Biosimilars for Cancer Emerge as Patents on Widely Used Drugs Expire

Biosimilar products can provide additional treatment options and create market competition, potentially lowering the costs of treatment

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When the patent on the cancer drug trastuzumab (Herceptin) expires next year, patients who have been receiving this biological therapy will have another treatment option: a biosimilar drug—a drug that is very similar, but not identical, to trastuzumab.

Last fall, the Food and Drug Administration (FDA) approved the first trastuzumab biosimilar for the treatment of some breast and stomach cancers based on research showing that, in terms of safety and effectiveness, the drug was comparable to trastuzumab.

To be approved as a biosimilar, a drug must be highly similar to the original biological drug—in this case, trastuzumab. And in terms of safety, purity, and potency, there can be no clinically meaningful differences between the biosimilar and the original product, which FDA calls the reference product.

When the trastuzumab biosimilar, trastuzumab-dkst (Ogivri), becomes available in 2019, it could be part of a wave of new biosimilars for patients with cancer.

“To date, eleven biosimilars have been approved in the United States, but nearly 70 more are in the development pipeline,” said Leah Christl, PhD, director of the Therapeutic Biologics and Biosimilars Staff (TBBS) in FDA’s Office of New Drugs, noting that the patents on some widely used biological drugs will expire in the coming years.

“The main advantage of biosimilar products,” Christl continued, “is that they can provide additional treatment options and create market competition, potentially lowering the costs of treatment and enabling greater access to biological therapies for more patients.”

Addressing the High Costs of Cancer Drugs

Biological drugs, or biologics, are generally large, complex molecules or mixtures of molecules that are derived from living organisms, such as yeast, bacteria, or plant or animal cells.

Unlike generic drugs, which have the same active ingredients as their corresponding brand-name

drugs, a biosimilar drug is not an exact copy of its reference product, in part because biological drugs are derived from living organisms, which are inherently complex.

For patients with cancer, biological products include some immunotherapies and targeted therapies.

“Many of today’s most innovative and necessary treatments for cancer are biological products, and many more are in development,” said Christl. “But these treatments can be enormously expensive.”

In 2005, biological products made up 39.1% of the $9.5 billion in Medicare drug spending. By 2014, these agents accounted for 62% of the $18.5 billion spent by Medicare on prescription drugs.

In a recent report on the rising costs of cancer drugs, the President’s Cancer Panel concluded that biosimilars may play a role in reducing these expenses.

“We have to address the problem of cancer drug costs, and biosimilars may help us,” agreed Sara A. Hurvitz, MD, of UCLA’s Jonsson Comprehensive Cancer Center, who moderated a panel on biosimilars at the 2018 American Association for Cancer Research (AACR) annual meeting.

The high prices of biological drugs represent one of the main challenges facing community cancer programs, Hurvitz noted.

She cautioned, however, that the potential impact of biosimilars on health care costs in the United States is still unclear and will depend on many factors, including the prices of biosimilars. Whether patients and clinicians view biosimilars as acceptable alternatives to the corresponding reference products will also play a role, she noted.

The Concept of Biosimilarity

Congress paved the way for the approval of biosimilars in 2010 with the passage of the Biologics Price Competition and Innovation Act, which created an abbreviated regulatory process for biosimilars. Five of the eleven biosimilars approved by FDA since then are for patients with cancer.

The first biosimilar to be approved in the United States, in 2015, was filgrastim-sndz (Zarxio), a biosimilar to filgrastim (Neupogen), which is used to prevent infection during chemotherapy. FDA has since approved ten other biosimilar products, including two drugs for treating cancer.

In addition to trastuzumab-dkst, FDA has also approved a biosimilar to bevacizumab (Avastin) for the treatment of multiple types of cancer. Called bevacizumab-awwb (Mvasi), the biosimilar could reach the US market by 2020, after the patent on bevacizumab expires.

And in May, FDA approved the first epoetin alfa biosimilar for the treatment of anemia caused by chronic kidney disease, chemotherapy, or the use of zidovudine in patients with HIV infection.

Manufacturers do not need to independently demonstrate the safety and effectiveness of biosimilars in large clinical trials to meet the approval standards of biosimilarity. If the same level of evidence from such trials were required for the approval of biosimilars as for the reference products, there would be less potential for cost savings, Hurvitz said.

For companies developing biosimilars, the goal is to establish biosimilarity, Sue Lim, MD, director of the Scientific Review Staff within TBBS, said at the AACR meeting. This means that a new biosimilar product is highly similar to, and has no clinically meaningful differences from, the reference product.

The first step in establishing biosimilarity, Lim explained, is to characterize the chemical structure and biological function of the proposed biosimilar in a comparative fashion to the reference product.

“The thinking is that if a biosimilar has a highly similar structure and function as the reference product, then it should behave like the reference product—that is, be as effective and safe as the reference product in the clinical setting,” she added.

Throughout the process of establishing biosimilarity, manufacturers work with FDA to determine the amount and the type of data required at each step. During the process, manufacturers may use existing, publicly available scientific data about the safety and effectiveness of a reference product to compare with the biosimilars they are developing.

