

# Biosimilar medical products: What a physician needs to know

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## Abstract

The first generation of approved biopharmaceuticals was developed a few decades ago. Drugs such as insulin, growth hormone, erythropoietin and cytokines were manufactured using recombinant DNA (rDNA) technology or hybridoma methods. They have improved the lives of countless patients of diabetes, short stature, anaemia, cancer, multiple sclerosis and hepatitis.<sup>1</sup> Patents for many of these first- generation biotechnology products have, or are soon going to, expire. In many parts of world , strict patent laws are not in force. This has led to the development of various ‘copies’ of these molecules by drug manufacturers. These products are known as biosimilars.

## INTRODUCTION

The first generation of approved biopharmaceuticals was developed a few decades ago. Drugs such as insulin, growth hormone, erythropoietin and cytokines were manufactured using recombinant DNA (rDNA) technology or hybridoma methods. They have improved the lives of countless patients of diabetes, short stature, anaemia, cancer, multiple sclerosis and hepatitis.<sup>1</sup>

Patents for many of these first- generation biotechnology products have, or are soon going to, expire. In many parts of world , strict patent laws are not in force. This has led to the development of various ‘copies’ of these molecules by drug manufacturers. These products are known as biosimilars.

## DEFINITIONS

A clear understanding of the various terms used in this field is necessary before one can reach an informed opinion on the matter.

A generic drug, or generic medicine, is one that is similar to a medicine which has already been authorized. (the ‘reference medicine’). It contains the same quantity of active substances (s) is used at the same dose to treat the same disease , is as safe and as effective as the reference medicine . A generic product has to demonstrate identical chemical composition and similar pharmacokinetic properties to the reference product<sup>2</sup> .

A biopharmaceutical is a biological medicinal product or

biological medicinal product or biological medicine, whose active substance is made by or derived from, a living organism<sup>3</sup> .

Example of biopharmaceuticals include hormones such as insulin , glucagon growth hormone , thyrotropin, human chorionic gonadotropin , follicle – stimulating hormone , luteinising hormone and erythropoietin, cytokines such as interferon – alfa, interleukin and granulocyte colony stimulating – factor (filgrastim), clotting factors VII, VIII and IX, monoclonal antibodies like bevacizumab, cetuximab , abciximab, rituximab infliximab, and teplizumab vaccines such as those against hepatitis B and human papilloma virus , enzyme like glucocerebrosidase, DNase , thrombolytics and urate oxidase , oval synthetic proteins , pegylated proteins , and covalently attached metal chelators , radioactive iodine and other products .

A biosimilar , also known as a similar biological medicinal product , follow -on biologic , or biogeneric is a medicine that is similar to a biological medicine that has already been authorized (the biological reference medicine). Their active substance are similar , substances are similar , yet not identical<sup>3</sup> .

Biosimilars are submitted for separate marketing approval after expiry of patent protection of the innovator product.

Biosimilars are different from generic drugs. Conventional generics are considered to be therapeutically equivalent to

the reference medicine once pharmaceutical equivalence (i.e. identical active substances) and bioequivalence (i.e. comparable pharmacokinetics) have been established. They do not require clinical efficacy and safety studies before approval. Biopharmaceuticals are made up of a collection of large protein isoforms, rather than a single molecular entity unlike conventional generics. As the manufacturing process is proprietary information it is unlikely that biosimilars can be exactly identical. There are no analytical techniques to establish biopharmaceutical equivalence.

### **DIFFERENCE BETWEEN BIOSIMILAR AND GENERICS**

Bio-pharmaceuticals are derived from or made by a living organism, and are polypeptides, proteins, glycoproteins, complex, polysaccharides or nucleic acids. They may have complex tertiary and quaternary structures, high molecular weights and may be subject to post translational modifications like glycosylation or sialylation, which are crucial for optimal activity.

Generics on the other hand, have small well defined, stable molecules with a low molecular weight, which can easily be reproduced.

Biopharmaceuticals are produced by biological reaction in living organism<sup>4</sup>, which are characterized by a high degree of inherent variability. The type of the host (yeast, bacteria), growth conditions, isolation procedures, storage and transport conditions all affect the final quality of biological medicine. Traditional generics are produced by chemical<sup>5,6</sup> reactions which are less variable, more easy to control, and more predictable. The chemical structure or efficacy is not markedly affected by storage or transport conditions.

Biopharmaceutical drugs are potentially immunogenic, unlike conventional drugs. Even slight structural deviations or impurities can lead to unwanted immune response in the receiving patient<sup>6,7</sup>.

Inter manufacturer, and intra – manufacturer, inter – batch heterogeneity is more obvious in biopharmaceutical products than in chemical generics.

