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Dear provider of pharmaceutical services,

As you may know, advances in science lead to changes in the treatment of many diseases. Nowadays, we have several FDA-approved biologic products available in the market for the treatment of many different diseases, and biosimilars for these biologic products have been emerging. Knowledge of biologics, biosimilars, their similarities and differences, among other related facts, is of great importance for providers of pharmaceutical services. Attached you will find a summary of these topics.

For more detailed information, you can visit the FDA website, "The Center for Biosimilars", "Biosimilar Resource Center", or to any other trustworthy reference of your preference.

Medical literature is dynamic and is continuously changing as new scientific knowledge is developed. We exhort the frequent revision of treatment guidelines to assure that your recommendations are consistent with the most actualized information.

On PharmPix we are compromised with the health and wellness of our insured. It is our priority to offer high quality services and to promote practices for health promotion and diseases prevention. If you have any doubt or wish to have more information regarding this document, you can call us to 787-522-5252, extension 137.

Regards,

Clinical Department





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# BIOSIMILAR BASICS FOR PROVIDERS OF PHARMACEUTICAL SERVICES

## Biologics

Biologic products (biologics) are different from conventional small-molecule drugs, which are made from chemical substances through a predictable chemical process. Biologics are large, complex molecules that comes from living organisms and are manufacture through a more complicated process using biotechnology methods. Because of biologics complexities, they usually cost much more than conventional drugs.

## Biosimilars

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an already FDA-approved biologic (reference product).

**"Highly similar" –** Comparative tests to compare characteristics of the products, such as purity, chemical identity, and bioactivity, along with other information, are used to demonstrate that the biosimilar is "highly similar" to the reference product. Minor differences between the biosimilar and the reference product in clinically inactive components are acceptable (e.g. minor differences in the stabilizer or buffer).

**"No clinically meaningful differences" –** Human pharmacokinetic and pharmacodynamics studies, clinical immunogenicity assessments, and, if needed, additional clinical studies, are performed to demonstrate that the biosimilar has "no clinically meaningful differences" from the reference product in terms of safety, purity, and potency.

An updated list of FDA-approved biosimilar products is publish in the FDA website at: https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.

## Biosimilars versus Generics

A generic drug is chemically identical to its brand-name product; both having the same active ingredient, dosage form, safety profile, strength, route of administration, performance characteristics, and intended use. In contrast, a biosimilar may have a difference in the structure, although the active substances are essentially the same in molecular and biological terms. However, there are no clinically meaningful differences between the biosimilar and reference product in terms of safety or effectiveness.

## Regulation

The Biologics Price Competition and Innovation Act (BCPIA), a provision in the Patient Protection and Affordable Care Act (Affordable Care Act) of 2010, created an approval pathway for biosimilars. Through this pathway, the FDA performs a very thorough process to ensure that all standards are meet. An FDA approval of a biosimilar means that the biosimilar is highly similar to the reference product.

## How is it known whether the biosimilar will work the same as the reference product?

No single study will demonstrate biosimilarity. The FDA uses a "totality of evidence" approach to review manufacturers' applications for biosimilars.

For the approval of reference biologic products, the FDA place more emphasis on results from large clinical trials that evaluate the safety and efficacy of the product. On the other hand, for the approval of biosimilars, the FDA places more emphasis on biological and physicochemical characterizations of the biosimilar molecule, because the safety and efficacy data for the reference product is already available. Figure 1 shows an overview of how the FDA reviews the evidence to approve reference biologic products versus biosimilars.

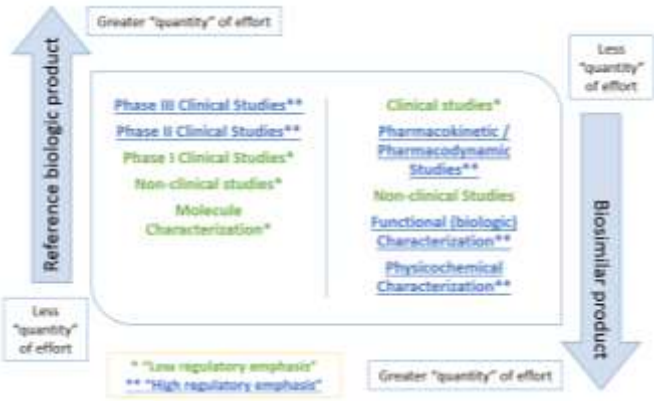


**Figure 1. Evidence required for biosimilar approval (Image adapted from: Cleveland Clinic – Center for Continuing Education).[5]**

In general, analytical studies must demonstrate minimal or no qualitative or quantitative differences in the structure and function of the proposed biosimilar and the reference product. The





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biosimilarity is confirm using subsequent animal studies. Residual uncertainty about the safety and efficacy of the proposed biosimilar is address in pharmacokinetics or pharmacodynamics studies and assessments of immunogenicity. If residual uncertainty remained after those studies, additional clinical studies would be conduct to confirm the safety and efficacy of the proposed biosimilar.

Although biosimilars are relatively new, studies have found that biosimilars are as safe and effective as the reference products. In addition, some studies have shown that switching from a biologic to a biosimilar is safe and effective. Lastly, some organizations have published statements supporting the use of biosimilars as they offer a less costly alternative.

**Can a pharmacist substitute a biosimilar for a reference product in the same way that he or she could do with a generic?**

No. Currently, a pharmacist is not permitted to automatically substitute a biosimilar for a reference product; the pharmacist has to contact the prescriber physician to see if he or she approves the substitution. So far, physicians must write the specific name of the biosimilar product on the prescription.

Maybe in the future pharmacists will be able to automatically substitute a biosimilar. Of important note, a provision in the BPCIA created a special category of biosimilars called "interchangeable biologics", which may be substituted for the reference product by a pharmacist without the intervention of the prescriber physician. However, to date, none of the FDA-approved biosimilars have been approved as interchangeable.

**US FDA approved biosimilars**

| Biosimilar product | Reference product |
|---|---|
| Zarxio (filgrastim-sndz)† | Neupogen |
| Inflectra (infliximab-dyyb)† | Remicade |
| Ixifi (infliximab-qbtx) | |
| Erelzi (etanercept-szzs) | Enbrel |
| Eticovo (etanercept-ykro) | |
| Amjevita (adalimumab-atto) | Humira |
| Cyltezo (adalimumab-adbm) | |
| Hyrimoz (adalimumab-adaz) | |
| Hadlima (adalimumab-bwwd) | |
| Renflexis (infliximab-abda)† | Remicade |
| Mvasi (bevacizumab-awwb)† | Avastin |
| Zirabev (bevacizumab-bvzr) | |
| Ogivri (trastuzumab-dkst) | Herceptin |
| Herzuma (trastuzumab-pkrb) | |
| Ontruzant (trastuzumab-dttb) | |
| Trazimera (trastuzumab-qyyp) | |
| Kanjinti (trastuzumab-anns)† | |
| Retacrit (epoetin alfa-epbx)† | Epogen |
| Fulphila (pegfilgrastim-jmdb)† | Neulasta |
| Udenyca (pegfilgrastim-cbqv)† | |
| Nivestym (filgrastim-aafi)† | Neupogen |
| Truxima (rituximab-abbs) | Rituxan |
| Ruxience (rituximab-pvvr) | |
| †Available in the market. | |

References:
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