Biosimilar Roadblock Removals Seem Tailor-Made for Trump/Democrats Agreement

Development of New Biosimilar Drugs and Marketing of Few Approved Drugs Stymied

Stephen Barlas

When the Veterans Administration (VA) health system announced it had awarded Merck a “national contract” on September 1, 2018, for its infliximab biosimilar Renflexis (infliximab-abda), it was a kind of shot heard round the world—or at least within the U.S. pharmaceutical industry. The announcement meant that Merck had priced its infliximab biosimilar, the second of two biosimilars in that category, below Janssen Biotech’s reference drug Remicade (infliximab) and Pfizer’s first-to-market biosimilar Inflectra (infliximab-dycl). The latter had previously been the VA’s favored infliximab but had nonetheless failed to gain market share beyond the VA because, in Pfizer’s view, propped up in court and in a Citizen’s Petition to the Food and Drug Administration (FDA) in August 2018, Janssen was using unfair marketing practices to stifle Inflectra’s sales growth.

Renflexis is the sole infliximab product listed on the VA National Formulary; however, both Remicade and Inflectra remain available for existing patients who were on these products prior to the contract award and for patients who have a clinical contraindication to Renflexis. The VA’s decision seems to reinforce what people have been saying about biosimilars: that as additional biosimilars populate individual disease/product categories, the price of all biosimilars and even the reference drug will decline with no diminution of patient safety or results.

Additional biosimilars are also on their way. The FDA’s Biosimilar Product Development program had enrolled 63 programs as of April 1, 2018, while the agency’s Center for Drug Evaluation and Research had received meeting requests related to 31 reference products.

At the moment, only two categories have two biosimilars accounting for four of the 12 biosimilars the FDA has approved since 2015, when Zarxio was the first out of the FDA’s chute. However, only five biosimilars are commercially available, including the two infliximabs and now two filgrastims, with the commercial availability as of October 1, 2018 of Pfizer’s Nivestim (filgrastim-afil). Pfizer has priced Nivestim 20 percent lower than Sandoz Biopharmaceutical’s Zarxio (filgrastim-sndz), which has been able to gain a significant but not overwhelming market share over Amgen’s Neupogen (filgrastim).

The more aggressive pricing strategies from biosimilars align with the Trump administration’s campaign to lower drug prices, a campaign that will be pushed to the front congressional burner as newly emboldened Democrats who have promised to make drug prices a top issue take over control of the House of Representatives.

If they want to populate more categories of biologics with competing, cheaper biosimilars, there are a number of steps Congress and the Trump administration can take, which become more imperative as the first biosimilars for blockbuster drugs—Roche’s Avastin (bevacizumab) and Genentech’s Herceptin (trastuzumab)—come on the market this year. Amgen will sell Mvasi (bevacizumab-awwb) and Mylan will market Ogivri (trastuzumab-dkst). Aimee Tharaldson, PharmD, Senior Clinical Consultant in the Emerging Therapeutics at Express Scripts, who was speaking at the Academy of Managed Care Pharmacy Nexus 2018 October meeting in Orlando, Florida, listed target launch dates of July 2019 for Mvasi, which has indications for several common forms of cancer, and June 2019 for Ogivri, a common treatment for breast cancer. Sales of Avastin and Herceptin are among the top five biologicals in the world, topping $7 billion a year in both instances.

“I’m not satisfied with the current state of the biologics market, and biosimilars in particular,” FDA Commissioner Scott Gottlieb said at an FDA public meeting on biosimilars on September 4, 2018. Some treatments for biologics and specialty drugs have annual costs exceeding $250,000 or more.

Gottlieb said that the FDA was trying to help circumvent those problems—which are only some of the roadblocks at issue—with the release of a Biosimilars Action Plan (BAP) in July 2018. Gottlieb has positioned the plan as an important piece of the Trump administration’s Blueprint to Lower Drug Prices. Many participants in the September meeting felt that the BAP was an important step forward, although some steps, such as the “shaming” of patent holders who refuse to make biologic samples available, have been criticized as ineffectual.

At the September meeting, Christine Simmon, Executive Director of the Biosimilars Council, said, “We are not aware of any companies who have changed their practices as a result of FDA’s naming and shaming.”

