Early Biosimilars Face Hurdles to Acceptance

The FDA Has Approved Few, So Lack of Competition Is Keeping Prices High

Stephen Barlas

The Food and Drug Administration (FDA) approval of Inflectra (infliximab-dyyb) in March as the second biosimilar cleared for sale in the U.S. gave the agency a small victory in a war of sorts that it has been losing badly. But the agency's green-lighting of a biosimilar is no guarantee that the market will receive the product with open arms, as the experience of Zarxio (filgrastim-sndz) proves.

Five years after Congress gave the agency the authority to approve supposedly cheaper alternatives to budget-busting biologics, the FDA has cleared only two. "I know people are anxious to see more progress and certainty," admits Janet Woodcock, MD, head of the FDA's Center for Drug Evaluation and Research. "Most of the progress so far has been under the hood."

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Pfizer's Inflectra will compete with Janssen's Remicade, the reference drug. Zarxio (marketed by Novartis subsidiary Sandoz) competes against both Amgen's Neupogen (filgrastim) and Teva's Granix (tbo-filgrastim); the latter was approved as a biosimilar in Europe but as a biologic in the U.S.

Pfizer says it will be selling Inflectra by the end of 2016, once all legal barriers fall. Hospital pharmacists are eagerly awaiting its arrival. In usage, infliximab is typically at or near the top among the drugs in a hospital pharmacy. Hospitals use it for rheumatoid arthritis, Crohn's disease, colitis, and a host of secondary and tertiary off-label purposes. Moreover, doses typically escalate. Remicade's cost was $3,159 per administration and $18,129 per beneficiary in 2013, according to a June 2015 report from the Medicare Payment Advisory Commission.[1]

But Zarxio's early experience shows that biosimilars, when first introduced, face hurdles. "Our P&T committee has not reviewed Zarxio yet and we have not used it in patient care," says John Fanikos, Executive Director of Pharmacy at Brigham and Women's Hospital in Boston, Massachusetts. "Granix was not approved as a biosimilar but through the biologics license application pathway. Since its list of indications is comparable to Neupogen but not all-inclusive, we added it to the formulary as our preferred growth factor."

When Zarxio first came to market, it was more expensive than Granix but less expensive than Neupogen. "We could not see a reason to use Zarxio on the inpatient or outpatient sides of care," Fanikos explains. "Sandoz has recently come forward with a contract favorable in terms of pricing, but the other companies have made adjustments in their pricing, too."

Moreover, physicians haven't been clamoring for Zarxio. "I was somewhat shocked; many of physicians had no idea what the biosimilar process even is," states one hospital pharmacist who did not want to be named. "Even those that do would have to be aware of the differences between Neupogen, Granix, and Zarxio. Physicians who have prescribed filgrastim for years are likely to keep prescribing Neupogen rather than going down the list to filgrastim alternatives with suffixes," he adds.

Even if physicians were totally up to speed on biosimilars, neither Granix nor Zarxio is available in a vial. Because children use filgrastim in lower doses, children's hospitals need it in a vial. Their only alternative is Neupogen. Pediatric hospitals such as St. Jude's Children's Hospital and Children's Healthcare of Atlanta make up about 5% to 10% of the client base for Vizient, Inc. "That is very influential when organizations like those cannot use a product in question," says Steven Lucio, Senior Director of Clinical Solutions and Pharmacy Program Development for Vizient, a large group purchasing organization that represents academic medical centers, pediatric facilities, community hospitals, integrated health delivery networks, and nonacute health care providers. Vizient represents almost $100 billion in annual purchasing volume.

Biosimilars in different therapeutic categories face different challenges. For example, Pfizer won't have to deal with a Granix-like competitor once Inflectra comes to market. The biosimilar will go head-to-head with Remicade. However, infliximab is a monoclonal antibody and therefore a more complicated biologic than filgrastim. Infliximab patients are not immune-compromised, which means the prescribing physician has to be much more concerned about potential side effects. Filgrastim patients are already immune-compromised. "Rheumatologists, dermatologists, and other physicians using infliximab will have to have more of a clinical conversation with patients before using Inflectra since it is not an exact copy of Remicade," Lucio says. "And that will pose a higher hurdle for its use."

