



# IFPMA

International Federation of Pharmaceutical  
Manufacturers *and* Associations

## IFPMA Points to Consider in the drafting of WHO Guidelines for Biosimilar Medicinal Products

November 22, 2007

The IFPMA Biologicals and Vaccines (B&V) Biotech Working Group welcomes and supports the recommendation made during the WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products, held 19 - 20 April, 2007, WHO HQ, Geneva, where it states in the conclusion:

*“It was agreed that WHO should develop a global regulatory guideline for biosimilar products. Issues of critical importance that should be addressed in this guideline include the principles for the evaluation of these products, as well as regulatory pathways for their licensing and regulatory oversight. Furthermore, the need for international standards and reference preparations for product evaluation should be considered. As a first step towards the development of guideline, a WHO working group should be established to take this issue forward.”*

In view of this initiative, the IFPMA B&V Biotech Working Group provides some points to consider for such a document, which are based on contributions from its member experts.

### Scope

These points to consider identify scientific standards that should be met for the approval of a similar biological medicinal product (a biosimilar).

The scientific standards apply only to biological medicinal products that contain biotechnology-derived therapeutic proteins as their active substances that are developed to be similar to already existing, approved products. They do not cover other biologicals such as vaccines and their derivatives, allergen products, blood and plasma products, gene therapy, cell processing or other biological medicinal products that do not contain biotechnology-derived therapeutic proteins as their active substances.

### Introduction

A biosimilar (or similar biological medicinal product) is a new biological medicinal product claimed to be “similar” to an already approved reference product<sup>1</sup>. A biosimilar product is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the originator product. Comparative quality, non-clinical and clinical studies are needed to substantiate the similarity of structure/composition, quality, safety and efficacy between the new biosimilar and the chosen reference medicinal product.

Biosimilars can be approved based in part on an exercise to demonstrate similarity to an already authorized reference product. The same reference medicinal product should be used throughout the entire assessment in order to generate valid data and conclusions. The active substance of a biosimilar must be similar, in molecular and biological terms, to the active substance of the reference medicinal product. The pharmaceutical form, strength and route of administration should be the same as that of the reference product. Any differences between

---

<sup>1</sup>The term, “reference product”, used throughout the text refers to “reference medicinal product”.

the biosimilar and the reference product should be justified by appropriate studies on a case-by-case basis.

Biosimilarity should be distinguished from comparability. Comparability is a process undertaken by a single manufacturer to assess the implications of manufacturing process changes on a specific product. Such an assessment can be based on the product's process-related parameters and quality attributes. In some cases, nonclinical and/or clinical data are required to demonstrate comparability. Regulatory guidance on this assessment is provided in ICH Q5E<sup>1</sup>. It should be noted that application of this guidance and the principles of comparability are limited to manufacturing changes made by a single manufacturer and are not applicable to biosimilar manufacturers with whom no contractual agreements or sharing of information with the innovator\* are in place.

This document focuses on the key elements that need to be addressed when developing guidelines for biosimilar products. Quality, non-clinical and clinical standards are addressed, followed by post-marketing surveillance/risk management, interchangeability and substitution, nomenclature and labeling.

### **Quality standards**

A biosimilar product is derived from a separate and independent master cell bank, using independent manufacturing and control methods, and should be required to meet the same quality standards as required by the National Regulatory Agency for innovator biological medicinal products. Such a quality standard is defined as the chemistry, manufacturing and controls information that would be submitted in support of a marketing authorization application (e.g., Module 3 of the ICH common technical document<sup>2</sup>) in addition to the appropriate standards relating to manufacture of the biosimilar (i.e., good manufacturing practice). Such standards apply to the manufacture of both the drug substance (active ingredient) and the drug product.

The biosimilar manufacturer should be required to conduct a comprehensive physicochemical and biological characterization of the biosimilar product and comparison to the reference product.

The base requirement for a biosimilar is that it is demonstrated to be “highly similar” to the reference product. Due to the heterogeneous nature of therapeutic proteins, the limitations of analytical techniques and the unpredictable nature of clinical consequences to structural/biophysical differences, it is not possible to define the exact degree of biophysical similarity that would be considered sufficiently similar to be regarded as biosimilar, and this has to be judged for each product independently.

Comparisons made against official data, e.g., pharmacopoeial monographs, are limited in their ability to draw meaningful conclusions and will not be sufficient to demonstrate similarity of the biosimilar to the reference product. Furthermore, reference standards are not appropriate for use as a reference product.