More Needed

Clearly, more needs to be done policy-wise in a number of areas, inside the FDA and at other federal agencies, which in some cases is only “doable” with the passage of congressional legislation. Biosimilar manufacturers are eagerly waiting for a final FDA guidance document on “interchangeability,” a designation that will allow pharmacists to switch a patient to an interchangeable biosimilar without first checking with the prescribing physician. The draft was published in January

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2017. Although the FDA has published a final guidance on the “naming” of biosimilars, its mandate that the nonproprietary name, such as filgrastim, must be followed by a meaningless four-letter suffix to distinguish it from the reference drug has been roundly condemned by a number of parties because the suffix “might generate inaccurate perceptions among patients and providers,” according to Biogen’s Tricia DeSantis, Vice President, Global Regulatory Policy.

The Department of Health and Human Services (HHS) could make some headway on reducing the impact of brand-name company rebates on the formulary decisions of insurers and pharmacy benefit managers. The HHS has a rulemaking on that topic in progress, although it applies only to Medicare Part D plans, not more broadly.

Congress could pass the CREATES Act, which says that if a generic company convinces the FDA that its manufacturing procedures guarantee the same level of safety as the brand-name’s procedures, that its handling of the product poses no risk to patients, and that it has tried but failed to get samples, the FDA can certify that the generic company is eligible to take legal action for damages against the brand-name company.

The Federal Trade Commission could start investigating deals between innovator biologic companies and biosimilar competitors, such as the one reached by AbbVie with Samsung Bioepis and Biogen, whereby the launch of the South Korean biosimilar to Humira (adalimumab) on the U.S. market will be delayed until 2023. The FTC has been very active in unwinding similar anti-competitive agreements between pharmaceutical companies selling small-molecule drugs and their generic competitors. The Biosimilars Competition Act (H.R. 6478) introduced last July would empower the Department of Justice and the FTC to take more aggressive action against “pay for delay” deals between innovator biologic manufacturers and biosimilar competitors. But the bill was inert, and had no cosponsors.

Congress could also give the U.S. Patent and Trademark Office additional leeway to interpret the patent provisions of the Biologics Price Competition and Innovation Act (BPCIA) in a way that diminished the length of time innovators could extend their patents preventing the introduction of biosimilars.

Confusion in the Marketplace

Part of the failure of commercially available biosimilars to gain market share, aside from pricing, is attributable to confusion, at least according to Pfizer, having to do with marketing campaigns by innovator companies to discourage physicians from prescribing biosimilars. The BPCIA says a biosimilar is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and has “no clinically meaningful differences” from the reference product in terms of safety, purity, and potency. A product deemed by the FDA to be an interchangeable biologic is a biosimilar that has met additional statutory criteria for product evaluation and testing. The FDA has yet to designate any of the 12 approved biosimilars “interchangeable.”

In a Citizen’s Petition it submitted to the FDA on August 22, 2018, Pfizer wrote: “We believe that a major factor contributing to this slow uptake is a lack of market confidence in biosimilars resulting from the efforts of certain reference product sponsors to disseminate false and misleading information that casts doubt about the safety and efficacy of biosimilars in the minds of patients and prescribers.” The petition complains about the tactics of a number of biologic manufacturers, particularly those of Janssen. Pfizer cites a Janssen patient brochure entitled, “Finely Tuned—Your Treatment, Your Choice,” which fails to mention that an approved biosimilar has no clinically meaningful differences from the reference product. Pfizer also claims that by stressing that its Inflectra is not “interchangeable” with Remicade, Janssen “is clearly attempting to mislead patients into believing they cannot safely be switched from Remicade to Inflectra by their physician.”

As asked to respond to the Pfizer petition, a Janssen spokeswoman simply repeated the statements in the “Finely Tuned” brochure.

