The Potential For Litigation In New Era Of Biosimilars

By Christian Frois, Richard Mortimer and Alan White; Analysis Group, Inc.

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Christian Frois


Richard Mortimer


Alan White

In recent years, there has been widespread litigation related to intellectual property disputes and alleged antitrust violations surrounding generic entry across a wide range of therapeutic classes. For example, over 90 percent of the drugs experiencing initial generic entry between 2011 and 2014 had one or more patent challenges associated with a generic application[1]. Furthermore, settlements in these cases have triggered numerous reverse-payment lawsuits. These cases frequently involve economic questions related to, among other things, class certification, market definition and damages. As biosimilars are now becoming available in the U.S., the question is whether a similar experience awaits with respect to the nature and extent of likely litigation. The answer is not that simple given the economics of biosimilars as well as some key differences between large-molecule (biologic) drugs and small-molecule (chemical) drugs.

Stepping Back: The Biosimilar Revolution Has Just Begun in the U.S.

The Biologics Price Competition and Innovation Act of 2009 paved the way for biosimilar entry, with three approvals to date and many more expected over the coming years. As of July 2015, there were 57 biosimilars in the U.S. Food and Drug Administration Biosimilar Product Development Program referencing 16 different innovative biologics[2]. The potential widespread introduction of biosimilars represents a massive change and one of the most impactful events to hit the drug industry in decades, with many top-selling biologic

drugs expected to be affected over the next few years. Not since the Hatch-Waxman Act of 1984, which paved the way for entry of generic small-molecule drugs into the marketplace, has there been as much speculation concerning the economic and legal impact on branded drugs and manufacturers. While biosimilar entry in the U.S. is still nascent, biosimilar applications to the FDA have already raised allegations of patent infringement and sparked a number of lawsuits.

The global market for biologic drugs has been forecast to exceed $390 billion by 2020, with some analysts predicting substantial cost savings from biosimilars[3]. For example, one study suggests that for the five major European Union markets and the U.S. combined, cost savings could exceed $50 billion over the next five years and may be as high as $110 billion[4]. Such predictions, particularly with respect to the U.S., are highly speculative given the limited experience of biosimilars in the U.S. to date.

As of late 2016, the FDA has approved three biosimilars for commercial sale in the U.S.:

- Zarxio (brand reference product Neupogen) in March 2015
- Inflectra (brand reference product Remicade) in April 2016, and
- Erelzi (brand reference product Enbrel) in August 2016.

Zarxio was launched in the fall of 2015, while Inflectra and Erelzi have not yet been launched in the U.S. In addition, there are several biosimilar applications currently under review by the FDA (see Table 1).

One goal of the BPCIA was to try to achieve the level of cost savings realized from the widespread adoption of generics. Research found that branded small-molecule drugs facing generic entry lose, on average, in excess of 80 percent of their sales within a year. In addition, they found that generic price discounts often exceed 75 percent relative to the brand's price[5]. For many small-molecule drugs, a rapid shift to generics can result in substantial cost savings for some health care payers, although there has been a range of experiences across therapeutic areas based on the number of generic entrants, the extent of generic penetration, and the associated price discounts from the brand.

Table 1: Selected biosimilars currently being developed for the U.S. market and global sales of the reference innovative biologics.

Originator brand	Biosimilar manufacturer	Global sales (2014, in $billions)
Lantus	Eli Lilly	$8.2B
Neulasta	Apotex and Novartis/Sandoz	$4.6B
Humira	Amgen	$13.0B
Rituxan	TBD	$7.4B
Avastin	Amgen/Allergan	$6.8B
Herceptin	Amgen/Allergan/Synthon and Pfizer/Hospira	$6.7B
Lucentis	Pfizer/Hospira/Pfenex	$4.3B

Biosimilars Are Different From Generic Drugs

The biosimilar experience is likely to differ from the typical generic experience in several important ways. Biosimilars are, on average, expected to achieve much more modest penetration rates and price discounts of less than 50 percent[6]. This has been the early experience with respect to Zarxio, where its sales penetration and price discount relative to the originator product, Neupogen, have been more limited compared with the average experience of small-molecule drugs (see Table 2)[7]. And, the experience of Zarxio is very similar to that of Granix, the quasi-biosimilar form of Neupogen that launched in the U.S. market in November 2013[8].