Subtle Differences Among Biological Products

Despite the requirement to be highly similar, biosimilars and reference products are allowed to have minor differences in clinically inactive ingredients. Furthermore, because biological products are produced in living cells, there may be slight variations between batches of biological products, including biosimilars, even among batches produced at the same facility.

“You can synthesize small-molecule drugs and expect to get the same product each time,” Simon Hotchin, executive director of Regulatory Affairs at Amgen, Inc., said at the AACR meeting. “But the manufacturing of biological products is a proprietary, highly complex, and multistep process.”

Biological products have “inherent variability,” agreed Hurvitz. But FDA’s manufacturing and quality-control standards ensure that naturally occurring variations in biological products do not affect a product’s safety or effectiveness, she noted. In addition, as with all biological products, FDA requires manufacturers to monitor the safety and side effects of new biosimilars in patients.

The Concept of Extrapolation

Although biosimilars do not need to be independently tested for efficacy and safety, conducting a trial can help establish biosimilarity. One of the largest such trials to date compared a proposed trastuzumab biosimilar with trastuzumab in more than 450 patients with HER2-positive metastatic breast cancer.

At 24 weeks of treatment, the overall response rates were similar for patients receiving the biosimilar and for those receiving trastuzumab (69.6% versus 64.0%, respectively), the study found.

There were no notable differences in side effects between the two treatment groups in the trial, but the study authors cautioned that additional follow-up is needed to ensure that the therapies have equal safety and effectiveness over the long term.

Although the proposed trastuzumab biosimilar was not tested in patients with stomach cancer, it was approved for both breast and stomach cancers—the same diseases for which the reference drug is approved. This is an example of a concept FDA calls "extrapolation."

"Understanding extrapolation is really important, and there are misconceptions about this concept," said Lim. If a company can show that its product is indeed biosimilar to its reference product for the agency to approve it for one indication, then, based on extrapolation, there is the potential for the biosimilar product to be approved for one or more conditions of use for which the reference product is also licensed, she explained.

Extrapolation is a familiar concept among regulators, Hurvitz noted. "Clinicians are going to have to be trained in the concept of extrapolation if they are to embrace the approval of biosimilars for applications beyond the initial approved setting."

Setting a Higher Bar for Interchangeability

Clinicians will also need to be educated about the idea of interchangeability, Hurvitz continued. An interchangeable product is a biosimilar product that may be substituted for the reference product without involving the health care provider who prescribed the drug.

Additional evidence is required from manufacturers for a biosimilar product to receive designation as an interchangeable product. For instance, manufacturers need to show that a biosimilar product is expected to produce the same clinical result as the reference product in any given patient.

And for a product that is administered more than once to an individual, manufacturers must show that switching between the proposed interchangeable drug and the reference product does not pose safety risks or compromise effectiveness.

FDA's high standards for approval of interchangeable products are intended to assure patients and health care providers that they can have confidence in the safety and effectiveness of an interchangeable product, just as they would for an FDA-approved reference product, Hurvitz noted.

No biosimilar has yet been approved as an interchangeable product, she added.

Lessons From the European Experience With Biosimilars

A theme of the AACR panel discussion was the need to educate clinicians and patients about biosimilar products, including what they are and how they are approved.

FDA has developed educational materials on biosimilars for patients and prescribers, as well as for nurses who will administer biosimilars and pharmacists who will dispense them. The agency intends to provide health care professionals with the information they need to consider prescribing these drugs as they become available, FDA Commissioner Scott Gottlieb, MD, has said.

Thirty biosimilars have been approved in Europe since 2006, and these agents have helped to "lower costs and increase patient access to biologics," the President's Cancer Panel noted in its report. The report highlighted a study on the use of biosimilars in Europe, which raised no concerns about the safety or effectiveness of these treatments.

"The fact that biosimilars have been used in Europe and in Japan should give us some assurance that the drugs are as safe and effective as the corresponding reference products," said Chadi Nabhan, MD, MBA, the chief medical officer at Cardinal Health Specialty Solutions, who conducted a survey of oncologists about their perceptions and acceptance of biosimilars.

"It's important to explain to clinicians and to patients that the FDA uses rigorous methods to approve biosimilars," continued Nabhan. "Many oncologists don't know how biosimilars get approved, but education can help address this gap in knowledge."

In the survey, many oncologists responded that once a biosimilar has been approved, they would be as comfortable prescribing it as they would a reference treatment—regardless of the patient's stage of disease and the goal of therapy, Nabhan explained.

"A lack of familiarity with—and concerns about—the concept of extrapolation also emerged in the survey as a barrier to adoption of biosimilars," he added.

Many More Biosimilars in the Pipeline

The favorable perceptions of clinicians toward biosimilars "are a critical first step" toward the adoption of these medicines, Nabhan concluded. But with so few FDA-approved biosimilars for cancer, it's too soon to know what impact biosimilars will have in the United States, including whether they will ultimately lead to lower costs for cancer care, he added.

That could change.

"As patents and exclusivity protections for biologics continue to expire in the US, we can expect many more biosimilars to be submitted for approval, creating greater competition within the marketplace," said Christl.

More products on the market "will influence uptake the most," she noted.

"Biosimilars," Nabhan added, "are here to stay. As more biosimilars come on the market, we can begin to assess the potential impact on health care costs."

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