Steven Lucio, Associate Vice President, Pharmacy Services at Vizient, Inc., believes that a small change in document disclosure by the FDA could remediate some existing uncertainty about biosimilars. The FDA has established the precedent of convening an advisory committee for the first biosimilar of an originator reference biologic (e.g., filgrastim, infliximab, adalimumab). As part of these meetings, the FDA also publishes the summary review document that serves as the basis for the advisory committee’s discussion. This information is extremely enlightening as it characterizes the “step-wise” process the FDA takes for each product. However, subsequent approvals of more biosimilars of the same originator biologic do not receive a hearing. To date, the FDA has not published any documentation related to biosimilars that are approved without a committee meeting. “FDA may view this information [as] unnecessary since any approved biosimilar has to meet the same standard,” Lucio states. “However, in this formative era of biosimilars, additional transparency would be extremely beneficial. We have had some members tell us that the absence of this detail has curtailed their enthusiasm for biosimilars that lack this additional documentation. Making this information public would not seem to require an inordinate effort and would help in the continued effort to demystify the biosimilar paradigm.”

Interchangeability Guidance

One of the most important things the FDA could do is to finalize its interchangeability draft guidance, which, in its draft form, has left open a host of technical issues, including the use of non-U.S. approved reference products, the kinds of “switching” (between the reference drug and biosimilar) and “bridging” studies that must be completed, and other issues.

Boehringer Ingelheim is the only company to have publicly announced the initiation of a clinical trial to demonstrate interchangeability—for its adalimumab biosimilar Cyltezo (adalimumab-adbm), which was approved by the FDA in 2017 but has not been marketed because of patent disputes between Boehringer and AbbVie, manufacturer of Humira, the innovator biologic. When Boehringer announced the interchangeability study in 2017, it said it had enrolled its first patient and would aim for 340 total patients. Susan Hatz, spokeswoman for Boehringer, says she cannot disclose the number of current participants for the trial, called VOLTAIRE-X. She says the company hopes to bring Cyltezo to patients “as soon as possible and certainly before 2023.” The other adalimumab
biosimilar, Amjevita (adalimumab-atto), manufactured by Amgen and approved by the FDA in September 2016, is not sold in the U.S. yet because of an agreement between AbbVie and Amgen. But it is sold in Europe.

Some of the innovator companies are pressing the FDA to raise the bar for interchangeability. Nathan Doty, Associate Director, Biotherapeutics Regulatory Affairs at AbbVie, says one interchangeable biosimilar should not be switched for another interchangeable because the clinical data needed to scientifically justify that automatic substitution has not been presented. Doty states, “We can’t use the generic paradigm for interchangeable biosimilars. For generics generally, active ingredients are chemically synthesized to be structurally identical to the reference. As the FDA recognized in the draft interchangeability guidance published last year, subtle differences in biosimilars matter.”

Some patient groups are also skittish about too low a bar for interchangeability. “Interchangeability determination should remain an extremely high bar that cannot be cleared unless it is true and supported by meaningful and unequivocal data, that any and all patients could be expected to experience the same clinical result in response to the therapy as required by statute,” states Randall Rutta, Federal Policy Consultant for the American Autoimmune Related Diseases Association. “For patients with complex conditions who are already stabilized on a therapy, it’s not appropriate to impose automatic substitutions or non-medical switching without the intervention and consultation of the prescriber and consent of the patient.”

Regardless of the opposing positions on the strength of interchangeability standards, final standards, whatever their form, would be a boon to additional research and additional new product applications, according to Anthony A. Barrueta, Senior Vice President, Government Relations at Kaiser Permanente. “From our perspective, clearer standards on interchangeability will lead to the development of more biosimilar products, which is a positive for KP, our members, the market, and the patient community at large,” he states.

Part of the reason for the dearth of interchangeability studies, aside from the lack of final guidance, has to do with the fact that the FDA currently requires a company to apply for “regular” approval of a biosimilar first, then apply a second time for an interchangeability designation. Soumi Saha, Senior Director of Advocacy at the Premier Health Alliance, which serves as a group purchasing organization of hospitals, describes it as “a bifurcated process that creates procedural inefficiency and potentially delays the introduction of interchangeable biosimilars to the marketplace.”

Formularies and P&T Committees at Ground Zero

A more vibrant biosimilars marketplace is important, of course, because of the potential savings to Medicare, Medicaid, federal marketplace plans, employer plans, and individuals. When he introduced the BAP in July 2018, Gottlieb said that had biosimilars been as successful in the U.S. as they are in Europe, savings would have been $4.5 billion in 2017.

