differences in efficacy may not, for example, be the same as the patient population(s) best suited for detection of potential differences in immunogenicity or safety.

A generic medicine contains an exact copy of the active pharmaceutical ingredient (API) of a reference chemically-synthesized small molecule originator medicine. Once these identical copies are proven to be bioequivalent to the originator medicine, their approval relies on the safety and efficacy of the reference medicine.



Understanding the concept of biosimilarity

In order to implement a science-based regulatory pathway for biosimilars consistent with international guidelines and standards, it is important to understand the concept of biosimilarity. As recognized by the WHO, the "ability for a similar biotherapeutic product to be authorized based on reduced non-clinical and clinical data depends on proof of its similarity to an appropriate reference biotherapeutic product through the comparability exercise". For biosimilars to be approved, it is essential that they undergo stepwise comparability exercises starting with a comparison of their quality characteristics against those of the RBP. The main objective of these exercises is to demonstrate a comparable clinical profile. This key element is a necessary prerequisite for the reduction of non-clinical and clinical data. To be "highly similar", a biosimilar must not have any relevant differences in terms of quality (e.g. demonstrate molecular similarity), safety, and efficacy. If the studies demonstrate a "high similarity" with respect to quality, then non-clinical and clinical studies may be abbreviated. As recognized by the WHO, however, if there are "relevant differences" found in the results of quality, safety and efficacy studies, "the product should not qualify as a [biosimilar]," and further clinical studies will likely be required to support market approval.

Regulating biosimilars

As previously mentioned, science-based regulatory standards for medicines are essential to ensure patient safety. Given the complex nature of biotherapeutic medicines and the resulting challenges in characterizing them, specialized testing is required to ensure the safety and efficacy of biosimilars, which should thus be regulated via pathways that are distinct from those applied to generic medicines.

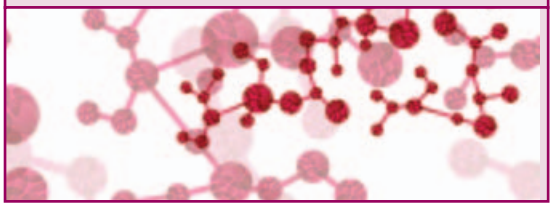
Like all biotherapeutic medicines, biosimilar must be evaluated on the basis of a rigorous regulatory pathway to ensure sound scientific principles and appropriate requirements for demonstration of high similarity in quality, safety, and efficacy to an approved RBP.

A robust, science-based pathway for the development and evaluation of a biosimilar should require thorough, comparative analytical characterization of the proposed biosimilar and an appropriate RBP. The purpose of the comparative analytical characterization is to demonstrate that the proposed biosimilar and RBP are highly similar at a molecular level. While comparative analytical characterization forms the foundation of the biosimilarity assessment, even state-of-the-art analytical technology may not identify all differences between a proposed biosimilar and the RBP. Even with a robust and comprehensive analytical characterization of the proposed biosimilar, uncertainties regarding the biosimilarity and the clinical implications of differences found will remain and must be investigated through additional comparative studies, including pre-clinical and clinical studies. The preclinical and clinical testing steps should be designed (and proceed) only once a robust analytical program has demonstrated high similarity between the proposed biosimilar and the RBP at a molecular level (step-by-step approach).

Further, given the complexity of biological products and the fact that products from different manufacturers may be similar, but not the same, a robust pharmacovigilance system is a key component of a science-based regulatory pathway for all biotherapeutics, including biosimilars.

Prior to the implementation of a science-based pathway for the approval of biosimilars, some biological products have been introduced on the market in some countries. Because the adequacy of the comparative studies to an appropriate RBP and the basis for approval are unclear, these products are best described as non-comparable biological products. As regulatory authorities around the world seek to implement distinct, science based-pathways for biosimilars, there is simultaneous recognition of the need to appropriately regulate non-comparable biological products that may not have been evaluated against internationally-recognized standards for biosimilars.

The WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.