The FDA Is Part of the Problem

The FDA's assignment of suffixes is one of a number of controversial regulatory issues that stymie acceptance of biosimilars. The agency published a proposed rule on suffixes[2] in the summer of 2015 and has still not produced a final rule. The agency received different opinions from different parties as to whether a suffix ought to mimic a biosimilar marketer's name, as is the case with filgrastim-sndz, or whether the suffix should not conjure up the marketer's name, or whether the reference drug ought to have a suffix, which is not now the case. Neupogen is simply filgrastim.

Numerous, important guidance documents are also stuck in the FDA's maw. The FDA's slow pace is not fully its own fault. Congress has never appropriated segregated funds for the biosimilars program. As part of the Patient Protection and Affordable Care Act (PPACA), the agency was allowed to charge companies user fees for submitting applications.

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But given the regulatory uncertainty, few applications have been submitted. Instead, the agency has charged companies for meetings during which the FDA advises them on what they need to do prior to submitting an application. Those fees totaled $6 million, $13 million, and $23.8 million in fiscal years (FY) 2013, 2014, and 2015, respectively. Meanwhile, a study by the consulting firm Eastern Research Group (ERG)[3] commissioned by the FDA had the agency spending $23.6 million in FY 2013, $21.4 million in FY 2014, and $28.7 million in FY 2015. That $74 million total compares to the $42 million the agency raised in user fees. Still, the mismatch in funding only partly explains why the agency has missed quite a few deadlines it set for itself in terms of answering sponsors' questions posed during user-fee meetings.

"The FDA infrastructure put into place for BsUFA I is insufficient to meet the objectives and manage the workload it currently faces," says Hubert C. Chen, MD, Chief Medical Officer of Pfenex. "This is consistent with the experience of Pfenex, as we have worked with the agency across multiple programs in diverse therapeutic areas." BsUFA is the Biosimilar User Fee Act included in the PPACA.

Dr. Woodcock paints the early troubles of biosimilars with the brush of perspective. She argues the small-molecule generic-drug approval program launched by the Hatch-Waxman law in 1984 took a while to gain momentum. "We didn't have success overnight with that program," she says. "But today, over 88% of prescriptions are filled by generics."

Of course, three decades ago the eight leading drugs in U.S. sales were not expensive biologics, all costing Medicare, for example, more than $1 billion a year and sapping the savings of Americans in all walks of life. So the exigencies surrounding the need for faster biosimilar introductions are magnitudes greater than they were for chemical generics in the 1980s. Express Scripts, one of the largest U.S. pharmacy benefit management organizations, estimates potential savings of $250 billion in the next decade with the approval of just 11 biosimilar products.[4] A 2014 RAND Corporation study estimates that biosimilars will lead to a $44.2 billion reduction in direct spending on biologic drugs from 2014 to 2024, with anti–tumor necrosis factor agents such as infliximab accounting for the largest chunk of savings (Figure 1).[5]

