



REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

Guidance for Registration of Similar Biological Medicinal products (Biosimilars)

Guidance and Regulations for Similar Biological Medicinal products (Biosimilars)

Introduction

Biotherapeutic products (biotherapeutics) have a successful record in treating many lifethreatening and chronic diseases. However, their cost has often been high, thereby limiting their access to patients, particularly in developing countries.

An increasingly wide range of 'SBPs' are under development or are already licensed in many countries and a need for guidelines for their evaluation and overall regulation was formally recognized by the WHO in 2007.

Lebanon choose to follow the "**GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs)**" issued by the WHO, as adopted by the 60th meeting of the WHO Expert Committee on Biological Standardization, 19-23 October 2009 to evaluate the submitted SBS Files.

File to be reviewed as

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

1) Scope:

This guideline applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins.

Vaccines, plasma derived products, and their recombinant analogues are excluded from the scope of this document. Regulatory guidance for these products will be issued separately.

The file is to be submitted as per CTD format (as per attached components).

2) Glossary

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

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.

Equivalent

Equal or virtually identical in the parameter of interest. Equivalent efficacy of two medicinal products means they have similar (no better and no worse) efficacy and any observed differences are of no clinical relevance.

Extrapolation

Involves extending data from clinical studies for a primary indication to other Extrapolation is the process of extending the data that show the safety and efficacy of a drug from one medical condition, disease or disorder to another medical condition, disease or disorder

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.

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.

Similarity

Absence of a relevant difference in the parameter of interest.

Similar biotherapeutic product (SBP)

A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

Well-established biotherapeutic product

Well-established biotherapeutic product is the one that has been marketed for a suitable period of time with a proven quality, efficacy and safety.

3) Special Considerations:

It was recognized that a number of important issues associated with the use of SBPs need to be defined by the national authorities. They include but are not limited to the following:

- interchangeability and substitution of Similar biotherapeutic product (SBP) with Reference biotherapeutic product (RBP); and
- labelling and prescribing information.

As such, for the purpose of this decision,

a) Interchangeability

Automatic substitution at Pharmacy level **is not allowed** and interchangeability should be the decision of the HCPs only.

Non-medical switch (not recommended by a treating physician, not driven by a clinical need but may be driven by economic needs) **is not allowed**.

Non-medical switch may complicate effective Pharmacovigilance:

- If physicians are not informed, it may subvert the ability to attribute adverse events to the appropriate agent.
- If the onset of the adverse reaction is delayed: Some adverse reactions, including immunogenic reactions such as pure red cell aplasia (PRCA) (case observed in the past with epoetin), may develop only after several months of treatment.

In biology, even small changes can have a big impact. This is why a treating physician should always be involved in the interchangeability decision

b) Extrapolation of efficacy and safety data to other clinical indications

If similar efficacy and safety of the SBP and RBP have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the RBP (not studied in independent clinical studies with the SBP) may be possible if all of the following conditions are fulfilled:

- A sensitive clinical test model has been used that is able to detect potential differences between the SBP and the RBP;
- The clinically relevant mechanism of action and/or involved receptor(s) are the same; e.g. GH action in different conditions of short stature in children; erythropoiesis-stimulating action of epoetins in different conditions associated with anemia or for the purpose of autologous blood donation. If the mechanism of action is different or not known a strong scientific rationale and additional data (e.g. "PD fingerprint", additional clinical data) will be needed;
- Safety and immunogenicity of the SBP have been sufficiently characterized and there are no unique/additional safety issues expected for the extrapolated indication(s), for which clinical data on the SBP are not being provided; e.g. immunogenicity data in immunosuppressed patients would not allow extrapolation to an indication in healthy subjects or patients with autoimmune diseases while the reverse would be valid;
- If the efficacy trial used a non-inferiority study design and demonstrated acceptable safety and efficacy of the SBP compared to the RBP, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications; e.g. results from a non-inferiority trial in an indication where a low dose is used may be difficult to extrapolate to an indication where a higher dose is used, from both efficacy and safety point of view.

If these prerequisites for extrapolation of efficacy and safety data of the SBP to other indication(s) of the RBP are not fulfilled, the manufacturer will need to submit own clinical data to support the desired indication(s).

If extrapolation of results from clinical studies for one indication to one or more different indications is intended, a detailed scientific discussion on the benefit/ risk of such a proposal should be provided based on the above criteria.

c) Dosage form and strength

A similar biotherapeutic product (SBP) must be of the same dosage form and strength as that of the Reference biotherapeutic product (RBP);

d) Naming

In order to maintain high Pharmacovigilance standards, recommendations are the following:

- Mandatory Prescription by Brand name for biologic drugs including biosimilars (not by INN)
- In PV reporting, mentioning of Brand name, INN and batch number
- The SBP should be clearly identifiable by a unique brand name. Where an INN is defined, this should also be stated. WHO policy on INNs should be followed.

e) Clinical studies to be conducted in Lebanon:

- Clinical studies are to be conducted in centers having GLP once guidelines issued.
- The centers should have an approved IRB the time for the GCP to be operational.

4) Labeling and prescribing information:

A biosimilar label would include a statement that the product is a biosimilar to a reference, give the name of the reference product and would provide a brief definition of what it means to be biosimilar in a footnote.

References:

1. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs); World Health Organization (2009).
2. FDA, Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Protein Product (Apr. 2015).
3. FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Apr. 2015).
4. FDA, Draft Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (May 2014).
5. FDA, Draft Guidance for Industry: Additional Questions & Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (May 2015).
6. FDA, Draft Guidance for Industry: Nonproprietary Naming of Biological Products (Aug. 2015).

7. FDA Proposed Rule, Designation of Official Names and Proper Names for Certain Biological Products, 80 Fed. Reg. 52,224 (proposed Aug. 28, 2015) .
8. Guideline on Similar Biological Medicinal Products; CHMP/437/04 Rev 1 (Oct. 23, 2014).
9. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues; EMEA/CHMP/BMWP/42832/2005 Rev. 1 (Dec. 18, 2014).
10. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues; EMA/CHMP/BWP/247713/2012

