Pharmacology Report

Biosimilar Basics

Susan Kleppin, RPh, FASHP

Susan Kleppin, RPh, FASHP, Director of Pharmacy, Chartwell Midwest Wisconsin

Brand name drugs, once approved by the US Food and Drug Administration (FDA), have an assigned period of time during which they can be marketed exclusively by the manufacturer before a generic version of the drug can be introduced into the marketplace. These medications are chemically synthesized. Generic medications are chemically identical to the brand name drug. Biologics (or biological products) are generally made from human or animal materials, and the chemical structures are large and complex. Biologics include products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.[1] Biologics have no generic versions because of the way they are produced.

Biologics are often very expensive and thus patient access to them to treat illness or disease can be limited. In an effort to make biologics more affordable, increase access, and create more competition in the health care market, Congress paved the way for the development and approval of biosimilars through the passage of the Biologics Price Competition and Innovation Act (BPCIA) of 2009. This legislation authorized the FDA to implement an abbreviated regulatory pathway for approval of biosimilars.[2] It is estimated that introduction of biosimilars could reduce the cost of biologics by $44 billion over the next decade, although this would be dependent on several factors.[3] Like other medications, brand name biologics are also allowed a period of exclusivity, and, until the last decade, no biosimilars were available. The first biosimilar was approved in 2015; the FDA has licensed additional biosimilars every year.[4] As of the writing of this article, the FDA has approved 26 biosimilars, and 7 have been introduced into the market (Table 1).

What are biosimilars? Not identical to the brand name biologic (often referred to as the reference product), biosimilars are copies of the complex medicines made from biological material. They are considered "highly similar" medicines, having the same clinical effect as the brand name or reference product with no clinically meaningful differences in safety, purity, and potency.[2] Since biosimilars are grown in living systems with unique cell lines, there is variability from the reference biologic product. It is important to understand the variation that occurs: (1) all biologics and biosimilars are "living" molecules that naturally vary; (2) the FDA requires extensive, state-of-the-art analyses that compare the biosimilars to their reference products; (3) any variations in the biosimilar must be within the boundaries established for the reference product; and (4) when the variations occur they are not clinically significant.[5] Biosimilars are marketed in the same dosage form, strength, and route of administration as the reference product.

The manufacturer of a biosimilar must generate data to compare the proposed product to the reference product. A variety of studies are conducted: (1) analytical studies demonstrating that the biologic product is highly similar to the reference product; (2) animal studies, including an assessment of toxicity; and (3) a clinical study or studies sufficient to demonstrate the safety, purity, and potency of the biosimilar in 1 or more of the indications for which the reference product is licensed.[2]

Each biosimilar that is FDA-approved will have a specific naming standard. The name of the biologic is followed by a suffix of 4 random letters to distinguish between them.[6] Each will also have a brand name associated with it, assigned by the manufacturer.

Unlike generic medications, the biosimilars cannot be automatically substituted for the reference product. The biosimilar can only be dispensed if a prescription order is written for that specific biosimilar. A manufacturer could seek to prove that their biosimilar is "interchangeable" per FDA standards. The FDA finalized its interchangeability guidance that addresses the requirements that need to be met to obtain an interchangeability designation in May 2019.[7] The manufacturer must have data demonstrating that the biosimilar is expected to produce the same clinical result as the reference product in any given patient. In addition, the

Author Affiliation: *Chartwell Midwest Wisconsin, Middletown, Wisconsin.*

Susan Kleppin, RPh, FASHP, *is the director of pharmacy for Chartwell Midwest Wisconsin.*

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TABLE 1

Biosimilars Approved in the United States as of December 2019[a]