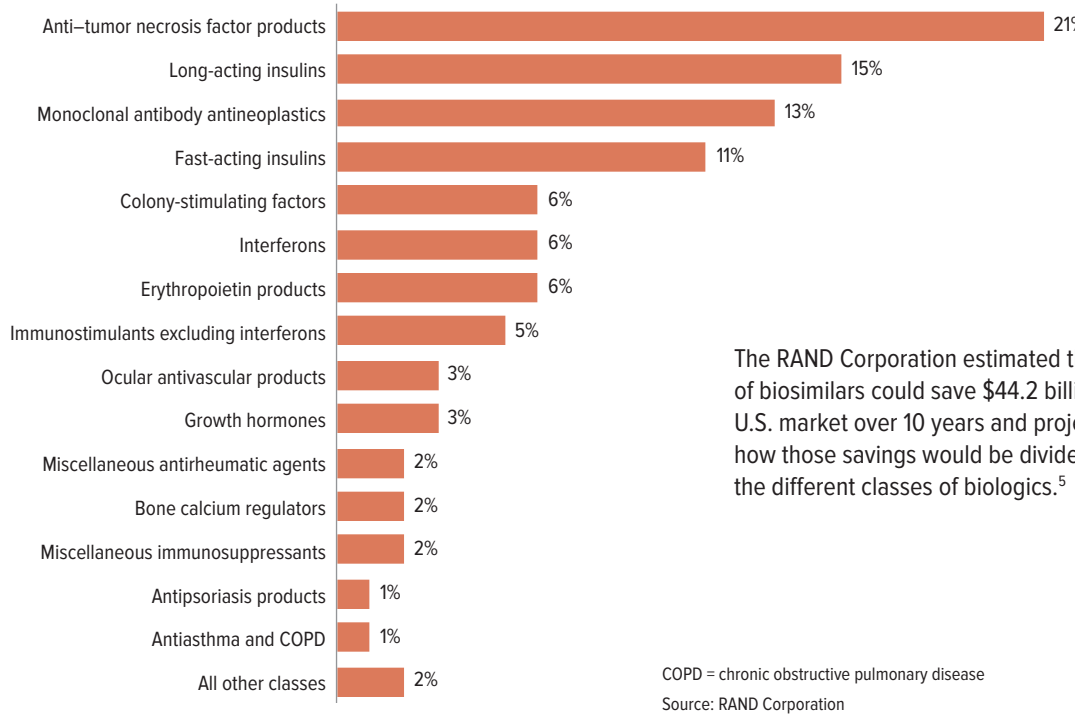
However, because of the shortage in funding, the FDA's progress on biosimilars may well get worse before it gets better. As of January 21, 2016, 59 proposed biosimilar products to 18 different reference products were enrolled in the Biosimilar Product Development (BPD) Program. "What I am concerned about is that the program is going to explode and we will not have the staff to handle it," Dr. Woodcock says.

At hearings of the House health subcommittee on February 4, 2016, Mary Jo Carden, RPh, JD, Vice President of Government and Pharmacy Affairs for the Academy of Managed Care Pharmacy expressed concern about the ability of biosimilars to reach their full potential in the United States because of incomplete guidance from the FDA, confusing federal and state regulatory guidance, and lack of clarity related to payment, coding, and reimbursement.

FDA Guidance Documents Are Coming Slowly

The FDA cleared Inflectra two months after the House subcommittee hearings. Manufactured by Celltrion, it is being marketed in the U.S. by Pfizer's Hospira subsidiary. Inflectra is approved for a half-dozen uses, including psoriasis and

Figure 1 Potential Cost Savings Across Biologic Classes[5]



The RAND Corporation estimated that use of biosimilars could save $44.2 billion in the U.S. market over 10 years and projected how those savings would be divided among the different classes of biologics.[5]

COPD = chronic obstructive pulmonary disease

Source: RAND Corporation

five other conditions in which the immune system attacks the body's tissues. The drug helps reduce inflammation and control the immune system, which slows those diseases. Remicade, first approved in 1998, is the top-selling medicine of Johnson & Johnson (Janssen's parent company), with sales of $6.56 billion in 2015.

Inflectra and Zarxio were approved while many critical FDA guidance documents were incomplete. Although the Biologics Price Competition and Innovation (BPCI) Act does not require the FDA to issue guidances before approving a biosimilar application, the FDA understands the importance of guidances in helping to ensure successful implementation of this new pathway.

Perhaps the most important upcoming guidance concerns interchangeability. The FDA did not deem Inflectra interchangeable with Remicade; the same was true for Zarxio, which is not interchangeable with Neupogen. If they were interchangeable, a pharmacist could substitute the biosimilar for the reference product without checking with the physician first. The FDA has not yet established the standard it will use when judging whether a biosimilar is interchangeable.