Table 2: Comparison of U.S. Biosimilar and Average Generic Drug (Six Months After Launch)[9]

	Share of sales vs. originator	Price discount vs. originator*
Generic Drug Average	≥75%	≥40%
Granix (quasi-biosimilar Neupogen)	5-10%	~11-23%
Zarxio (biosimilar Neupogen)	~10%	15%

Even in Europe, where biosimilars have been marketed for over a decade, biosimilar adoption and price discounts have been relatively modest, although there has been significant variation across countries and therapeutic areas. Analogies with Europe should be made with caution, however, given the markedly different health care, legal and regulatory environment for drugs relative to the U.S[10].

The differences experienced to date in the average price and volume impact of biosimilars compared with generics are not surprising. One reason is that biologic drugs are substantially more complex than small-molecule drugs, as they are derived from living organisms. This greater complexity often creates substantial scientific and manufacturing challenges, and can greatly increase the costs and risks associated with developing and producing biosimilars. For example, it is more difficult to characterize the structure of biologic drugs, making the development and production of biosimilars more susceptible to variability.

Given these differences, biosimilar competition may well share more features with traditional brand-brand drug competition than with brand-generic competition. For example, the variability between innovator and biosimilar drugs makes it unlikely that the FDA will initially approve many biosimilars as interchangeable with their reference innovator biologic. In the absence of an AB-rating by the FDA, pharmacies will not be allowed to automatically substitute a biosimilar for the innovator biologic, and payers may be reluctant to push for automatic substitution or implement formulary/managed care mechanisms that encourage switching between the innovator and biosimilar. Furthermore, biosimilar manufacturers will need to use distinct "brand" names for their biosimilars, and may need to invest substantially in marketing and sales to encourage their adoption. Indeed, current biosimilars in the U.S. and Europe are developed and marketed as branded competitors with distinct names. Finally, the high costs of development (e.g., the FDA requires costly Phase III trials to approve a biosimilar) and high

manufacturing costs, are likely to limit entry to a small number of competitors relative to the experience with respect to many small-molecule drugs.

The FDA is still reviewing how best to address the issue of interchangeability ratings for new biosimilars in the U.S. Given the potential safety concerns, it is likely to wait for more information on the experience of the first set of biosimilars before taking a strong stance in favor of interchangeability. This will likely take several years. Even if it is made available, it is unclear how payers and physicians would respond to such a rating, as well as how varied their response would be across therapeutic areas.

Looking Ahead: What Are the Implications for Biosimilar Litigation?

Because of the many key differences between biologic and generic drugs, it is not exactly clear what the litigation landscape will look like for biosimilars. But given the complex manufacturing process and the array of associated patents, as well as the challenging nature of establishing "similarity" to the referenced brand, the potential for lawsuits is broad.

While FDA applications for biosimilar approval under the BPCIA are still in their infancy, they already have triggered a number of patent infringement lawsuits (see Table 3).

These lawsuits have sparked debate on the validity of the associated patents and the process for patent litigation as set out in the BPCIA.

There remains substantial uncertainty and dispute regarding the provisions of the BPCIA with respect to patent litigation and presuit requirements (e.g., whether or not the so called "patent dance" exchange of information is mandatory, application of the 180-day notice of commercial marketing). Patent litigation for biosimilars may be complex and the substantial uncertainty surrounding the outcomes of such litigation could result in a wide range of follow-on litigation, similar to what has been observed with respect to small-molecule drugs.