Considerations for a clear, science-based regulatory pathway for biosimilars:

1. Establish a regulatory framework that is distinct from that for generic chemically-synthesized small molecule medicines
2. Require that sponsors of the biosimilar select an appropriate RBP approved on the basis of a complete dossier for use in comparative studies
3. Require that the proposed biosimilar and the RBP can be demonstrated to share the same mechanism of action (to the extent known), dosage form, strength, and route of administration
4. Require that sponsors of biosimilars demonstrate a comprehensive understanding of the physicochemical and biological characteristics of the biosimilar product and RBP through thorough comparative analytical studies
5. Require sponsors of biosimilars to confirm high similarity of the proposed biosimilar to the RBP in terms of safety and efficacy through appropriately designed tailored non-clinical and clinical studies
6. Require that immunogenicity of the proposed biosimilar be adequately evaluated (i.e. in an appropriate number of patients to permit the detection of differences in the types and rates of immunogenic events) pre-market and also appropriately evaluated post-market, and compared to that of the RBP
7. Provide for mechanisms to ensure clear prescribing, dispensing, use and pharmacovigilance of biosimilars once marketed (e.g., clear labeling, unique identifiers, patient and physician education, and an appropriate pharmacovigilance plan)

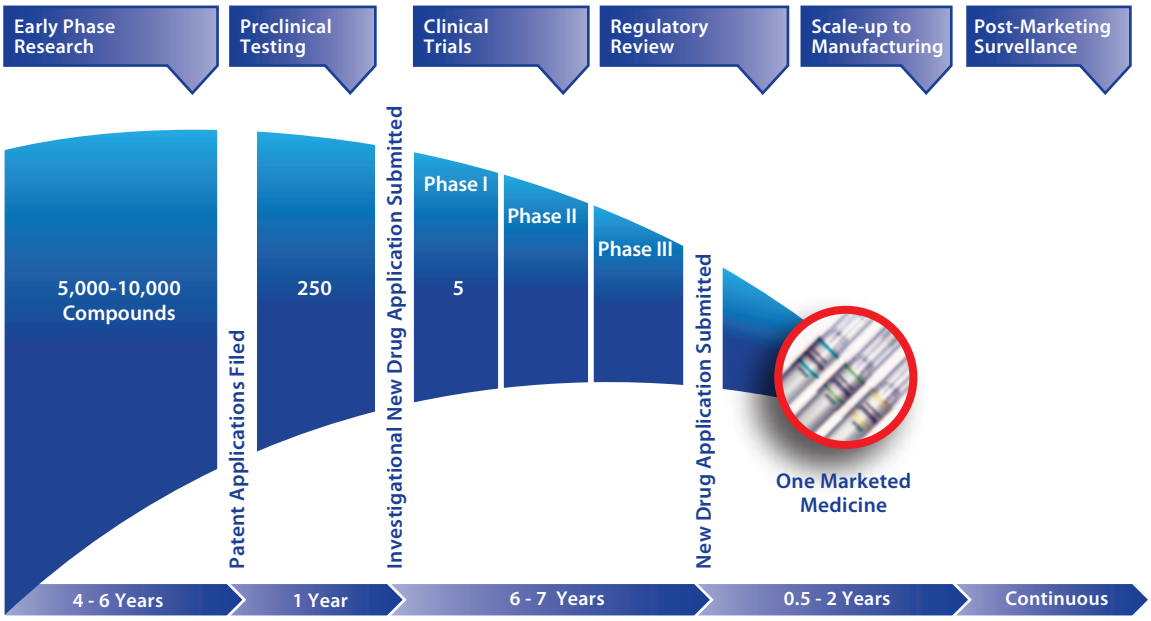
The reference product

The WHO defines the reference biotherapeutic product (RBP) 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 an RBP". The RBP also provides the basis for dose selection and route of administration. The rationale for the choice of the RBP should be provided by the manufacturer of the biosimilar in the submission to the national registration agency.

Development and manufacturing of biosimilars

Manufacturers of similar biotherapeutic products have to establish their own process and manufacturing method with appropriate controls. Demonstrating similarity between an RBP and a proposed biosimilar will require more extensive and comprehensive data than assessing the comparability of an approved product before and after a manufacturing process change. A manufacturer modifying an established and approved manufacturing process will have extensive knowledge and information about both the product and the existing process, including established controls, acceptance parameters and a broad analytical data base that is linked to the product's clinical development experience. This will facilitate the establishment of analytical comparability, e.g. the demonstration that pre- and post-change products are highly similar with respect to safety and efficacy.

Since the manufacturer of a proposed biosimilar has no access to the development and manufacturing data of the originator, it will use a different manufacturing process (meaning a different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) as compared to the one used to produce the RBP. Given the high sensitivity of biotherapeutic products to even seemingly negligible manufacturing process changes, minor structural differences between the biosimilar and the RBP are expected. Where quantitative and/or qualitative differences are detected, such differences should be demonstrated to have no relevance for the clinical performance of the biosimilar, and only be accepted if they are clinically meaningless. The potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone, and therefore a stepwise development approach will always be required including targeted, comparative pre-clinical and clinical studies driven by the results of the analytical comparability assessment and followed by strong post-marketing surveillance (pharmacovigilance). A strong pharmacovigilance system can in fact ensure the clear prescribing, dispensing, using, and tracking of biosimilars once marketed.