The FDA expects to publish the eagerly awaited draft interchangeability guidance by the end of 2016. To meet the standard for *interchangeability*, an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient. The applicant must also demonstrate that if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switching.

"Interchangeability is the thing about biosimilars that makes a lot of physicians nervous," explains Donald Miller, PharmD, a Professor of Pharmacy Practice at North Dakota State University. "Interchangeability means a pharmacist could switch products without physician authorization, and thus potentially expose a patient to a product with slightly different immunogenicity without the physician being aware of it." Dr. Miller is a member of the FDA advisory committee that recommended approval of Inflectra in February.

While the FDA will determine interchangeability, the states will control automatic substitution—and states are already approving a variety of limits on that still-to-come process.

Even if pharmacists don't have to notify physicians when a biosimilar is rated interchangeable, pharmacists could still be in an uncomfortable position. Pharmacists may feel that they are "under the microscope" when switching to a biosimilar based on their own judgment, and they may hope that any unilateral substitution doesn't come back and cause trouble for them, for whatever reason.

However, the publication of draft guidance does not suddenly quiet controversy. That wasn't the case after the FDA published its draft labeling guidance in March.[6] The guidance says biosimilars can use the clinical data gathered by reference product sponsors. That is a point of controversy, with some companies and patient groups saying the company producing the biosimilar ought to include its own clinical trial data on the label. Regulators would also allow biosimilar labels to include the statement that the product is biosimilar to the reference product.

That doesn't mean the biosimilar's label has to be identical to the reference product label. It does not. It needs to reflect currently available information necessary for the safe and effective use of the product. Certain differences between the biosimilar and reference product labeling may be appropriate. For example, biosimilar product labeling conforming to the physician labeling rule and/or pregnancy and lactation labeling rule may differ from reference product labeling because the reference product labeling may not be required to conform to those requirements at the time of licensure of the biosimilar product. In addition, biosimilar product labeling might have to reflect differences such as administration, preparation, storage, or safety information that do not otherwise preclude a demonstration of biosimilarity.

The Generic Pharmaceutical Association (GPhA) and its Biosimilars Council praised the draft guidance. Chip Davis, Jr., GPhA President and Chief Executive Officer, says the guidance takes steps to avoid confusion and in many aspects mirrors the protocol for the labeling of generic drugs. For example, a statement defining biosimilarity would be included rather than lengthy and already established scientific data proving biosimilarity. And immunogenicity details would mirror the label content of the reference product. "GPhA and the council are especially pleased that the proposed label contents avoid causing confusion or raising unnecessary questions about the safety and efficacy of biosimilar products," he adds. "We also commend the agency for postponing guidance on interchangeable biologic labeling at this time."

Andrew Powaleny, Senior Manager of Communications for Pharmaceutical Research and Manufacturers of America, declined to provide his group's views on the draft guidance in advance of the deadline for written comments.

The Undermanned FDA

The FDA's tentative decision in the draft labeling guidance not to require biosimilar companies to cite their own data from their own clinical trials may be a practical necessity given that the FDA clearly does not have the staff to review all that data. Budget begets staff, of course, and budgets have not been kind to the FDA's biosimilars program. The ERG study proved that.[3] User fees have simply not been sufficient for the FDA to provide necessary staff resources for prospective biosimilar marketers who pay for one of five types of meetings the FDA offers under its BsUFA program. The number of those meetings has far outpaced what the FDA projected when the user-fee program was put in place. There were 59 BPD program participants as of November 2015. When the BsUFA went into effect, the FDA had anticipated a total of 11 participants in the BPD program by FY 2015.

In December 2015, the FDA held a meeting to get input on the changes it needs to the biosimilar fee program. Any modifications would be made by Congress when it reauthorizes the BsUFA. David R. Gaugh, RPh, Senior Vice President for Sciences and Regulatory Affairs at the GPhA, says the meetings the FDA holds with potential biosimilar sponsors are extremely useful, but at times there are uncertainties about the outcomes. "With that said, the meetings should have well-

defined objectives, clear outcomes, and meaningful decisions about future development options," he explains. "Where the outcome or guidance is unclear to the sponsor, there should be an opportunity for a timely follow-up teleconference to promote better understanding, communication, and transparency."

