

Challenges of Integrating Biosimilars Into Clinical Practice

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Presenters at JADPRO Live 2019 discussed the chemical and clinical nature of biosimilars, reviewed biosimilar development in oncology, and discussed implementation strategies for biosimilars.

The U.S. Food & Drug Administration (FDA) has approved 23 biosimilars, including seven in 2019 alone. Despite this spate of approvals, however, only nine biosimilars are available to be purchased (Cohen et al., 2016). What's more, a recent survey of more than 1,200 US physicians across all specialties showed that providers have major knowledge gaps when it comes to biosimilars. According to the survey, no responders were able to answer more than 50% of questions pertaining to biosimilar fundamentals correctly. At JADPRO Live 2019, Kate Jeffers, PharmD, MHA, BCOP, Megan May, PharmD, BCOP, and Wendy H. Vogel, MSN, FNP, AOCNP®, identified key differences in the development of biologics and biosimilars, appraised the safety and efficacy of biosimilars as compared to the originators, and evaluated the significance of factors that may affect the adoption of biosimilars.

“One thing we have learned is that biosimilar market uptake great-

ly depends on health-care providers' willingness to promote, prescribe, and use biosimilars in clinical practice,” said Dr. May, clinical oncology pharmacy specialist at Baptist Health Lexington in Kentucky.

As Dr. May explained, several studies evaluating health-care providers' knowledge, perceptions, and prescribing behaviors with biosimilars have demonstrated inadequate understanding of biosimilars' basic science, safety and efficacy, and the FDA regulatory process, and this knowledge deficit is greater among office-based physicians than hospital-based ones. According to the FDA definition, a biosimilar is “a biological product that is highly similar to a US-licensed reference biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”

BIOSIMILARS ARE NOT GENERICS

Compared to the structure and size of small molecule drugs, which are very simple drugs with a low molecular weight, said Dr. May, biologic products have a high molecular weight and are very complex.

“On average, biologics are about a hundred to a thousand times larger than our small molecule drugs,” she explained. “If a small molecule drug were a bicycle, then a biologic product would be an airplane, and this complexity is reflected in the price: they are very expensive to manufacture.”

Although both biosimilars and generic drugs are both created to provide patients with affordable treatment options, they are not the same, Dr. May continued. They differ in terms of the approval process, manufacturing, naming, size, and the physical makeup.

“Manufacturing biologic products is very complex, and it’s a multistage process,” Dr. May explained. “It involves cloning of relevant proteins of interest, transfection into the host cells, cell screening and selection, and then lastly large-scale protein expression and purification.”

Unlike generics, said Dr. May, biologic products differ from batch to batch, no matter who the manufacturer is. Even a small change in temperature or sterility can lead to different adverse events and effectiveness. Because of this complexity, biosimilars undergo a different approval process. Ultimately, said Dr. May, the goal of biosimilar development is to demonstrate no clinically meaningful differences based on the totality of evidence.

“We’re not trying to re-establish the total clinical benefit,” she emphasized. “We’ve already done that with the biologic product, so there is a robust analytical component to our biosimilar pathways.”

As Table 1 shows, 23 biosimilars have been approved in the US, with seven in 2019 so far, but only nine are available to be purchased.

FORMULARY REVIEW

Dr. Jeffers, ambulatory oncology clinical specialist at UCHealth Memorial Hospital in Colorado, described how biosimilars are added to hospital formularies. This is typically done by Pharmacy & Therapeutic (P&T) Committees, which review