As we have seen, biosimilarity is demonstrated when a product is highly similar in terms of quality, safety, and efficacy to an RBP. So then, how are these assessments made during the biosimilar development?

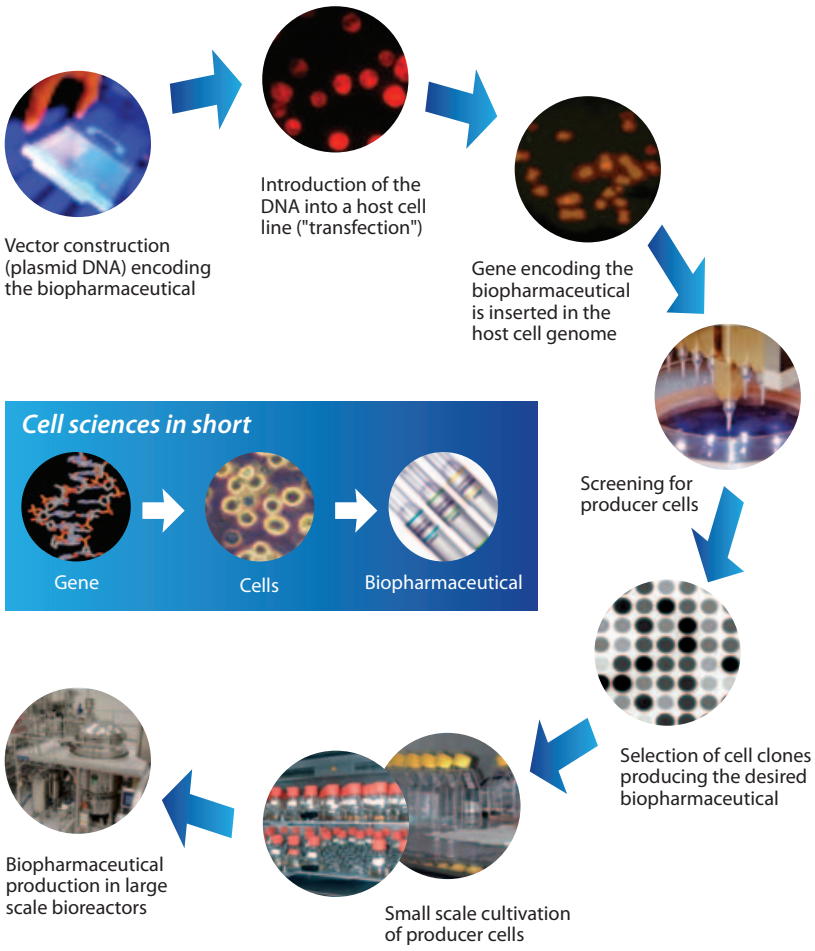
1 Quality considerations:

A full quality dossier for both drug substance[15] and drug product[16] will have to be submitted, in compliance with the standards required by national regulatory authorities for originator products, along with an extensive structural and functional characterization comparison of the proposed biosimilar with the RBP. A biosimilar is generally derived from a separate and independent master cell bank – though based on a gene construct encoding the same amino acid sequence as the RBP – and manufactured by using an independent process and control system. These should be selected and designed to meet the required criteria for product similarity. In order to evaluate analytical (also known as "Chemical, Manufacturing and Control" or "CMC") comparability, the manufacturer will have to carry out a comprehensive physiochemical and biological characterization of the proposed biosimilar in head-to-head comparison with the RBP. The development of a biosimilar involves thorough characterization of a number of representative lots of the RBP, and then engineering a manufacturing process that will produce a product that is highly similar to the RBP with respect to critical product quality attributes, mainly for those product attributes that may impact clinical performance, also known as "critical quality attributes".

2 Efficacy considerations:

The biosimilar manufacturer will not have to establish patient benefit for the product, since this is done by the originator, along with dose targeting studies. A targeted clinical study program has, however, to be designed in order to confirm high similarity in safety and efficacy of the biosimilar to its RBP. As certain factors - such as concomitant medications, illnesses, dose selection, patient demographics and immune status - may impact the ability to detect clinically important differences, the program should be conducted in a setting or settings sensitive to potential differences. Independent from the study design, the results obtained from the clinical trial(s) will determine whether the biosimilar and the RBP can be considered clinically similar. If clinically relevant differences are found, the new product should not be considered similar to the RBP but may be developed as a stand-alone product. It should be noted, however, in some instances, that the indication most sensitive for establishing efficacy may not necessarily be the indication most sensitive for establishing difference in immunogenicity. Considerations regarding immunogenicity are further discussed below.