### **REGULATORY ISSUES**

The FDA does not have any legal or regulatory pathway in place for approval of biosimilars. The EMA<sup>5,6,7</sup> has extensive rules and regulations governing the approval of biosimilars, which are more stringent than those for generics, quality, tolerability and efficacy, pharmacodynamic

equivalence and limited toxicology studies need to be done for a biosimilar. Clinical studies may be limited to first indication, in a sensitive patient population. It is stated by the Committee for Human Medicinal Products<sup>5</sup> (CHMP) that while the active substance in the biosimilar should be similar to the one in the reference product, it is not expected that the quality will be identical. An innovator molecule has to demonstrate proof of non-clinical studies viz, pharmacokinetics and toxicology (safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity) and clinical studies (efficacy and tolerability for each indication) before it is approved.

This data is not required for a biosimilar. Quality studies, non clinical data such as pharmacodynamics, repeat dose toxicity and local tolerance testing, clinical data on pharmacokinetics and pharmacodynamics, as well as a pharmacovigilance plan are required by both the innovator and biosimilar molecule. The biosimilar has to demonstrate comparable short term efficacy and tolerability for just one indication before it gets approval for all indications of the reference medicine. These rules have made it much easier to get approval for biosimilar product.

### **ISSUES OF PRACTICAL IMPORTANCE PHARMACOVIGILANCE**

Post –Approval safety data is collected by means of pharmacovigilance programmes. This is of importance because there is limited clinical data, of regulatory short term, at approval. Many adverse effects and effects may become apparent or clear only after a drug is used more extensively, for a longer period of time, in a greater number of patients.

Pharmacovigilance is even more important for biosimilar products, because they are of different manufacture from the reference products. Both manufacturers and prescriber should be aware of the importance of post marketing vigilance, and keep a watchful eye on patients taking biosimilar especially in those patients with a clinical indication which has not been evaluated directly.

### **SUBSTITUTION**

Automatic substitution implies dispensing of generic drug instead of a prescribed innovator brand name, by a pharmacist, without knowledge or consent of a physician. While this may be valid for small – molecule generics, it is not advisable for biopharmaceutical products.

Doctors, pharmacists and patients should be aware of the

fact that biopharmaceutical products can not be substituted by biosimilars. The prescribing clinician must be aware, and must consent to, any change in drug dispensing.

## **LABELLING AND NAMING OF BIOSIMILAR**

For accurate pharmacovigilance, it is essential to distinguish and identify biosimilars. As multiple drugs have the same International Non proprietary Name (INN), e.g, insulin glargine, or erythropoietin, the brand or source should also be specified.

Labelling should clearly identify the character of the molecule, its source, and its approved indications.

## **EXTRAPOLATION OF CLINICAL DATA**

While an innovator molecule has to prove efficacy and safety separately for all indications that it is approved, a biosimilar needs to be evaluated in just one indication.

Extrapolation involves approval of a drug for an indication in which it has not been evaluated in clinical trials. Though extrapolation has a rationale behind it, it is applicable only in limited settings, such as line extensions, new formulations, or new indications in closely related diseases<sup>12</sup>. Prescribers should be aware of the exact method or process by which or biosimilar has been approved. They should also be aware of which indication the biosimilar has been studied in, and which indication has been approved based on data extrapolation.

The labeling and summary of product characteristics (SmPc) of biosimilar should (but does not) provide this information to clinicians to help them make informed choices.

## **ECONOMIC CONSEQUENCE**

The use of biopharmaceuticals is increasing gradually, and biosimilars provide a seemingly economical or cheaper version of the same.

General public opinion, insurance companies and administrators in general prefer economic alternatives. The long term economic consequence of using biosimilars have not been studied, and the total costs of medical care have not been analysed with biosimilars. It is possible that final costs may rise if so called 'economical' biosimilars with less efficacy or less safety are used.

## **CURRENT BIOSIMILARS**

The European Medicine Agency (EMA) has recently approved two biosimilar growth hormone preparations, five erythropoietin products and is considering four filgrastim biosimilars. The regulators are attempting to meet the demands of the healthcare market while ensuring the quality and safety of biopharmaceutical drugs, and have rejected a biosimilar version of interferon alfa-2a recently<sup>9</sup>.

## **CONCLUSION**

Biosimilars are complex molecules which are different from conventional generic drugs. A mere demonstration of pharmaceutical equivalence and pharmacokinetic equivalence is not enough to allow therapeutic substitution of reference products. Strict pharmacovigilance should be maintained for all these drugs, and awareness about potential dangers and mishaps spread, so that no adverse events occur because of misleading labeling or unwarranted substitution.

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