FACT SHEET 3

INTRODUCTION TO BIOSIMILARS & REGULATORY REQUIREMENTS

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SOURCES

1. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. In: (CHMP) ECfMPfHU, ed. London, United Kingdom, 2006.

2. Rak Tkaczuk KH, Jacobs IA. Biosimilars in Oncology: From Development to Clinical Practice. Seminars in Oncology 2014;41, Supplement 3:S3-S12. doi: http://dx.doi.org/10.1053/j.seminoncol.2014.03.008

3. World Health Organization, INN Working Doc. 14.342, Proposal for Assignment of Biological Qualifiers (BQ), 2015

INTRODUCTION TO BIOSIMILARS

Biosimilars are designed to be **highly** similar to their reference biologic.

Traditional chemically synthesized drugs are small molecules. Generic copies are considered to be identical to the originals; they have the same active ingredients and work exactly the same way. Biologics are large complex compounds made from living organisms. A biosimilar is a highly similar but not identical version of the original (also known as “reference”) biologic. While there are inherent variations from batch to batch of a biologic, these differences are minor and tightly controlled by the manufacturing process within a certain range so quality is not affected. This is not the same as differences between the original biologic and biosimilar. Because the cell cultures (starting material) and production steps are the exclusive knowledge of the originator, it is not possible for a biosimilar company to precisely replicate the original manufacturing process.

BIOSIMILARS ARE NOT GENERICS

Table 1.

Unlike generic medicines, biosimilars will not be identical to their reference biologics.

Size	Large
Structure	Complex
Production	Biologic synthesis; derived from living systems, using recombinant DNA technology.
Administration	Usually injected

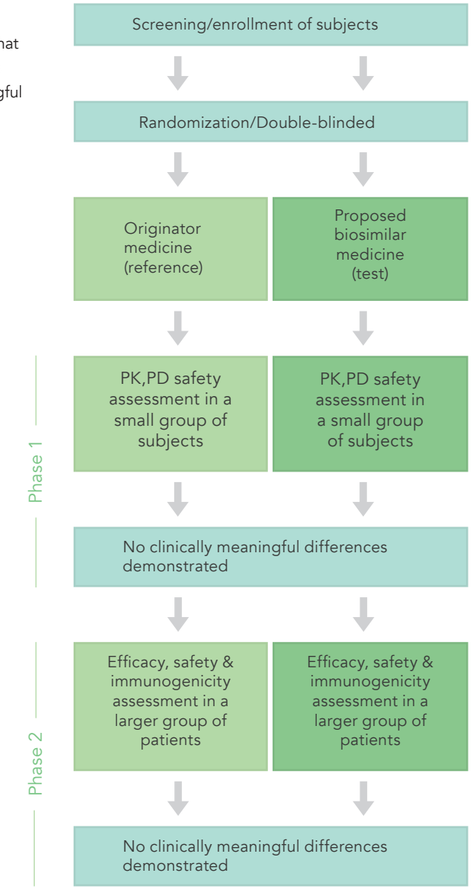
A generic drug is, by definition, an identical copy of its reference small-molecule medicine.

Size	Small
Structure	Simple and well defined
Production	Produced through standard chemical synthesis.
Administration	Most can be swallowed

COMPARATIVE CLINICAL STUDY: MAIN FEATURES

Figure 2.

This diagram illustrates some of the studies that biosimilars undergo before approval. For this process to be successful no clinically meaningful differences can be found.



The main principles are as follow:

Clinical evaluation: Approval of biosimilars is based on clinical evidence, ideally from comparative Clinical Study trials with target patients, demonstrating a highly similar level of clinical benefit and safety compared to their reference biologics. Generics do not require clinical trial evidence, as they are considered identical to their reference medicine.

Immunogenicity testing: Specific testing is needed in patients during the development of biosimilars to ensure that they do not cause any severe immune reactions. This level of testing is not required from generics as they are not produced from living organisms, and unlikely to elicit immune reactions.

Pharmacovigilance: Individual patients must be closely monitored to identify desired beneficial outcomes as well as adverse effects. Additionally, there should be systems to record and analyse collected information to capture how biosimilars are working in all types of patients in real-world settings.

