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2015: The Pathway to Biosimilars

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In 2015 there were many important developments in the biosimilar industry. The FDA approved its first biosimilar application, Zarxio, a biosimilar of Amgen's Neupogen, after which the Federal Circuit affirmed that the notification procedures described by the biologics license application, or "patent dance," are not mandatory. States have been increasingly regulating the use of biosimilars, before any drugs have entered the market. These developments have helped clarify the regulatory path for biosimilar manufacturers and indicate the potential for a promising future for the growing biosimilar market.

Recent Litigation:

In July 2015, the Federal Circuit held that certain procedures under the Biologics Price Competition and Innovation Act (BPCIA) are no longer mandatory, limiting the information available to biologic drug makers regarding a competitor's application for a biosimilar product.[1] Sandoz' Zarxio product is the first product approved under the BPCIA. Zarxio was approved as a biosimilar of Amgen's Neupogen product. After receiving notification from the FDA, Sandoz had 20 days to provide Amgen with a copy of its biosimilar application and other information describing how the product is made. Sandoz did not provide a copy of the application within the 20 day period, and in October 2014 Amgen filed a complaint against Sandoz for failing to follow the procedure under 42 U.S.C. § 262(l)(2)(A) and patent infringement.

Congress enacted the BPCIA in 2010, which established an abbreviated pathway for regulatory approval of biosimilars, as part of the Patient Protection and Affordable Care Act ("ACA"). An applicant filing a biologics license application ("BLA") can instead submit information to demonstrate that its product is "biosimilar" through the pathway codified under 42 U.S.C. § 262(k). Pursuant to § 262(k), applicants submit information demonstrating their product is biosimilar together with publicly available information regarding the FDA's previous determination that the reference product is "safe, pure, and potent." This process allows biosimilar applicants to use the approved license of another product in achieving FDA approval.

The BPCIA also amended the Patent Act to create an artificial "act of infringement" and allow infringement suits based on biosimilar applications prior to FDA approval and prior marketing of the biological product.[2] Another provision created a process for biosimilar applicants to exchange information to resolve patent disputes with the reference product sponsor, which is codified in 42 U.S.C. § 262(l). The process involves a biosimilar applicant granting the reference product sponsor confidential access to its BLA and the manufacturing information regarding the product no later than 20 days after the FDA accepts the application for review. The parties can then exchange lists of patents and positions on infringement, validity, and enforceability of the patents. After this exchange, known as the "patent dance," the parties negotiate to formulate a list of patents that would be subjected to an immediate infringement action,[3] and the reference product sponsor can sue the biosimilar applicant within 30 days.[4]

Applicants may also give notice of commercial marketing to the reference product sponsor at least 180 days prior to commercial marketing of the product licensed under 262(k), which then allows the reference product sponsor to seek a preliminary injunction based on the non-listed patents. The non listed patents include newly issued or licensed patents in addition to the patents the parties identified during the exchange of information, but were ultimately not selected for the immediate infringement action.[5]

In October 2014, Amgen sued Sandoz asserting claims of (1) unfair competition for unlawful business practices; (2) conversion for allegedly wrongful use of Amgen's approved license on Neupogen; and (3) infringement of Amgen's U.S. Patent 6,162,427.[6] On March 6, 2015, the FDA approved Sandoz's aBLA for all approved uses of Amgen's Neupogen. Sandoz gave a further notice of commercial marketing to Amgen on the date of FDA approval. Later that month, the district court granted partial judgment on the pleadings to Sandoz on its BPCIA counterclaims, stating that Sandoz's interpretation of the statute was consistent with the courts' interpretation.

The District Court held that the notification process pursuant to § 262(l)(2)(A) is entirely optional. Specifically, the court concluded that it was permissible under the BPCIA not to disclose the aBLA and manufacturing information to the reference product sponsor, and that such a decision does not offer a basis for the reference product sponsor to obtain injunctive relief, restitution, or damages against the applicant. The court also held that an applicant can give notice of commercial marketing under § 262(l)(8)(A) before FDA approval.

Upholding this interpretation, the Federal Circuit found that an applicant's noncompliance with the notification provisions of the statute is specifically contemplated within the statute.[7] Furthermore, this noncompliance does not exculpate an applicant from the consequences contained within the statute.[8] Therefore, the Court held that where a subsection (k) applicant completely fails to provide its aBLA and the required manufacturing information to the RPS by the statutory deadline, the requirement of paragraph (l)(8)(A) is mandatory.[9] The Court found that Sandoz did not violate the BPAIA by failing to disclose its aBLA, because Sandoz took a path

expressly contemplated by 42 U.S.C. § 262(l)(9)(C) and 35 U.S.C. § 271(e)(2)(C)(ii). It is only when notice follows licensure that a "fully crystallized controversy" regarding the need for injunctive relief exists.[10] Because the only notice Sandoz provided was when FDA approved its aBLA, the Court held that Sandoz could not launch until September 2, 2015.[11]

Value Proposition

Globally, the biosimilar industry is expected to have a market value of $20 billion by the end of 2015.[12] Biologics currently are approximately 20% of a $200 billion dollar industry, and biosimilar products have the potential to account for up to 70% of that industry. That biologics already possess within the market in addition to the FDA beginning to approve new biosimilar applications, indicates that the biosimilar market is poised for rapid growth in the near future.

Regulatory Framework: FDA Guidance

The FDA released multiple guidance documents to help manufacturers understand the biosimilar regulations. These documents include descriptions on how manufacturers must demonstrate biosimilarity and what similarity factors are important to the FDA when submitting a marketing application.

In April 2015, the FDA released guidance titled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product." The nonbinding recommendations included a stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed product and reference with respect to the structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.

