



Biosimilars



As drug prices have soared in recent years, in part due to the approval of high-cost biologic medications, stakeholders including public and private insurers are seeking to control prescription drug spending. This whitepaper explores biosimilar history, challenges to implementation, and implications for managed care.

Signed into law in March 2010, the Affordable Care Act created an abbreviated licensure pathway for biological products as part of the Biologics Price Competition and Innovation Act (BPCI Act). The BPCI Act allows for biosimilar products to be reviewed by the Food and Drug Administration (FDA) in an abbreviated manner which helps reduce biosimilar research and development costs. The abbreviated licensure pathway is specifically for reviewing biological products that are highly similar (biosimilar) or interchangeable with an already FDA-approved reference product.

The approval of the first biosimilar product in the U.S. in March 2015 marked new potential for cost saving strategies. Predicted savings from approval and integration of biosimilars into the U.S. drug market vary substantially — one analysis found U.S. savings could reach \$44 billion in a 10-year period.

Defining Biologics

It is important to understand how a biosimilar product is different from a generic drug, which necessitates an understanding of how a biological product is different from a traditional drug.

Biologics vs. Traditional Drugs

Biological products (biologics) are very large, complex molecules generally derived from living cells (e.g., human, animal, microorganism, yeast) through a complicated manufacturing process. These drugs are typically injected subcutaneously or intravenously. In contrast, traditional drug products are typically small, chemically manufactured molecules formed as a capsule or tablet taken by mouth.

Biosimilars vs. Generics

After patents expire on these small molecules, other drug manufacturers may begin making their own version of the product and seek approval of their copycat version from the FDA. These copycats of small molecule drugs are called generics. Large,



A biosimilar product is a biologic product that is determined to be highly similar, though not identical, to an FDA-approved biological product.

complex biologic molecules cannot be reproduced as easily as small molecule generics due to their size and complicated manufacturing process. As a result, copycat drugs may not be identical to the original biologic product. Therefore, they are deemed 'biosimilar' products rather than generics.

Biosimilars

A biosimilar product cannot have any clinically significant differences in safety or effectiveness from the originator biologic product. However, minor differences in inactive components are acceptable. The FDA-approved originator biologic product is commonly referred to as the reference product. In general, biosimilar products can only be substituted for the reference product with authorization from the healthcare provider prescribing the product.

Interchangeable Biosimilars

Biosimilar products that meet additional FDA requirements for interchangeability are deemed interchangeable biologic products. Depending on state laws, a pharmacist could substitute an interchangeable biosimilar for the reference product without prescriber intervention.

The First Biosimilars

The FDA approved the first biosimilar in March 2015. The product, Zarxio® (filgrastim-sndz), is a biosimilar to Amgen's Neupogen® (filgrastim). Zarxio was approved for all five of Neupogen's indications. However, it was not approved as an interchangeable biological product and therefore cannot be substituted for Neupogen without prescriber intervention. Market launch of this first biosimilar in the U.S. was delayed until September 2015 due to patent litigation. Pricing for Zarxio is at a 15% discount to Amgen's Neupogen.

The FDA approved the second biosimilar in April 2016. The product, Inflectra® (infliximab-dyyb), is a biosimilar to Janssen Biotech's biological product Remicade® (infliximab). Inflectra was approved for most of Remicade's indications. However, Inflectra was not reviewed for the indication of pediatric ulcerative colitis, as Remicade is protected from competition for this indication due to orphan drug exclusivity until 2018. Inflectra is the first monoclonal antibody biosimilar to be approved in the U.S. Although Inflectra is not yet commercially available, its expected to be priced at a 20% to 30% discount to Remicade.

The FDA approved the third biosimilar, Erelzi® (etanercept-szzs), and fourth biosimilar, Amjevita® (adalimumab-atto), in August 2016 and September 2016, respectively. Erelzi is a biosimilar to the reference product Enbrel® (etanercept) and is approved for all of the indications of the reference product. Amjevita is a biosimilar to the reference product Humira® (adalimumab) and is approved for seven of the indications of the reference product.

It is unclear when Erelzi and Amjevita will become commercially available as patent litigation will likely delay market entry. A preliminary injunction has been issued prohibiting the manufacture or commercialization of Erelzi and a court date has been set for April 2018. Experts have predicted a commercial launch of Amjevita between 2018 and 2022.



Challenges for Integrating Biosimilars Into Clinical Practice

Reference product: An FDA-approved biologic product on which the biosimilar is based is called the reference product or the originator biologic product.