However, the following structural or biophysical differences would not be allowed in a biosimilar when compared to the selected reference product:

- Different amino-acid sequence
- Different number and structure of glycans

---

<sup>1</sup> ICH Q5E Guidelines on “Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process”: <http://www.ich.org/LOB/media/MEDIA1196.pdf>

<sup>2</sup> ICH Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality <http://www.ich.org/LOB/media/MEDIA556.pdf>

\*The term, “innovator”, used throughout the text refers to the original manufacturer who has researched, developed and has obtained the original authorization for a specific biological medicinal product.

- Different locations of glycans
- Significantly different isoform (and glycoform for glycosylated proteins) distribution
- Presence/absence of conjugated moieties (e.g., PEG, Fc-antibody portion) as compared to the reference product

### **Non-clinical standards**

Biosimilars should undergo appropriate non-clinical testing sufficient to justify the conduct of clinical studies in healthy volunteers or patients.

Such studies should include comparative studies and be of sufficient size and duration to establish with reasonable certainty sufficiently similar pharmacological, pharmacokinetic and toxicological characteristics as the reference product.

### **Drug Product**

As it has been shown that dosage form can impact clinical outcomes, the dosage form for the biosimilar should be the same as the one used for the reference product.

### **Clinical Standards**

An applicant for a biosimilar must demonstrate the safety and efficacy of the product. A biosimilar must have similar clinical characteristics to the reference product for each of the different therapeutic applications (i.e., indications) for which approval is sought. Clinical similarity should be demonstrated by appropriate comparative, well-designed and appropriately powered clinical studies proving a similar benefit-risk ratio and the absence of clinically meaningful differences between the biosimilar and the reference product (e.g., unexpected lack of efficacy, high immunogenic potential compared to the reference product). The studies should be designed to detect differences and to allow a conclusion of similarity (i.e., a non-inferiority design is not appropriate). Such studies are expected to demonstrate the following outcomes:

- The biosimilar should display similar efficacy at the same doses as the reference product in comparative clinical studies within appropriately defined equivalence margins (e.g. non-inferiority margins). Such margins should be pre-defined by regulation or guidance in agreement with clinical experts, and should exclude a clinically meaningful difference of efficacy.
- The clinical efficacy endpoint(s) used in the clinical study should be appropriate measures of clinical outcome, or where applicable, appropriately validated surrogate markers for the clinical outcome.
- The safety of the biosimilar should be demonstrated to be similar to the reference product in terms of nature, seriousness and frequency of adverse events.
- The immunogenic potential of the biosimilar should be adequately assessed and compared to the innovator product in appropriately designed clinical trials by sufficiently sensitive and appropriately validated testing platforms. Such testing should be capable of not only detecting antibodies, but also characterizing their binding and/or neutralizing capacity.

### **Post-Marketing Surveillance and Risk Management**

Post-marketing surveillance systems (pharmacovigilance) should be in place, to enable continued evaluation of benefit/risk and potential identification of less frequent adverse events

that could not be adequately studied before approval. Such systems should include provisions for passive pharmacovigilance and active evaluations such as registries and post marketing clinical studies.

Such systems should be capable of distinguishing between and tracking different products and manufacturers of products in the same class of medicinal products (e.g., epoetins, insulins, somatropins). Such capability is essential to help ensure adverse events are properly attributed to the relevant medicinal product (i.e. traceability).

It is a responsibility of National Authorities to have a regulatory framework in place to help ensure that appropriate pharmacovigilance and risk-management requirements are fulfilled.

### **Interchangeability**

Biosimilars are not generic products and cannot be identical to their reference products. Further, the formulations may be different and this can have a profound effect on their clinical behavior. In addition, a biosimilar does not necessarily have the same indications or clinical use as the reference product. Therefore, given current science, they cannot be considered interchangeable with the reference product or products of the same class. Equally, automatic substitution (i.e. the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) cannot apply to biosimilars. Such an approach ensures that treating physicians can make informed decisions about treatments in the interest of patients' safety.

### **Naming of products**

In order to facilitate effective pharmacovigilance monitoring and tracing of adverse safety events and to prevent inappropriate substitution, the specific medicinal product (innovator or biosimilar) prescribed by the treating physician and dispensed to the patient should be clearly identified. Therefore, all biological medicinal products should be distinguishable by name.

### **Labeling**

The labeling of biosimilars should provide transparent information to healthcare professionals and patients on issues that are relevant to the safe and effective use of the medicinal product.