How does a biotech process work?



3 Safety considerations:

Non-clinical evaluation – comparing the biosimilar and the RBP in relevant *in vitro* and, if necessary, *in vivo* models – is required before proceeding to any clinical studies in humans. If these data are acceptable, clinical studies can begin to collect the needed safety data for the biosimilar product in a justified, relevant patient population prior to marketing authorization. Realizing that some rare adverse events may not be detected during clinical trials, close monitoring of clinical safety of the biosimilar and appropriate post-marketing studies are necessary to ensure patient safety.

The potential for a biosimilar to produce an immune reaction must be assessed during the development phase, before the medicine is made broadly available to patients. Indeed, immunogenicity of biotherapeutic products should always be investigated pre-authorization in the most sensitive patient population – ideally not having a compromised immune system and over a relevant period of time in case the treatment regimen requires repeated product administration.

Even if efficacy and safety of a biosimilar and RBP appear to be similar in one patient population, immunogenicity may still be different in another patient population, and may significantly impact the pharmacokinetics, safety and efficacy of any biotherapeutic product if not specifically assessed, e.g. in case the data were extrapolated. Since pre-licensing immunogenicity data may be limited, further characterization of the immunogenicity profile may be necessary post-marketing, particularly if rare antibody-related serious adverse events occur that are not likely to be detected in the pre-marketing phase.

If similar pharmacokinetics and efficacy of the biosimilar to the RBP have been demonstrated in the patient population(s) most sensitive to potential differences, extrapolation of these data to other indications of the RBP (not studied in independent clinical studies with the biosimilar and less sensitive to detect respective differences) may be possible under certain circumstances – e.g. if the clinically relevant mechanism of action is known and the same for the indications in question, and if no aspect of the new indication is deemed likely to make it more sensitive to potential differences in the product.

Considerations on multiple indications – extrapolation of clinical data from one indication to another

Where a biosimilar meets the requirements for licensure for one indication of use that has been approved for the originator medicine, it cannot be assumed that it is appropriate to automatically extrapolate clinical data to support a different condition of use. Any extrapolation of clinical data to additional indications in the originator product requires sound scientific justification[17, 18, 19]. This justification requires adequate consideration of:

- The fact that the mechanisms of action are the same and are sufficiently understood
- That fact that comparative clinical testing has been done in the setting(s) most sensitive to potential differences in safety, efficacy and immunogenicity
- The differences in benefit-risk balance between studied and unstudied indications
- Differences in the patient populations within and between indications.

The complex issues surrounding extrapolation of indications for biosimilar medicines affirm that the biosimilarity exercise and the regulatory review of a biosimilar application cannot be reduced to a technical, analytical exercise – in-depth understanding and consideration of the above principles, and how they apply to a particular product, is needed to warrant extrapolation. Potential risk to patient safety must be considered when evaluating the justification for extrapolation.

Summing up – key facts on biosimilars

1. Biosimilars are similar, but not identical versions of their originator biotherapeutic product of reference.

2. Biosimilars are not the same as chemically-synthesized small molecule generic medicines, which have simpler chemical structures and whose active pharmaceutical ingredients are identical to those of their reference originator medicines.

3. Biosimilars are large, complex molecules that require distinct regulatory pathways from those applied to generic medicines.

4. Biosimilarity is a regulatory assessment. In order to be approved as a biosimilar, a medicine must be proven to be highly similar to its RBP in terms of quality, safety, and efficacy. This high similarity is determined through specific biosimilarity exercises at all three levels (analytical; pre-clinical; and clinical studies), which consist of head-to-head comparison between the proposed biosimilar and its RBP. Where a biosimilar meets the requirements for licensure for one indication of use that has been approved for the originator medicine, it cannot be assumed that it is appropriate to automatically extrapolate clinical data to support a different condition of use.

5. Science-based regulatory standards and pathways, together with robust pharmacovigilance systems, are of critical importance to ensure the safety of patients around the world.

References

1 Biotherapeutic medicines are referred to also as biologics; biological medicines; and biopharmaceuticals

2 IFPMA (2012) Biotherapeutic medicines: grasping the new generation of treatments. Geneva: International Federation of Pharmaceutical Manufacturers and Associations. Available at http://www.ifpma.org/fileadmin/content/Publication/2012/IFPMA_BiotheraputicsWeb4.pdf

3 An innovative biotherapeutic medicine may be subject to a period of exclusivity due to applicable intellectual property protection. This is usually a combination of applicable patents, protecting inventions embodied in or related to a particular product, and regulatory data protection, which protects the clinical test and other data submitted to marketing approval authorities.