Biosimilar product: A biologic product approved on the basis of demonstrating high similarity to a reference product, and exhibits no clinically significant differences in safety or effectiveness from the reference product.

Interchangeable product: A biosimilar to an FDA-approved reference product that has met additional requirements for interchangeability. Depending on state laws, a pharmacist could substitute an interchangeable biosimilar for the reference product without prescriber intervention.

Naming Convention

How should biosimilar products be distinguished from reference products? In a draft guidance, the FDA proposed that biologic and biosimilar products should have a designated unique suffix following the nonproprietary core substance drug name (e.g., filgrastim-sndz, infliximab-dyyb). The FDA is in the process of finalizing the naming guidance.

Package Labeling

What information should and shouldn't be included in the prescribing information/package labeling? The FDA has issued draft guidance recommending biosimilar product labels include a 'biosimilarity statement' describing the biosimilar product's relationship to the reference product. The FDA is in the process of finalizing labeling guidance.

Interchangeability Requirements

How will interchangeability be defined and what will be required to demonstrate interchangeability? The FDA has stated an interchangeable biosimilar product is "expected to produce the same clinical result as the reference product in any given patient." However, the FDA has not released guidance on how a sponsor can demonstrate interchangeability. The guidance is expected to be published in 2017.

Substitution of Interchangeable Biosimilar Products

What will state laws require for interchangeable biosimilar products to be substituted for the reference product? As of August 2016, 25 states and Puerto Rico implemented state-specific legislation regarding substitution of interchangeable biological products. For states that enacted laws allowing substitution of an FDA-approved interchangeable biological product, the laws generally require some form of prescriber notification, patient notification, and substitution record retention.

Patent Litigation

After approval of a biosimilar product, when will the product become commercially available? A federal appeals court recently ruled that manufacturers of biosimilars are required to notify the reference product manufacturer six months before the launch of the biosimilar. Last year, it was ruled that biosimilar manufacturers must wait until FDA approval of the biosimilar has been received before the 180-day notice can be given to the reference product manufacturer. In other words, most biosimilars will not be launched until at least six months after FDA approval.

Biosimilars in the Pipeline

Currently, there are more than 50 biosimilars to 18 reference molecules in the FDA's Biosimilar Development Program, and a number of these biosimilar applications have been submitted to the FDA for review. Since the beginning of 2016, the FDA has approved three biosimilar products, however patent litigation



Potential savings from biosimilar products could be substantial if biosimilars are:

- Priced competitively
- Accepted into clinical practice
- Integrated into cost-saving strategies

may delay the commercial launch of these products. For example, although the Humira® biosimilar, Amjevita, was approved in September 2016, the biosimilar may not become available in the U.S. until 2022. Other products in the pipeline include biosimilars to Epogen® (epoetin alfa), Neulasta® (pegfilgrastim), and Herceptin® (trastuzumab).

Implications for Managed Care

While insurers are optimistic that biosimilars will ultimately cost the public up to 50% less than the original reference product, others think the market impact will be less pronounced. In a study sponsored by AbbVie, manufacturer of the blockbuster biologic Humira, it was concluded that overall savings may be less than anticipated due to fewer prescriptions written for high-cost specialty biologics, concerns regarding interchangeability, and delay in acceptance of biosimilars by stakeholders.

A recent analysis conducted by IMS Institute for Healthcare Informatics predicted savings from biosimilars could reach as high as \$110 billion for Europe (Germany, France, Britain, Spain) and the United States by 2020. However, the analysis is based on biosimilars being priced at a 40% price discount to the reference product. Currently, the only commercially available biosimilar in the U.S., Zarxio (filgrastim-sndz) is priced at only a 15% discount to the reference product. Stakeholders remain optimistic that the potential cost savings with use of biosimilar products could be significant due to more competition.

Biosimilars: The NPS Strategy

National Pharmaceutical Services (NPS) has added Zarxio (filgrastim-sndz), the only commercially available biosimilar, to standard formularies as a specialty medication and incorporated the drug into other cost-management strategies where appropriate. NPS is planning to review the other U.S. biosimilar products, Inflectra (infliximab-dyyb), Erelzi (etanercept-szzs), and Amjevita (adalimumab-atto), for formulary inclusion after they become commercially available.

Preferred status on the NPS standard formularies will be considered for biosimilar products, as clinically appropriate. NPS may require a trial of a biosimilar product before coverage of the reference product, as deemed clinically appropriate.

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