It is expected that the labeling of the biosimilar meet the following criteria:

- A clear indication that the medicine is a biosimilar of a specific reference product.
- The invented name, common or scientific name and the manufacturer's name.
- Unique clinical data for the biosimilar describing the clinical similarity (i.e., safety and efficacy) to the reference product and in which indication(s).
- Clear guidance that automatic substitution rules should not be applied to the biosimilar, its reference product or other medicinal products of the same class.

## GLOSSARY OF TERMS

### **Antibody**

A spectrum of proteins of the immunoglobulin family that is produced, in the human (or animal) body, in response to an antigen (e.g., a virus or bacterium, or a foreign protein unknown to the body's immune system). Antibodies are able to combine with and neutralize the antigen, as well as to stimulate the immune system for defense reactions.

Retrieved from "<http://www.biology-online.org/dictionary/Antibody>" :This page was last modified at 21:16, October 3, 2005.

### **Antigen**

A substance that reacts with the products of a specific immune response.

### **API (Active Pharmaceutical Ingredient, or Drug Substance)**

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product by formulation with excipients and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

(ICH Q7A, [http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272\\_96843](http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843))

### **Biogeneric**

Term sometimes used for therapeutic protein drugs similar to an originator's product launched after patent expiry of the originator's product. However, since the standard generic approach for marketing authorization application (i.e., demonstration that it is the same active ingredient and of bioequivalence with a reference medicinal product), which is normally applied to chemically derived medicinal products, is scientifically not appropriate for biological/biotechnology-derived products due to their complexity, the term "biogeneric" does not describe these products in an appropriate way. Therefore, the regulatory authorities have chosen to describe these products as "similar biological medicinal products" (or "biosimilars") in the European Union, and "follow-on protein products" (or "follow-on biologics") in the U.S., respectively.

### **Biologic (Biological medicinal product)**

Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. They often are at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other treatments are available.

(Taken from: <http://www.fda.gov/Cber/faq.htm#3>).

### **Biosimilar (or similar biological medicinal product)**

A new biological medicinal product claimed to be "similar" to an already approved reference medicinal product, which is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the originator product.. In Europe, the term "biosimilar" is used as a short designation for "similar biological medicinal products". The requirements for the Marketing Authorization Applications for biosimilars are based on the demonstration of the similar nature of the two biological medicinal products (biosimilars versus reference product) and require comparative quality, non-clinical and clinical studies to demonstrate safety and efficacy.

For details, see <http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf>.

### **CMC (Chemistry, Manufacturing, and Control)**

The section of a submission dealing with the substance properties, manufacturing and quality control, intended for evaluating the provided information in the context of the current standards in chemical science and technology, and the current regulations.

### **Comparability**

A conclusion that a given product has highly similar quality attributes before and after manufacturing process changes, and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, non-clinical or clinical data might contribute to the conclusion.

(ICH Q5E, <http://www.ich.org/LOB/media/MEDIA1196.pdf>).

### **Drug substance**

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. Also termed “active pharmaceutical ingredient” (API). (Taken from: <http://www.fda.gov/CDER/guidance/4286fnl.htm>).

### **Drug product**

The dosage form of a medicinal product in the final immediate packaging intended for marketing.

(ICH Q1A, <http://www.ich.org/LOB/media/MEDIA419.pdf>).

### **Follow-on Biologic**

Term used to describe similar biological medicinal products (biosimilars) in the U.S.

### **Follow-on Protein Product**

Term used to describe similar biological medicinal products (biosimilars) in the U.S. The term follow-on protein products generally refers to protein and peptide products that are intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product.

(Taken from: <http://www.fda.gov/cder/drug/infopage/somatropin/ga.htm>).

### **Formulation**

Formulation is the process of devising a recipe or formula for a product, i.e. deciding what quantities of what ingredients/excipients should be added in what sequence, and what processing steps should be taken to provide the final product. This recipe is then termed a formula or a formulation.

(Adapted from: <http://en.wikipedia.org/wiki/Formulation>)

### **Generic**

A generic medicine contains the same active ingredient as and is bioequivalent to an innovator prescription medicine and is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the originator product.. Generic medicines can be approved by abbreviated regulatory procedures, such as under section 505(j) of the FD&C Act in the U.S., established through the 1984 Hatch-Waxman Amendments, or based on the concept of “essential similarity” as described in the European Community legislation. However, for complex drug substances such as proteins where “sameness” of the active ingredients cannot be demonstrated the generics approval pathways are considered inappropriate.