4 EMA (2005) Guideline on similar biological medicinal products [online] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf

5 Ibid.

6 WHO (2009) Guidelines on evaluation of similar biotherapeutic products (SBPs) [online] http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

7 Current new draft EMA Guidelines on Similar Biological Medicinal Products (March 2013)

8 US FDA (2009) Biologics price competition and innovation act [online] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf

9 Japan PMDA (2009) [online] http://www.jpma.or.jp/english/parj/pdf/2012_ch02.pdf

10 The WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) define a reference biotherapeutic product as follows "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".

11 WHO (2009) Guidelines on evaluation of similar biotherapeutic products (SBPs) [online] http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

12 Ibid.

13 EU draft 2013 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [online] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf

14 For more information on pharmacovigilance for biotherapeutic medicines, please see the IFPMA Position Paper "Pharmacovigilance principles for biotherapeutic medicines" available at http://www.ifpma.org/fileadmin/content/Innovation/Biotherapeutics/Pharmacovigilance_Principles_vF.pdf

15 The WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) define a drug substance as "The active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product. It may be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain other components such as buffers".

16 The WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) define a drug product as "A pharmaceutical product type that contains a drug substance, generally in association with excipients".

17 EU draft 2013 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [online] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf

18 WHO (2009) Guidelines on evaluation of similar biotherapeutic products (SBPs) [online] http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

19 US FDA draft guidance "Biosimilars: Questions and answers regarding implementation of the Biologics Price Competition and Innovation Act" of 2009

Glossary

Active ingredient: The component of a drug that provides medicinal value. Many drugs combine several active ingredients, and the interaction between these ingredients may be critical to the function of the drug.

Biosimilar or Similar biotherapeutic product (SBP): A product that is similar to an already authorized originator biotherapeutic product, with demonstrated similarity to the latter in terms of quality, efficacy and safety assessed through a direct (or head-to-head) comparison.

Biotechnology: The collection of processes that involves the use of biological systems. For some industries, these processes involve the use of genetically engineered organisms.

Biotherapeutic medicines: Medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances produced by living organisms (such as cells, viruses and bacteria). They are larger and more complex than chemically synthesized drugs and their characteristics and properties are typically dependent on the manufacturing process itself.

Chemically-synthesized small molecule medicines: Medicines produced through a step-by-step chemical synthesis process. They are characterized by a small molecule composition and are relatively simple organic compounds containing few functional molecular groups.

Comparability exercise: The head-to-head comparison of a biotherapeutic product with a licensed originator product, with the goal to establish similarity in quality, safety, and efficacy.

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

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

Generic medicines: A medicine that contains an exact copy of the active pharmaceutical ingredient (API) of a reference chemically-synthesized small molecule originator medicine. Once these identical copies are proven to be bioequivalent to the originator medicine, their approval relies on the safety and efficacy of the reference medicine.

Growth hormone: Human growth hormone is a non-glycosylated protein (solely composed of a specific sequence of amino acids) containing 191 amino acids and is produced in the anterior pituitary. It regulates important metabolic functions, has effects on almost all organs of the body, and is essential for the development of the body. Insufficient secretion leads to dwarfism and other forms of short stature in children.

Immune response: The way in which the body recognizes and defends itself from foreign substances.

Immunogenicity: The ability of a substance to trigger an unwanted or unanticipated immune response or reaction.

Insulin: Human insulin is a relatively small protein; it contains 51 amino acids arranged in two chains, and is absolutely essential for the metabolism of carbohydrates.

Monoclonal antibodies (MABs): Discovered in 1972, these therapeutic antibodies bind specifically to certain molecules and can prevent them from causing illness. They also guide the body's immune system to help it target agents that can cause illness – including infectious diseases, breast cancer and rheumatoid arthritis.

Non-comparable biological products: Those biological products introduced in a given market prior to the implementation of a science-based pathway for the approval of biosimilars.

Non-clinical evaluation: The comparing of the biosimilar and the RBP in relevant *in vitro* and, if necessary, *in vivo* models. This step is required before proceeding to any clinical studies in humans.

Originator medicine: 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 problem.

Reference biotherapeutic product (RBP): 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 an RBP.

Similarity: The absence of a relevant difference in the parameter of interest that is studied.

About the IFPMA:

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 1.3 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

IFPMA manages global initiatives including: IFPMA Developing World Health Partnerships Initiatives, which studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries; IFPMA Code of Practice, which sets standards for ethical promotion of medicines; IFPMA Clinical Trials Portal, which helps patients and health professionals find out about on-going clinical trials and trial results.

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