There are different reasons why pharmacy and therapeutics (P&T) committees and the formularies they establish and administer may keep their distance from biosimilars. First, P&T committees sometimes mandate “fail first” policies that essentially keep physicians from switching patients to cheaper biosimilars unless the patients “fail first” on their current drug, often a reference biologic that in many cases the patient has been on prior to the biosimilar(s) being approved. Pharmacy benefit managers (PBMs) also prefer to put reference drugs in favored formulary positions because they are more expensive and therefore lead to higher rebates for the PBM. Lisa Skeens, Vice President of Global Regulatory Affairs for Pfizer Essential Health, alleges that contracts that require payers to exclude biosimilars from coverage to obtain rebates from the reference biologic manufacturers impose substantial financial penalties on insurers. Skeens did not respond to an email asking for examples of such contracts.

Madelaine Feldman, a rheumatologist from Louisiana who represented the Alliance for Safe Biologic Medicines at the September 2018 FDA meeting, explained that rebates are based on the list price, present discount, and market share. As biosimilars have no market share and a lower price, they’re behind the eight ball to begin with. “So, we really need to penetrate the formulary wall,” she stated.

Updating the Purple Book

Transparency would also be helped if the FDA revamped its Purple Book, the reference guide that lists licensed biological products with reference-product exclusivity and biosimilarity or interchangeability evaluations.

Mariana Socal, Assistant Scientist in the Department of Health Policy & Management at the Johns Hopkins Bloomberg School of Public Health, says the Purple Book does not include all the information a biosimilar product developer would need to determine whether to move forward on the studies required to file a 351(k) application. That is a reference to the section of the Public Health Act under which biosimilars are approved. “The uncertainty generated by the lack of readily available information may also prevent investors and manufacturers from considering becoming 351(k) applicants in the first place,” Socal said. The 351(k) of the Public Health Service Act contains requirements for biosimilar approval applications. Socal advocates for the addition of three types of information: 1) drug identification information should be expanded to include the manufacturer’s name, the drug’s route of administration, dosage form, strength, and other information; 2) all unexpired exclusivity periods should be published; and 3) information on all unexpired patents that the BLA licensee reasonably believes protect their biologic product should be published. “Absent readily available information, a potential new market entrant must engage a scientific expert or a patent attorney or both to sift through hundreds and hundreds of complex pharmaceutical patents,” she stated. Gottlieb committed to updating the agency’s Purple Book as part of the BAP. Details were not available at the time this article was written.

Beyond the FDA’s Reach

But greater transparency on biologic patents won’t help biosimilar developers if innovator companies are able to constantly extend the patent life of their drugs by asserting new patents. An August 2018 report from I-MAK, a global nonprofit organization of attorneys, scientists, and health experts, detailed that use of patents. The report is called “Overpatented, Overpriced: continued on page 68
How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving Up Drug Prices.” It analyzes the 12 best-selling drugs in the United States and reveals that drugmakers file hundreds of patent applications—the vast majority of which are granted—to extend their monopolies far beyond the 20 years of protection intended under U.S. patent law. The report found that, on average, across the top 12 grossing drugs in America, many of them biologics, there are 125 patent applications filed and 71 granted patents per drug. AbbVie, which markets Humira, now the subject of patent lawsuits, is the worst patent offender with 247 patent applications.

When he announced the BAP last July, Gottlieb singled out AbbVie’s patent-blocking strategy for Humira—citing the deal AbbVie reached with Samsung Bioepis and Biogen to delay their introduction of adalimumab in the U.S. until 2023—when he referred to legal settlements between brand-name companies and biosimilar competitors as being the “most spectacular” of the sources of opposition to biosimilars that are beyond the reach of the FDA. AbbVie’s Doty, who spoke at the FDA’s September meeting, did not respond to an email requesting AbbVie’s response to Gottlieb.

There is something of a chicken-and-egg dilemma going on with biosimilars: Too few are available in the U.S. and when they are available, their prices are underwhelming compared to the reference drug. Additional entrants in a category push prices down further, as Renflexus and Nivestim prove. But additional entrants aren’t becoming available for a number of reasons, all of which could be addressed either by federal agencies or by Congress, which have, in both instances, been very slow to take any significant action.

REFERENCE