Biosimilar Product (Brand Name)	Manufacturer	Date Approved	Date Marketed
Filgrastim-sndz (Zarxio)	Sandoz	3/2015	9/2015
Infliximab-dyyb (Inflectra)	Celitrion/Pfizer	4/2015	11/2016
Etanercept-szzs (Erelzi)	Sandoz	8/2016	Not yet marketed
Adalimumab-atto (Amjevita)	Amgen	9/2016	Not yet marketed
Infliximab-abda (Renflexis)	Samsung/Merck	4/2017	7/2017
Adalimumab-adbm (Cyltezo)	Boehringer Ingelheim	8/2017	Not yet marketed
Bevacizumab-awwb (Mvasi)	Amgen/Allergan	9/2017	Not yet marketed
Trastuzumab-dkst (Ogivri)	Mylan	9/2017	Not yet marketed
Infliximab-qbtx (Ixifi)	Pfizer	12/2017	Not yet marketed
Epoetin alfa-epbx (Retacrit)	Pfizer	5/2018	12/2018
Pefilgrastim-jmdb (Fulphilia)	Mylan	6/2018	7/2018
Filgrastim-aafi (Nivestym)	Pfizer	7/2018	10/2018
Adalimumb-adaz (Hyrimoz)	Sandoz	10/2018	Not yet marketed
Pefligrastim-cbqv (Udenyca)	Coherus Biosciences	11/2018	1/2019
Rituximab-abbs (Truxima)	Celltrion/Teva Pharmaceuticals	11/2018	Not yet marketed
Trastuzumab-pkrb (Herzuma)	Celltrion/Teva Pharmaceuticals	12/2018	Not yet marketed
Trastuzumab-dttb (Ontruzant)	Samsung Bioepis	1/2019	Not yet marketed
Trastuzumab-qyyp (Traximera)	Pfizer	3/2019	Not yet marketed
Etanercept-ykro (Eticovo)	Amgen/Allergan	4/2019	Not yet marketed
Trastuzumab (Kanjinti)	Amgen/Allergen	6/2019	Not yet marketed
Bevacizumab-bvzr (Zirabev)	Pfizer	6/2019	Not yet marketed
Rituximab-pvvr (Ruxience)	Pfizer	7/2019	Not yet marketed
Adalimumab-bwwd (Hadlima)	Samsung/Merck	7/2019	Not yet marketed
Pegfilgrastim-bmez (Ziextenzo)	Sandoz	11/2019	Not yet marketed
Adalimumab-afzb (Abrilada)	Pfizer	11/2019	Not yet marketed
Infliximab-axxq (Avsola)	Amgen	12/2019	Not yet marketed

[a]Data compiled from the US Food and Drug Administration website.[1]

risk in switching between the biosimilar and the reference product in terms of safety or decreased efficacy cannot be any greater than using the reference product alone.[7]

If a manufacturer follows this guidance and can demonstrate that a biosimilar is interchangeable with its reference product, pharmacists may be able to substitute a biosimilar for the reference product on receipt of a prescription order. State pharmacy laws would govern this, and laws vary from state to state.[8] Some states will require that both the prescriber and the patient be notified before an interchangeable biosimilar could be dispensed.[8]

Data in Table 1 shows that several biosimilars have been FDA approved for 2 years or more but are not yet marketed in the United States. The marketing of these agents has been slowed by ongoing patent litigation.[9,10] The accelerated approvals of biosimilars over the last 2 years demonstrates that manufacturers are interested in the biosimilar market and that the abbreviated approval pathway is having the desired effect. Yet the biosimilars that are being marketed currently are not dominating the market. There are several factors that are limiting the widespread use of the biosimilars that are currently available. The cost of the biosimilar products in some cases is not dramatically different from the reference product.[11] Proven interchangeability might help reduce the price of biologics, and market share can be shifted more rapidly from one product to another.

Some insurance companies have restricted patient access to biosimilars because of contract provisions with the manufacturers of the biologic reference product in which the insurer grants formulary exclusivity to the reference product in exchange for rebates.[11] There is also prescriber and patient reluctance to use biosimilars, and this reluctance is also having an impact on the use of biosimilars. Prescribers may not have a good understanding of the biosimilar approval process and thus have concerns about the efficacy and safety of the products. A national

survey of specialty physicians that have high utilization of biologic products demonstrated that 55% of the physicians surveyed did not believe that the biosimilars were safe and effective.[12] Similar surveys of patients have found the same. A survey of adult patients with rheumatologic disease published in 2019 showed overall patient satisfaction with a switch to an infliximab biosimilar, but those surveyed expressed concern regarding safety and efficacy as well.[13]

Nurses should educate themselves about biosimilars to be able to respond to questions posed by patients. The FDA has educational material on its website for health care providers that can be accessed for more information.[14] There is also information for patients that nurses could share with patients and use to address patient questions and concerns.[15]

When preparing and/or administering a biosimilar, nurses should follow the directions provided by the manufacturer, pharmacy, or hospital for the specific product being given. As always, know which product you are administering. Nurses can contribute to the postmarketing surveillance of these products by reporting patient side effects and/or adverse reactions to a biosimilar promptly and through the appropriate channels.

The introduction of biosimilars has the potential to decrease treatment costs and improve access to biologics. The education of nurses, pharmacists, and prescribers will lead to better adoption in clinical practice. The collaboration of these 3 disciplines can lead to sound formulary decision-making in hospitals, the development of biosimilar treatment protocols, and shared responsibility in the education of patients about biosimilar use.

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