Critics Complain About Medicare Policy, Too

Criticism over biosimilar policy has also encompassed the Centers for Medicare and Medicaid Services (CMS). In October 2015, the CMS clarified its policy on reimbursement for biosimilars, which are paid for mostly under Medicare Part B, where physicians administer the drugs in their offices or outpatient infusion clinics provide the drugs. But reimbursement also goes through Part D when patients are able to self-administer. The new policy managed to offend nearly every pharmaceutical sector; both generic and brand-name industry associations decried a number of aspects of the new policy, in some instances the same aspect.

The final rule clarifies that the payment amount for a biosimilar is based on the average sales price (ASP) of all National Drug Codes assigned to the biosimilars included within the same billing and payment code.[7] So all biosimilars citing Remicade as their reference drug would be paid the same. This is the way Medicare pays for chemical generics, which are considered multiple-source drugs. The CMS would assign the first biosimilar, such as Zarxio, a code under the Healthcare Common Procedure Coding System (HCPCS). All other Remicade biosimilars would have the same HCPCS code. Zarxio's code is Q5101 Injection, Filgrastim (G-CSF), Biosimilar, 1 mcg. Zarxio would then pick up a modifier to help track its use and potential adverse effects. For Zarxio, that would be *ZA-Novartis/Sandoz.*

Sandie Preiss, Vice President of Advocacy and Access for the Arthritis Foundation, says, "We believe that treating biosimilars as multiple-source products stands counter to other biosimilar policies and the intent of Congress in passing the Biologic Price Competition and Innovation Act. Further, this proposal is not consistent with other CMS reimbursement policies, which treat biosimilars as single-source drugs within certain Part D programs and Medicaid."

The Cost of Biosimilars Is at Issue

Based on the experience in Europe, where biosimilars have been available longer, it had been a given that a biosimilar coming onto the U.S. market would have a price somewhere in the neighborhood of 15% to 25% lower than the reference drug. But early anecdotal experience with Zarxio doesn't bear that out.

Vizient's Lucio says the prices of Neupogen, Granix, and Zarxio have all come down between 15% to 20% since Zarxio's introduction in September 2015. Typically Neupogen is the most expensive of the three, with Granix and Zarxio trading second and third place depending on the market they are selling to. But the price difference between the three is normally not great. "Until you have two or three biosimilar providers for same-molecule competitors to branded [products], biologicals will not be priced definitively lower," Lucio says.

Some of the other biosimilars now in the application phase at the FDA (there are seven or eight, but the FDA doesn't confirm those numbers) will be much more likely to be self-administered than Zarxio or Inflectra. That means they will ostensibly be available for retail purchase, and therefore reimbursed under Medicare Part D and outpatient drug plans in the private sector or through the PPACA. A study from the consulting firm Avelere, published in April, found that Medicare patients in Part D plans are likely to pay more for biosimilars than for the reference drug.[8] That is because the Part D plans, under federal law, get a discount from the brand-name manufacturer when a Medicare recipient hits the so-called "doughnut hole," the gap in Part D coverage where a senior must pay more of the cost of a drug. The reference-drug manufacturer must provide rebates to Part D plan members who fall into that coverage gap. Biosimilar marketers cannot match those rebates. "Any voluntary point-of-sale discounts would be viewed by the OIG [Office of the Inspector General] as a kickback and would likely lead to punitive action," says Caroline Pearson, Senior Vice President at Avalere.

"The unintended consequence of the ACA is that consumers have a financial disincentive to switch to a lower-cost biosimilar," Pearson adds. "While the Medicare program will save money if beneficiaries take biosimilars, higher consumer out-of-pocket costs are a barrier to patient adoption."

It may be that biosimilars will become a boon to patients, payers, and providers. But until the FDA moves more quickly to approve biosimilars and they start to populate therapeutic categories in numbers that lead to lower prices, their success won't be a given.

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