Table 1. FDA-Approved Biosimilar Products

Reference biological product	Approved biosimilar product(s)	Date approved	Release to market	Indication
Adalimumab (Humira)	Adalimumab-adaz (Hyrimoz)	10/30/18	2023	Rheumatoid arthritis, psoriatic arthritis, Crohn’s disease, ankylosing spondylitis, juvenile idiopathic arthritis, ulcerative colitis, plaque psoriasis
	Adalimumab-adbm (Cyltezo)	08/25/17	2023	
	Adalimumab-atto (Amjevita)	09/23/16	2023	
	Adalimumab-bwwd (Hadlima)	7/23/19	June 2023	
Bevacizumab (Avastin)	Bevacizumab-awwb (Mvasi)	09/14/17	Yes	Metastatic CRC, nonsquamous NSCLC, glioblastoma, metastatic renal cell carcinoma, cervical cancer
	Bevacizumab-bvzr (Zirabev)	06/27/19	2020	
Epoetin alfa (Epogen/Procrit)	Epoetin alfa-epbx (Retacrit)	05/15/18	Yes	Anemia due to: CKD, zidovudine in HIV patients, and chemotherapy; reduction in RBC transfusions in patients undergoing elective, non-cardiac, non-vascular surgery
Etanercept (Enbrel)	Etanercept-szsz (Erelzi)	08/30/16	Before 2029	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis
	Etanercept-ykro (Eticovo)	04/25/19	Before 2029	

Note. As of September 2019. CRC = colorectal cancer; NSCLC = non-small cell lung cancer; CKD = chronic kidney disease; RBC = red blood cell; AML = acute myeloid leukemia. Information from FDA Highlights of Prescribing Information (2015–2018); FDA Purple Book (2019).

Table 1. FDA-Approved Biosimilar Products (cont.)

Reference biological product	Approved biosimilar product(s)	Date approved	Release to market	Indication
Filgrastim (Neupogen)	Filgrastim-aafi (Nivestym)	07/20/18	Yes	Non-myeloid malignancies receiving chemotherapy with high risk for neutropenic fever or being followed by bone marrow transplant, induction/consolidation therapy with AML, leukapheresis, symptomatic neutropenia
	Filgrastim-sndz (Zarxio)	03/06/15	Yes	
Infliximab (Remicade)	Infliximab-abda (Renflexis)	4/21/17	Yes	Adult and pediatric Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis
	Infliximab-dyyb (Inflectra)	04/05/16	Yes	
	Infliximab-qbtx (Ixifi)	12/13/17	2020	
Pegfilgrastim (Neulasta)	Pegfilgrastim-cbqv (Udencya)	11/02/18	Yes	Non-myeloid malignancies receiving chemotherapy with high risk for neutropenic fever
	Pegfilgrastim-jmdb (Fulphila)	06/04/18	Yes	
Rituximab (Rituxan)	Rituximab-abbs (Truxima)	11/28/18	-	Non-Hodgkin lymphoma
	Rituximab-pvvr (Ruxience)	7/23/19	2023	
Trastuzumab (Herceptin)	Trastuzumab-anns (Kanjinti)	06/13/19	Yes	HER2/ <i>neu</i> receptor overexpressing breast cancer and metastatic gastric or gastroesophageal junction adenocarcinoma
	Trastuzumab-dkst (Ogivri)	12/01/17	End of 2019	
	Trastuzumab-dttb (Ontruzant)	01/18/19	End of 2019	
	Trastuzumab-pkrb (Herzuma)	12/14/18	End of 2019	
	Trastuzumab-qyyp (Trazimera)	03/11/19	End of 2019	

Note. As of September 2019. CRC = colorectal cancer; NSCLC = non-small cell lung cancer; CKD = chronic kidney disease; RBC = red blood cell; AML = acute myeloid leukemia. Information from FDA Highlights of Prescribing Information (2015–2018); FDA Purple Book (2019).

products for inclusion onto hospital/organizational formulary and approve policies and procedures. These committees may include subcommittees for specific areas, such as an antimicrobial subcommittee, oncology subcommittee, and biosimilar subcommittee. According to Dr. Jeffers, the challenges faced by P&T committees will likely center around approval data for each new biosimilar (Ventola, 2013):

- Are differences from the reference agent related to any of the FDA-approved indications?
- What pharmacovigilance requirements exist for each agent? (similar to Risk Evaluation and Mitigation Strategies [REMS] programs)
- Does the agent have any additional safety or

efficacy data that separate it from other biosimilars or the reference product?