Traceability of biosimilars: Ideally, each biosimilar should be clearly identified with a unique brand name, international non-proprietary name (INN), and batch number. This allows patients and health professionals to clearly know exactly which medicine they are receiving and will be increasingly important as more than one biosimilar is developed to the same reference biologic. By contrast, generics generally do not have unique brand names and share the same INN as their reference. To avoid proliferation of separate and distinct national qualifier systems, the WHO INN Expert Group proposed a scheme in which "a unique identification code named a Biological Qualifier (BQ) is assigned to all biological substances having (or eligible to have) INNs. The BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance to aid in the prescription and dispensing of medicines, pharmacovigilance and the global transfer of prescriptions."[3]

REGULATION OF BIOSIMILARS

Biologics are sensitive to variations in the manufacturing process and the starting materials; therefore, a biosimilar will never be an exact copy of the reference biologic, as explained earlier. To be approved as a biosimilar, products must demonstrate high similarity to the reference biologic in manufacturing quality, biologic activity, clinical safety and efficacy, and in the rate of immune reactions. Specific clinical studies are required to demonstrate this equivalence.

The European Medicines Agency (EMA) developed the first biosimilar guidelines in 2005.[1,2] In 2009, WHO developed a set of global (non-country specific) guidelines for similar biotherapeutic products (SBPs) (more commonly known as biosimilars) to assist and ensure local regulatory authorities adhere to international standards. WHO guidelines set out basic principles considered mandatory to assure safety, efficacy, and quality of biosimilars. A synopsis of these principles follows (a more extensive overview on these principles can be found in **Fact Sheet 8**).

Reference product: The reference product (RBP) is the originator products, which should be licensed based on full quality, safety, and efficacy data and should be authorized in the country or region in question. Wherever it may not be feasible, such as countries lacking nationally licensed RBPs, additional criteria (such as the product should be licensed and widely marketed in another jurisdiction with robust regulatory review processes) may be applied.

Quality: All aspects of quality and heterogeneity should be assessed, including comparative studies with the reference product (most often the commercial product). Where possible, the product should be tested with and without manipulation.

Nonclinical data: Data should include pharmacodynamics (PD), pharmacokinetic (PK), and comparative repeat-dose toxicity studies in a relevant species. The PK of the biosimilar and RBP are compared in terms of absorption, bioavailability, and elimination characteristics. Clinically relevant PD markers should be selected and may be investigated in the context of combined PK/PD studies.

Clinical studies: Similarity of the efficacy of the biosimilar and the RBP will usually have to be demonstrated in adequately powered, randomized, and controlled clinical trial(s). Immunogenicity should always be investigated in humans before authorization. Efficacy trials with biosimilars are not designed to determine whether the medicine works but whether there are any clinically meaningful differences between the biosimilar and the RBP.

Pharmacovigilance: Drug safety monitoring or a pharmacovigilance plan, at the post-marketing phase is included in the guideline to supplement the limited clinical data that is present during marketing authorization. In **some** cases an associated risk management plan is advised.

While the definition of biosimilar and specific regulatory pathway varies across jurisdictions, most well established regulatory authorities (EMA, Health Canada, US FDA, Japan, Korea) incorporate these principles. In these settings, the approval process is tailored for biologic medicines, and the final conclusion on biosimilarity is based on the totality of evidence provided.

The inverted pyramid illustrates how the focus on certain aspects of product development changes when we compare biosimilars to originator. For Biosimilars, more test are required to assure quality, whereas for the originator the largest array of tests are the clinical studies, performed during the final part of product development.

Regardless of the regulator, the comparability exercise involves **three steps implemented hierarchically:**

1. Analytical comparability, based on physical chemical structure and biologic activity.
2. Pre-clinical comparability, based on studies in cell cultures (*in vitro*) and in animals (*in vivo*).
3. Clinical comparability, based on how the biosimilar performs in clinical trial settings in patients with the appropriate condition, including how the biosimilar is absorbed (pharmacodynamics) and broken down (pharmacokinetics) in the body, how it works and the beneficial outcomes and potentially harmful effects.

Biosimilars require less investment to develop and can be expected to be available at a potentially lower cost than the original biologics. However, several examples of the risks of introducing biosimilars without rigorous regulatory guidelines have reinforced the need for adherence to international standards in evaluation. (See **Fact Sheet #4: Biosimilars and the Importance of Adherence to International Regulatory Standards**).

As importantly, **the WHO regulatory guidelines** for biosimilars identify requirements beyond the evaluation process to assure their safe and effective use.

ORIGINATOR VS. BIOSIMILAR

Figure 1.

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