In the case of Zarxio, Sandoz chose to launch it on an "at-risk" basis while the patent litigation was ongoing, leaving open the potential for follow-on litigation should Amgen's patents on Neupogen be upheld and Sandoz be found to infringe on those patents. In other cases, settlements of patent disputes could lead to follow-on litigation with claims of antitrust violations and allegations of "delayed biosimilar entry," as has been prevalent with respect to many small-molecule drugs.

Table 3: Selected Biosimilar Related Patent Infringement Litigation

Plaintiff	Defendant	Brand Biologic At Issue
Amgen	Sandoz	Neupogen
Amgen	Hospira	Epogen
Amgen	Apotex	Neulasta
Amgen	Sandoz	Neulasta
Immunex / Amgen / Hoffmann-La Roche	Sandoz	Enbrel
Janssen	Celltrion / Hospira	Remicade

In addition to patent-related litigation, entry of biosimilars may result in product safety lawsuits or allegations of improper promotion. Product safety may be a concern if some patients react differently to the biosimilar than to the reference brand biologic. Even though biosimilar approval requires demonstrated similarity to the reference product on average, individual patients could have a range of different reactions. Furthermore, for Zarxio, Inflectra and Erelzi, the FDA approved the biosimilars not only for the indications where clinical data were provided, but also for the other approved indications of the reference brand, commonly referred to as "indication extrapolation." In other words, these biosimilars are now approved even for indications where the manufacturer did not submit any corresponding trial data. In addition to potential resulting concerns related to product safety, the expected competitive marketing of brand and biosimilar products raises the specter of lawsuits alleging improper or misleading promotion.

Thus, as biosimilars continue to enter in the U.S., the impetus for litigation of several different types will likely grow. However, the nascent nature of competition in this area leaves a lot of uncertainty as to how exactly this will unfold.

Endnotes

1 Grabowski, Henry, Genia Long, Richard Mortimer, and Ani Boyo, "Updated Trends in US Brand-Name and Generic Drug Competition," Journal of Medical Economics, April 2016; and IMS Institute for Healthcare Informatics, "Price Declines after Branded Medicines Lose Exclusivity in the U.S.," January 2016.

2 "Biosimilar Implementation: A Progress Report from FDA," Statement of Janet Woodcock, M.D. Before the Committee on Health, Education, Labor and Pensions, United States Senate, Sept. 17, 2015.

3 IMS Institute for Healthcare Informatics, "Delivering on the Potential of Biosimilar Medicines, The Role of Functioning Competitive Markets," March 2016, p. 1. (IMS 2016). Figures reported in Euros have been converted to U.S. dollars.

4 IMS 2016

5 See supra note 1.

6 Grabowski, Henry, Genia Long, and Richard Mortimer, "Implementation of the Biosimilar Pathway: Economic and Policy Issues," Seton Hall Law Review 41(2), 2011: pp. 542-543.

7 http://www.biopharma-reporter.com/Markets-Regulations/Sandoz-s-biosimilar-Zarxio-gradually-eroding-Amgen-s-Neupogen-sales (viewed 4/7/16).

8 Granix (tbo-filgrastim) was approved through the full Biologics License Application (BLA) pathway (rather than the abbreviated biosimilar pathway), but is based on a similar underlying filgrastim molecule as Neupogen.

9 http://www.biopharma-reporter.com/Markets-Regulations/Sandoz-s-biosimilar-Zarxio-gradually-eroding-Amgen-s-Neupogen-sales (viewed 4/7/16); IMS Institute for Healthcare Informatics, "Price Declines after Branded Medicines Lose Exclusivity in the U.S.," January 2016; Grabowski, Long, Mortimer, Boyo (2016).

10 Berndt, Ernst R. and Mark R. Trusheim, "Biosimilar and Biobetter Scenarios for the U.S. and Europe: What Should We Expect?", in Amy Rosenberg and Barthelemy Demeule, eds., Biobetters: Protein Therapeutics to Approach the Curative, New York: Springer Science + Business Media, LLC, in Partnership with the American Association of Pharmaceutical Scientists, 2015, PP. 315-360.