

Interchangeability of Biosimilars

Biosimilars are biopharmaceutical products that are approved after patent expiry of the originator (“reference”) product. In 2004, Europe was the leading region/country when implementing a specific regulatory pathway for the approval of biosimilars. Biosimilars are judged on the same quality, efficacy and safety standards as the original biologic. Biopharmaceuticals, including biosimilars, are generally and in multiple ways more complex than small chemical compounds. This complexity makes the development of a follow-on version after patent expiry by a different manufacturer much more challenging for a biosimilar than for a generic. The requirements laid down in the European approval pathway for biosimilars, which is more stringent and extensive than an approval for a small molecule generic (e.g. data from extensive, comparative pre-clinical and clinical studies have to be provided), adequately mirror the complexity of biologics. For small molecule medicines, many countries have introduced generic substitution, which enables, obliges or incentivizes the pharmacist to dispense a usually cheaper generic product to the patient, in substitution for a branded pharmaceutical product. The physician may explicitly forbid substitution for medical or treatment related reasons. The European Medicines Agency (EMA) has so far refrained from providing guidance on interchangeability and substitution. The decision on substitution of medicines falls under national authority.

Novartis perspective

A biosimilar is developed to have a comparable profile to its respective reference product with regards to quality, safety and efficacy. Provided the high scientific standards of comparability requirements for quality, safety and efficacy are met¹, the biosimilar product has demonstrated to be clinically comparable² with its reference product after having received approval by the relevant authority.

Regulators have already (i.e. EMA) or will define the necessary requirements that accommodate varying levels of complexity for different classes of biosimilars in order to conclude the clinical comparability of biosimilar products to their respective reference products.

1. EMA’s [“Questions and Answers on biosimilar medicines”](#) states that the “legislation defines the studies that need to be carried out in order to show that the biosimilar medicine is similar and as safe and effective as the biological reference medicine”.
2. EMA [“Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues”](#) and corresponding annex [“Guidance on similar medicinal products containing recombinant erythropoietins”](#).

With the approval as a clinically comparable version of the reference product, the biosimilar product should generally be considered as interchangeable, meaning that a patient can expect a comparable outcome with regards to safety and efficacy with either treatment.

The ultimate therapeutic responsibility has to remain with the treating physician based on the verdict of clinical comparability made by the regulatory authority. As for small molecule generics, a physician should be empowered to exclude individual patients from being switched from one product to another for individual medical or treatment related reasons.

In contrast to a regulatory decision process on interchangeability, substitution of medicinal products is an administrative process (different in every country), which allows a pharmacist to substitute a certain prescribed product by another equivalent product.

To reach evidence to support substitution for biopharmaceuticals at pharmacy level will be more challenging than for small molecule drugs. However, biosimilars are a heterogeneous group of medicinal products with different degree of complexity. Based on this differing complexity of the different product-classes of biopharmaceuticals and upon collection and evaluation of data (patient safety years) and experience with the products in the market, some product-classes might be substitutable in the future without compromising patient safety.

Appropriate record-keeping needs to ensure traceability and pharmacovigilance for all medicinal products. Given the inherent higher variability of biopharmaceuticals, record-keeping and adverse event reporting in general might be more extensive than for small molecule products since the tracing of the individual batch that was administered to an individual patient is especially important for biopharmaceuticals.