

LIFE SCIENCES

US BIOSIMILARS UPDATE – WHERE WE ARE AND THE ROAD AHEAD

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Sales of biologics in the United States topped \$30B in 2015 and are growing much more rapidly than sales of small molecule drugs. No system existed in the US for approving generic versions of biologics until 2010, when Congress passed the Biologics Price Competition and Innovation Act (“BPCIA”) to permit the approval of so-called “biosimilars.” Six and a half years of the US biosimilars era is an adequate amount of time to assess how the BPCIA has been implemented and how biosimilars are faring in the US market. By a comparable point of time after passage of the Hatch-Waxman Act, the market for small generic drugs was thriving in the United States and many key legal and policy issues related to approval and marketing had been settled. Yet with only four biosimilars approved as of this date, FDA vacillation or lack of decision on some key issues, and biosimilar marketing delayed by patent litigation, the US biosimilar world remains in a state of, if not infancy, at least prolonged adolescence. This article will examine how we have gotten to this point, including FDA implementation, the current state of biosimilar patent litigation and the limited commercial experience so far.

BPCIA Overview

The BPCIA became law in March 2010 as part of the Affordable Care Act. In broad terms, it establishes an approval

system for copies of complex biologic drugs that allows biosimilar makers and FDA to rely on data generated by pioneer manufacturers to support approval, sets up a complicated system for patent litigation and provides exclusivity to newly approved biologics.

Drugs v. Biologics

Biologics are therapeutic products derived from living systems such as animals, plants, bacteria, viruses and human tissues. While drugs have simple chemical structures, are typically chemically synthesized and can usually be readily characterized, biologics in contrast are large, complex molecules or mixtures of molecules, are produced by using recombinant DNA technology and other advanced techniques, and may be difficult, or even impossible, to characterize by available testing methods. Biologics also are more likely than drugs to change characteristics in response to changes in environmental parameters such as heat, and are more susceptible than drugs to microbial contamination.

Although the BPCIA biosimilar system is somewhat analogous to the Hatch-Waxman system for approving generic copies of small drug molecules, approval of biosimilars under the BPCIA is very different, taking longer and being more expensive and difficult. Approval of a biosimilar product must be based on a showing that it is “highly

similar” to another FDA-approved product, known as a reference product, and that it has no clinically meaningful differences in terms of safety and effectiveness from the reference product. The rationale for the law setting such a high approval standard is the aforementioned complexity of biologic products and the corresponding need to protect patients by assuring that these products have appropriate safety and efficacy.

FDA Implementation of the Approval Standard - Approval Numbers are Low and Amount of Data Required is High

So how has FDA implemented this high approval standard? First of all, it is worth commenting on the pace of approvals. FDA approved the first biosimilar in March 2015, a full five years after BPCIA approval, and has approved only two more since then. In contrast, the European Union approved 11 biosimilars within five years of passage of its implementing legislation.

Turning to how these approvals have been granted, it is fair to call FDA’s approach as very cautious. Each of the approved biosimilars (Sandoz’s Zarxio biosimilar of Amgen’s Neupogen (filgrastim), Sandoz’s Erelzi biosimilar of Amgen’s Enbrel, and Celltrion’s Inflectra biosimilar of J&J’s Remicade) has been supported by large and robust amounts of data. (Editor’s note: On Sept. 23, 2016, the FDA

approved a fourth biosimilar. Amjevita, manufactured by Amgen, is a biosimilar of Humira (adalimumab), made by AbbVie.)

For example, the Inflectra application included extensive analytical data, a single dose pharmacokinetic study comparing Inflectra to both US-sourced and EU-sourced Remicade, a 54-week, randomized, double-blind, parallel-group clinical study comparing Inflectra and EU-Remicade study in approximately 600 patients with moderate to severely active rheumatoid arthritis, a 54-week randomized, double-blind, parallel-group study conducted in 250 patients with moderate to severe ankylosing spondylitis, and an assessment of safety and immunogenicity in patients undergoing switches in an open label extension of the rheumatoid arthritis study. Gathering this amount of data typically represents years of work and an investment of tens of millions of dollars.

While significant amounts of data have been required for each biosimilar approval, it is worth noting that FDA has been liberal in allowing extrapolation, meaning permitting data gathered in support of one use or indication of a biosimilar to support approval in other indications for which the pioneer is approved. Inflectra, for example, is approved for eight of the nine Remicade indications, despite having gathered clinical data in only two of the indications.

No Interchangeable Biosimilar Has Been Approved and Approval Standards Remain Unclear

The BPCIA establishes an even higher

standard for interchangeable biosimilars; that is, a biosimilar that could be readily substituted for the pioneer product by pharmacists and pharmacy benefit managers. The BPCIA requires that such an interchangeable product must be expected to produce the same clinical result as the pioneer in any given patient *and*, if administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the interchangeable product and the pioneer is no greater than the risk of using the pioneer without such alteration or switch. Many observers believe that interchangeable products will be key to broad acceptance of biosimilars. None of the approved biosimilars were approved as interchangeable, although apparently at least one of the sponsors generated data aimed at getting an interchangeable approval. FDA has promised but missed a self-imposed deadline for issuing guidance explaining how it intends to implement this part of the law.

Unique Generic Names for Biosimilars May Hinder Acceptance

Another regulatory hurdle for biosimilars stems from the question of what their name will be. FDA assigns a so-called generic name to each approved drug. Although manufacturers may in addition use brand names for their products, the non-proprietary generic name must appear prominently in labeling and is used throughout the healthcare system for many purposes.

