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Biosimilars in the U.S.: It's All Shook Up

Weighing the Risk and Benefits of Patent Disputes

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Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2010 to create a framework for the introduction of biosimilar and interchangeable drugs into the U.S. market. Like the predecessor Hatch-Waxman Act, which regulates market entry of generic small molecule drugs, the BPCIA outlines a process whereby companies can gain an abbreviated approval of more complex protein-based drugs if the drug is highly similar to one already on the market.

Four companies have announced submission of applications to the FDA for approval of their biosimilars. These include biosimilars for Neupogen (filgrastim) and Neulasta (peg-filgrastim), Remicade (infliximab) and Epogen (epoetin). On March 6, the FDA approved the first biosimilar, Zarxio (filgrastim). Many more companies have biosimilars in their pipelines.

The statutes governing FDA approval of small molecule and biologic drugs each provide for a period of exclusivity for the originator drug. New small molecule drugs typically have five years of exclusivity. The BPCIA grants new biologic drugs a much longer life—12 years of exclusivity.

There has been considerable political debate over the longer length of time provided for biologics exclusivity, with some suggesting it should be reduced to seven years. Notably however, this factor has not been in the spotlight with the current biosimilars. These biosimilars are related to biologics approved by the FDA between 1991 and 2002. As such, the 12 year exclusivity has already expired. The same is true with many of the other biosimilar drugs in the clinical pipeline.

Perhaps due to the expiration of market exclusivity, a key issue for the first crop of biosimilars has been the procedure for patent disputes. Like the statute governing generic entry for small molecule

drugs, the BPCIA also includes a mechanism for the copycat drug to enter the market before the patents covering the original drug have expired. This process includes challenging and proving non-infringement, invalidity, or unenforceability of the unexpired patents in federal court. The Hatch-Waxman process sets out a fairly short timeline, whereas the BPCIA process is significantly longer.

The BPCIA provisions prescribe pre-litigation steps for the companies controlling the original biologic and the biosimilar to exchange product and patent information. This process, sometimes referred to as the patent dance, can consume more than six months before patent litigation is initiated in court. The BPCIA also includes provisions for litigating some of the patents in an initial lawsuit and then addressing others in later litigations once the biosimilar gives notice 180 days prior to commercial marketing.

As the first biosimilars make their way through the system, this complex process has made for some false starts, particularly because biosimilar companies may file declaratory actions. In June 2013, the Northern District of California dismissed a declaratory action related to a biosimilar for Enteracept (enbrel) as premature because the action was brought before the biosimilar application was filed with the FDA. Thus, the applicant had not complied with the BPCIA framework. In a District of Massachusetts case involving a biosimilar of Remicade, the defendant brought a motion to dismiss the declaratory action on similar grounds and in October 2014, the biosimilar company voluntarily dismissed the case. Similarly, the Southern District of New York dismissed a declaratory judgment case against a third party holding patents related to a biosimilar antibody drug, reasoning that an actual case or controversy did not exist until the biosimilar company had completed the BPCIA process and entered the market.

In October 2014, a new ground of controversy arose in the biosimilar litigation arena. In a case involving a biosimilar of Neupogen, the biosimilar company refused to provide its FDA application and manufacturing processes to the company marketing the branded drug, asserting that these steps of the BPCIA were not mandatory.

The Northern District of California agreed with the biosimilar's interpretation of the statute. The court viewed the statute as setting out a series of choices and consequences. Under this view, the parties may choose to engage in the patent dance and then be required to comply with prescribed disclosure steps. As a consequence of this choice, the parties then can avail themselves of the benefits, such as an assessment of the risk of a biosimilar launch based on the patents disclosed in the exchange. Alternatively, if the parties do not choose to dance, as a consequence they forgo this assessment and the availability of certain declaratory action. Instead, the parties engage immediately in litigation without the pre-litigation steps set out in the statute.

The Northern District of California also ruled on a second area of controversy. The statute requires that the biosimilar company provide notice to the branded company no later than 180 days before the

date of first commercial marketing. At that point, the original biologic ("reference sponsor") can seek a preliminary injunction or declaratory action against the biosimilar. At issue was whether the FDA must grant approval for the biosimilar before the company can provide its notice. The court found that the statute did not require FDA approval before such notice, noting that this would have the unintended consequence of adding six months to the 12 years of exclusivity already granted to the original biologic.

The Northern District of California's rulings came as a surprise to many in the industry. However, the circumstances of the current biosimilars may play a role in how the court viewed the issues. Neupogen received FDA approval in 1991; the market exclusivity thus had expired long before the biosimilar litigation commenced. Requiring the patent dance and delaying market notification until FDA approval would have, in essence, further extended the branded drug's exclusive position of the market.

For a biosimilar preparing for market while the 12-year exclusivity period for the original biologic is still in force, these circumstances may look very different. The patent dance may be more attractive as a mechanism to gather information and mitigate risk before significant investment of time and money. However, given the position of the courts that a case or controversy is not ripe until the biosimilar developer files its application with the FDA, this only leaves the period following FDA filing to use the patent dance. A large amount of investment occurs before this time. Based on publicly released information, the development of a biosimilar for enbrel first began in 2004, with pre-clinical work initiating in 2009. Phase I studies occurred in 2011–2012, followed by a Phase III study initiated in 2013. Yet as of April 2015, the submission of an application to the FDA has not yet occurred. Similarly, clinical trials for the biosimilar of infliximab began in March 2010, but the FDA did not accept the biosimilar application until October 2014. Realistically, therefore, the patent information and risk assessment must occur long before the biosimilar files with the FDA, rather than during the patent dance.

Perhaps the benefit of the patent dance lies more in risk mitigation for launch. If the biosimilar chooses not to engage in the dance, it risks a preliminary injunction shortly after it gives its notice of commercial marketing. If no injunction is granted, it may then be faced with an at-risk launch relative to the patents potentially covering the product, its use and methods of manufacture. The patent dance creates some benefits for the biosimilar through its use-it-or-lose-it provisions directed to the reference sponsor. If patents are not disclosed during the dance, the reference sponsor cannot later assert them against the biosimilar. Similarly, if the reference sponsor engages in the patent dance but chooses not to bring litigation within the prescribed time frame, later assertion of the patents may be limited to reasonable royalty damages with no permanent injunction. Thus, engaging the reference sponsor in the dance can help frame and mitigate the scope of liability for the biosimilar.

The current biosimilars have chosen to take the risk and forgo the dance. So, at almost five years out from the BPCIA's enactment, is the process working as intended? These initial starts and stops and the complexity of the litigation process suggest that it may take some time before everything settles into place.