



Biosimilar Product Regulatory Review and Approval

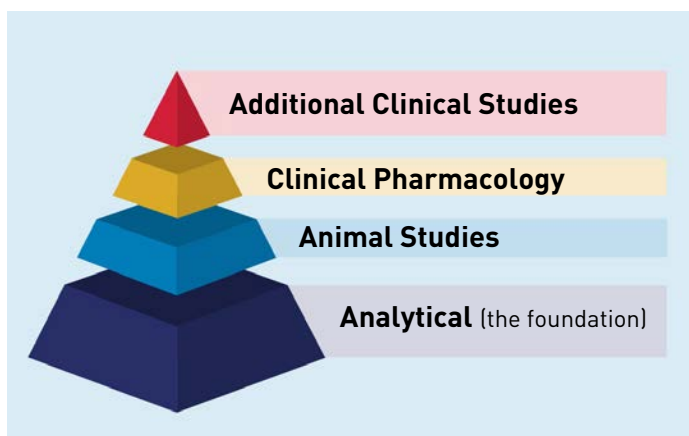
What is the approval process for biosimilar products?

All FDA-approved biological products, including reference products and biosimilar products, undergo a rigorous evaluation so that patients can be assured of the efficacy, safety, and quality of these products.

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved in a “standalone” application that must contain all data and information necessary to demonstrate its safety and effectiveness. Generally, the data and information necessary to demonstrate the safety and effectiveness of a reference product will include clinical trials for the disease indications being sought by the manufacturer.

A biosimilar is highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from, an existing FDA-approved reference product. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety and effectiveness of the proposed product.

The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity. The comparative data are generated and evaluated



When considering licensure of a biosimilar product, FDA reviews the totality of the data and information, including the foundation of detailed analytical [structural and functional] characterization, animal studies if necessary, then moving on to clinical pharmacology studies and, as needed, other comparative clinical studies.

in a stepwise fashion that begins with a foundation of detailed analytical [structural and functional] characterization and comparison of the products, moving on to animal studies if necessary and then to comparative clinical studies.

Consequently, rather than generating the same full profile of nonclinical and clinical data as the reference product, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on FDA’s previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.

What data are required for approval of a biosimilar or interchangeable product?

A biosimilar product application must include data demonstrating biosimilarity to the reference product. This usually includes data from

- › Analytical studies demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;
- › Animal studies, including an assessment of toxicity; and
- › A clinical study or studies sufficient to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study.

In addition to the data listed above, an application for an interchangeable product must also include information or data demonstrating that:

- › The proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient; and,
- › For a product administered more than once to an individual, switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products.

Do all biosimilar applications have the same types of data?

The bullets above outline the types of data and information to be included in a biosimilar product application. FDA evaluates each biosimilar product on a case-specific basis to determine what data are needed to demonstrate biosimilarity and which data elements can be waived if deemed scientifically appropriate. This determination may be informed by what is already publicly known about the reference product.

Many factors can help tailor the data requirements for each biosimilar application. Some examples include:

- › The strength and robustness of the comparative analytical studies showing similar structure and function between the proposed biosimilar and the reference product. For example, analytical similarity data showing very few analytical differences may provide strong support that the proposed product is highly similar.
- › How similar the PK and PD profiles are between the biosimilar and reference product.
- › Pre-existing information about the safety profile of the reference product. For example, if it is known that patients have the potential to develop immune responses with adverse outcomes to the reference product, FDA will likely require a more rigorous evaluation of immune responses with the biosimilar.

Why do we need an abbreviated approval pathway for biological products?

Biological products are the fastest-growing class of therapeutic products in the United States and account for a substantial and increasing portion of health care costs. Congress, through the Biologics Price Competition and Innovation Act, created an abbreviated approval pathway to provide the public with greater access to safe and effective biological products. This pathway provides more treatment options, potentially lowering health care costs through competition and increasing access to lifesaving medications.

The concept of extrapolation is based on:

- ✓ All available data and information in the biosimilar application
- ✓ FDA's previous finding of safety and efficacy for other approved indications for the reference product
- ✓ Knowledge and consideration of various scientific factors for each indication



The abbreviated licensure pathway does not mean that a lower approval standard is applied to biosimilar or interchangeable products. In fact, as described above, the data package required for approval of a biosimilar or interchangeable product is extensive. If a biosimilar manufacturer can demonstrate that its product is biosimilar to the reference product, then it is scientifically justified to rely on certain existing scientific knowledge about the safety and effectiveness of the reference product to support approval. This allows for a potentially shorter and less costly drug development program for a biosimilar.

Can a biosimilar be approved for an indication that is approved for the reference product even if the biosimilar is not directly studied in that indication?

Yes, a biosimilar product may be approved for an indication without direct studies of the biosimilar in that indication. If the total evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications, then it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer. This concept is called "extrapolation" and is critical to the goals of an abbreviated pathway—improving access and options at a potentially lower cost.

Extrapolation is based on (1) all available data and information in the biosimilar application, (2) FDA's previous finding of safety and efficacy for other approved indications for the reference product, and (3) knowledge and consideration of various scientific factors for each indication. Extrapolation is not an assumption that the data from one directly studied indication or population alone is sufficient to support approval in a different non-studied indication or population. The biosimilar manufacturer must provide scientific justification to support extrapolation.

These scientific justification factors include knowledge of the mechanism(s) of action, PK, PD, efficacy, safety, and immunogenicity of the reference product in each of its approved indications. FDA evaluates all of the biosimilar product data to assess whether there are differences between the biosimilar and the reference product that may affect these scientific factors in any of the indications or populations not directly studied by the biosimilar manufacturer. If no such differences are identified, approval of the biosimilar for other non-studied indications or populations is generally supported.

FDA works with biosimilar manufacturers during product development to determine what data are needed to support extrapolation. Remember that a reference product manufacturer must show its product is safe and effective for each indication for which approval is sought, most often through indication-specific clinical trials. Since the goals of a biosimilar development program are different from those of a reference product development program (see the first question above), it is generally unnecessary from a scientific perspective to require a biosimilar manufacturer to conduct clinical trials in all the same disease indications for which the reference product was studied and approved.