Although the BPCIA is silent on naming, it became one of the most commented-upon and contentious topics in this arena. Biosimilar proponents asserted that biosimilars should have the same generic name as the pioneer drug because they share the same essential chemical structure. Pioneer manufacturers argued that a different generic name should be assigned to each biosimilar because they are physically different – the three dimensional structure and other physical characteristics of biologics depends on the way in which they are made, and that will differ from manufacturer to manufacturer, resulting in potential effects on product safety and efficacy. Behind both arguments is an assumption that a different generic name will make it more difficult for biosimilars to be accepted in the healthcare system.

FDA issued a draft guidance in August 2015 that came down in favor of a unique generic name for each biologic – not just biosimilars, but all pioneer biologics as well. Under this proposed system, biological products will have a “core name” and an FDA-designated four letter suffix. FDA proposed that the suffixes be random consonants “devoid of meaning” but solicited comments on this proposal. The agency now seems to be in favor of suffixes being assigned to each manufacturer. In fact, this is precisely what it did with the first biosimilar – Zarxio’s generic name is filgrastim-sndz, with the “sndz” standing for Sandoz.

In explaining the basis for this decision, FDA cites safety: “There is a need to clearly identify biological

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products to improve pharmacovigilance and, for the purposes of safe use, to clearly differentiate among biological products.” It remains to be seen whether FDA’s siding with pioneer manufacturers on the naming issue will significantly impede the market’s acceptance of biosimilars.

Litigation Poses a Significant Hurdle to Biosimilar Market Success

While an arduous task, getting FDA approval may prove to be a far less significant market barrier for biosimilars than overcoming the patents of pioneer manufacturers. At least 8 patent infringement lawsuits have been filed against biosimilars and a couple of more against biosimilar insulins that are regulated as drugs.

Because of their scientific complexity and the way in which they are manufactured, pioneer biologics are typically protected by many more patents than are small molecules. This poses a significant barrier to market entry. For example, Amgen asserted that Sandoz’s Zarxio could violate as many as 400 Amgen patents. But other current barriers to entry stems from the law itself.

The BPCIA establishes a complicated process for resolving biosimilar patent disputes that is commonly referred to as the “patent dance.” Biosimilar applicants and pioneer product makers exchange information about the application and the pioneer’s patents with the goal of identifying a few that the parties will include in an immediate patent infringement action. Other patents held by the pioneer maker could

be asserted later in a second round of post-approval litigation.

Two significant statutory interpretation issues are currently being contested in the courts. The first involves the law’s requirement that a biosimilar maker provide a pioneer with notice of its intention to commence commercial marketing at least 180 day before that marketing begins. In the very first biosimilar patent litigation filed (*Amgen v. Sandoz*, N.D. Cal. 3:14cv4741 (J. Seeborg), Fed. Cir., (J.J. Lourie, Newman, Chen) 794 F.3d 1347), Sandoz asserted that this notice can be given prior to FDA approval while Amgen argued that it can only be given after approval. Amgen prevailed on this issue in the Federal Circuit but that decision is now the subject of a pending certiorari petition to the Supreme Court. The Court has asked the Solicitor General to weigh in on this case, which frequently is an indication that the Court will hear the appeal.

The second statutory interpretation issue is whether the patent dance is a mandatory or an optional process. Biosimilar makers have asserted that the dance is optional and refused to engage in it in whole or in part in various litigations, denying pioneers access to their biosimilar applications and information about their manufacturing processes. Sandoz won on this issue in its filgrastim lawsuit with Amgen, but Amgen has requested that the Supreme Court also review this issue if it decides to weigh in on the notice of commercial marketing issue.

While Zarxio is on the market, lawsuits so far have kept Inflectra and Erelzi from launching. It’s a small sample size, but if that rate were to continue, biosimilar market penetration will be slow indeed.

Marketing Challenges Loom

For those biosimilars that navigate between the Scylla of FDA and the Charybdis of patent litigation, the challenges of successfully marketing biosimilar products remain. Most observers agree that, unlike most generic drugs, biosimilars will need to be supported by extensive marketing and sales teams in order to achieve marketing success. It is unclear how willing US healthcare professionals and patients will be to use biosimilars and what cost concessions will be necessary to significantly influence adoption. It appears that thus far Zarxio has achieved very limited sales, although this may be attributable to reported net discounts to Neupogen of less than 20%.

Down the road, another significant obstacle looms for interchangeable biologics. Twenty-three states have passed laws regulating and restricting the eventual use of interchangeable biologics by imposing requirements such as pharmacists notifying prescribing physicians of a proposed switch.

Conclusion

Biosimilars present a large and tempting market in the US and are therefore being targeted by many drug makers, including large brand name companies such as Merck, Amgen and Novartis. But in contrast to

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Europe and some other global markets, implementation of the biosimilar law in the US has been slow. FDA has been cautious and conservative in approving products and in making key policy decisions. Patents are and will remain a barrier to entry for many proposed biosimilar products. Because of the small amount of approvals and legal issues, there is not a large enough sample to make predictions about the eventual commercial success of biosimilars.

The prospects for a significant change in this situation appear to be remote. The only biosimilars policy proposal to attract much national attention late is a proposed reduction in the period of pioneer exclusivity from 12 years to 7 years, which has been endorsed by Secretary Clinton. Such a change would not affect the issues discussed above. Thus, it is unlikely that there will be any dramatic change in the landscape and US adoption of biosimilars will continue to proceed slowly.

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