### **Glycoform**

A glycoform is defined as an isoform of a glycosylated protein with identical polypeptide sequence, but with different sugar (saccharide) structures attached to the sites of glycosylation by either post-translational or co-translational modification. Such differences in glycosylation may affect properties of the glycoprotein such as biological activity, half-life, receptor binding, etc.

### **Glycosylation**

Glycosylation is the process or result of enzyme-catalyzed addition of sugar residues (saccharides) to proteins and lipids. The process is one of the principal co-translational and post-translational modification steps in the synthesis of membrane and secreted proteins.

### **ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)**

ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

For more information, see <http://www.ich.org/>.

### **Immunogen**

Any substance that is recognized as “foreign” by the immune system in a (particular) higher organism and induces an immune response which may include the formation of antibodies and developing immunity, hypersensitivity to the antigen, and tolerance.

### **Immunogenicity**

The ability of a substance to trigger an immune response in a particular organism.

### **Impurity**

Any component present in the intermediate or API that is not the desired entity.

(Taken from: [http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272\\_96843](http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843))

### **In-process control (or: Process control)**

Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

(Taken from: ICH Q7A, [http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272\\_96843](http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843))

### **Isoform**

A protein isoform is a version of a protein with some small differences, e.g. a splice variant or the product of some posttranslational modification (such as glycosylation).

### **Originator product**

An originator product is defined as the product for which a marketing authorization is granted to a given marketing authorization holder (MAH) for a given active substance based upon a complete dossier.

(Taken from: [http://medagencies.org/mrfg/docs/rec/rec\\_annexII.pdf](http://medagencies.org/mrfg/docs/rec/rec_annexII.pdf))

### **Pegylation**

Pegylation is the covalent (chemical) attachment of polyethylene glycol (abbreviated PEG), a chemically inert and non-toxic polymer, to another substance or material, e.g. to a protein. In drug development, pegylation is an established method to improve on the pharmacokinetic profile of therapeutic compounds. Pegylation has been very successfully applied to the development of second-generation biotherapeutics, such as pegylated interferon-alpha.

### **Pharmacovigilance**

According to the WHO definition, pharmacovigilance is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.” The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient populations and the number of patients exposed. In particular, during the early post-marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use.

(For details, see <http://www.emea.eu.int/pdfs/human/ich/571603en.pdf>)

### **Pre-clinical (non-clinical)**

During preclinical drug development (which precedes the clinical trials in patients), a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. Generally, genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body. (Taken from: <http://www.fda.gov/cder/handbook/preclin.htm>)

### **Reference product**

A medicinal product already authorized on the basis of a complete dossier chosen as a reference product by the biosimilar manufacturer. The chosen reference medicinal product should be used throughout the development program for quality, safety and efficacy studies during the development of a biosimilar product.

### **Similarity**

If a company chooses to develop a new biological medicinal product claimed to be “similar” to a reference medicinal product, comparative studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product.

(eg. <http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf>)

### **Specification**

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. “Conformance to specification” means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

(ICH Q6B, <http://www.ich.org/LOB/media/MEDIA432.pdf>)

### **Structure (primary, secondary, tertiary, quaternary)**

Terms used to describe the two- and three-dimensional arrangement of the polypeptide chain in a protein. “Primary structure” is a synonym for the sequence of amino acid residues; the “secondary structure” is formally defined by hydrogen bonds between backbone amide groups (forming structure elements such as the  $\alpha$ -helix and the  $\beta$ -pleated sheet), whereas “tertiary structure” describes the protein’s overall shape, also known as its “fold”. The arrangement of multiple folded protein subunits which are assembled in a multi-subunit complex is called “quaternary structure”.

**Substitution, generic**

Generic substitution is the dispensing of a different brand or an unbranded drug product for the drug product prescribed; i.e., the exact same chemical entity in the same dosage form but distributed by a different company.

(Taken from: World Medical Association Statement on Generic Drug Substitution, 1989/2005, see <http://www.wma.net/e/policy/d9.htm>)

**Validation**

The process of demonstrating that the system (or process) under consideration meets in all respects the specification of that system or process. Also, the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements. In the manufacturing of medicinal products, production processes, cleaning procedures, analytical methods, in-process control test procedures, and computerized systems all have to be validated according to the ICH guidelines for Good Manufacturing Practice.

(see <http://www.ich.org/LOB/media/MEDIA433.pdf>)