P&T committees may rely on analytical or scientific equivalence data to review rather than clinical data, Dr. Jeffers added.

FINANCIAL CONSIDERATIONS

As Dr. May explained, financial concerns are one of the major challenges with biosimilars, which are approximately 15% cheaper than the reference product, on average. That may seem great, she said, but a generic product is typically 80% cheaper than its reference product, and this difference is due to the high cost of developing a biosimilar. The price that an institution pays for a biosimilar,

and thus the profit margin that they get, really depends on their purchasing power. However, there are contracting opportunities to consider.

“You make sure your institution has a good contracting team to get contracts from different manufacturers that could be the reference product or the biosimilar manufacturers,” she said, noting that reimbursement also comes into play. “If you are able to get a great contract for one product but your reimbursement is less, you might be saving money for the institution on the front end, but are you saving money on the back end? From a pharmacy perspective, we must consider all of these factors when we’re analyzing a biosimilar for addition.”

These financial considerations also factor into EMR integration. While defaulting to a brand product is less work up front, said Ms. Vogel, an oncology nurse practitioner from Wellmont Cancer Institute, there are no cost savings, and insurance may dictate a change. Defaulting to a biosimilar product, on the other hand, is more work up front but provides an opportunity for larger cost savings. Because these products are not considered interchangeable, FDA regulation requires picking one directly.

Dr. Jeffers underscored the balance that P&T committees must strive for as they compare biosimilars with their reference products and weigh cost against effectiveness.

“From a P&T perspective, you have to look at the entire picture,” said Dr. Jeffers. “Cost is certainly a factor, but we have to make sure that we’re doing the best thing for our patients.”

ADMINISTRATION CONSIDERATIONS

According to Dr. May, there are also administration considerations, including differences in infusion rates, concentration or fluid differences (tubing differences), and administration device (Onpro vs. syringe).

“Our institution has largely switched to biosimilars for everyone, with one exception,” said Dr. May, who noted that when biosimilars come to the market, they are required to have the same dosing and routes as the original reference product. “We decided that we wanted to use the subcutaneous formulations, so until the biosimilars offer the same administration route, we will stick with the reference product.”

Dr. Jeffers added that smart-pump technology is another administration consideration. Most organizations now have some type of smart-pump technology, which is a safety feature for patients (and providers) to ensure medications are given at the correct rates and infusion times.

BARRIERS TO PATIENT ACCEPTANCE

The gaps in knowledge are not only limited to providers, either. Patients also lack adequate knowledge regarding biosimilars, said Ms. Vogel, which can be a real barrier to acceptance.

“We know that our patients lack sufficient knowledge, whether it’s basic information, safety, or efficacy,” she observed. “There are a lot of fears around these products. When we’re trying to receive consent from our patients, we need to make sure that they have a basic understanding.”

According to Ms. Vogel, however, the influence of cultural bias against biosimilars extends beyond treatment consent. The nocebo effect, the negative effect of treatment as a result of a patient’s perceived expectations, has been shown to impact adherence rates, but this can be minimized by education.

“Biosimilars are still in their infancy in the US, but we know more and more are going to be approved and on the market,” said Dr. May, who noted that most major monoclonal antibodies will have a biosimilar in the near future. “Make sure that you go back to your institution and discuss biosimilars with your peers, your colleagues, and your patients.” ●

Disclosure

Dr. Jeffers has served on speakers bureaus for Amgen, Genentech, Ipsen, and Tesaro. Dr. May has no conflicts of interest to disclose. Ms. Vogel has served on speakers bureaus for Amgen, Celgene, Genentech, Ipsen, Lily, and Novartis.

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