The stepwise approach involves applicants reviewing the similarity in a sequential manner as opposed to simultaneously. Generally, the sponsor should evaluate the uncertainties relating to biosimilarity, and come up with a mechanism of addressing them, using this principle to guide the assessment. First, an applicant should pursue an extensive analysis of the structure to assess biosimilarity. Second, the applicant should pursue a functional characterization of the proposed product. Next, the sponsor should consider the role of animal data. Finally, the sponsor should conduct comparative human PK and PD studies to compare the clinical immunogenicity of the two products in an appropriate study population.

Structural data should include tests comparing the primary structures, higher order structures (including secondary, tertiary, and quaternary structures), enzymatic posttranslational modifications (glycosylation and phosphorylation), other potential variations (oxidation or protein deamidation), and intentional chemical modifications. The Guidance suggests that sponsors should conduct structural characterization of the proposed product and reference product in multiple representative lots to understand the variability of both products in manufacturing. This same multiple lot analysis is also recommended for the finished dosage form.

Functional assays can provide information that compliments that animal and clinical data to assess potential clinical effects of differences in structure. Functional assays should include in vitro and in vivo assays to provide additional evidence that the biologic activity and potency of the proposed product are similar to those of the reference product.

Demonstrating biosimilarity through animal studies is also required, and can include animal toxicity data and animal PK and PD measures, depending on the circumstances.

Clinical studies are also required and sponsors are required to demonstrate that there are "no clinically meaningful differences between the biological product and reference product in terms of the safety, purity, and potency of the product." These, like animal studies, vary in their requirements depending on the exact nature of the biosimilar product.

Specifically with regards to protein products, the FDA stated that proteins are unlikely to be shown to be structurally identical. Because even minor structural differences may affect a protein's safety, these differences must be clearly highlighted. The Guidance highlighted three key areas of difference (1) primary amino acid sequence; (2) modification to amino acids (including glycosylation) and (3) higher order structure. The Guidance states that demonstrating biosimilarity in the case of proteins can be particularly difficult because a manufacturer of a proposed product will likely have a different process of the manufacturer of the referenced product. Therefore, the FDA anticipates more data and information is needed to establish a manufacturer's post-manufacturing change product is comparable to a pre-manufacturing change product.

In January 2015, the FDA released an advisory discussing the evidence the Zarxio BLA used to demonstrate biosimilarity to a single reference product, the US-licensed Neupogen. Zarxio presented analytical data to demonstrate that their reference product was highly similar from an analytical and functional standpoint. The provided data included primary and higher order structure, function, purity, stability, as well as bioactivity. Zarxio also was compared with Neupogen in five animal studies which assessed pharmacodynamics, toxicity, toxicokinetics, and local tolerance. Nonclinical results confirmed the profiles of Zarxio and Neupogen are similar. The clinical studies assessed immunogenicity, pharmacokinetics, pharmacodynamics, and the clinical efficiency and safety of Zarxio. The data was collected in a total of 174 healthy volunteers, 388 breast cancer patients receiving myelosuppressive chemotherapy, and 121 healthy stem cell donors. Zarxio was shown to have the same mechanism of action and there were no qualitative differences found. Based on this data, no clinically meaningful differences between Zarxio and Neupogen were found.

Interestingly, many states have begun to actively regulate the substitution of biosimilars before biosimilars have entered the market.[13] As of July 1, 16 states have enacted legislation or promulgated administrative rulings governing biosimilar substitution by pharmacists. Four states also have pending legislation that could pass regulating biosimilars.[14] Most of the regulations involve requiring pharmacists to notify providers of the substitution (14 states) or notify patients of the substitution (10 states). Other states require that the biosimilar be priced less to the prescription product. Certain states have also regulated the circumstances in which biosimilars may be prescribed.[15]

For example, Tennessee requires prescribers to demonstrate the prescribed biological product is medically necessary for the particular patient by adhering to stringent standards. The bill defines medically necessary provisions into three scenarios. First, where an adverse reaction was experienced by a patient. Second, where an interchangeable product was previously deemed ineffective for the patient. Third, for any other clinically based or prescriber determined need. While the third criterion is vague enough to allow for flexibility, the other two requirements indicate an exhaustion of alternatives is suggested before biosimilars are to enter the market.

Aside from Tennessee, most state laws regulate communication and are much less strin-

gent. A representative example took place in April 2015, when Colorado joined other states in passing a law regulating biosimilar substitutions that addresses the circumstances under which the FDA-approved interchangeable products may be substituted for the prescribed biological product. The Colorado law allows pharmacists to substitute a biosimilar for a prescribed reference product if the FDA has approved the biosimilar drug and found it "interchangeable" with the reference, if the prescriber has not limited substitution through means described by the statute, if the substituted product will cost the purchaser less than the prescribed product. The pharmacist must also communicate the substitution to the purchaser orally and in writing.

The recent regulatory developments have helped clarify the regulatory path for biosimilar manufacturers. The approval of the first biosimilar application for Zarxio, and lessening of the mandatory notification procedures under the BPAIA are both promising developments. However, state regulation could make it more difficult for patients to obtain access to biosimilars before these products even hit the market. The increased regulatory guidance will assist biosimilar products in obtaining regulatory approval. Over time, a more streamlined path to access will allow manufacturers to take advantage of this growing market.

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1 Amgen Inc. v. Sandoz Inc., No. 2015-1499, 2015 WL 4430108, (Fed. Cir. July 21, 2015)
2 See 35 U.S.C. § 271(e)(2)(C), (e)(4), (e)(6)
3 42 U.S.C. § 262(l)(4)-(5)
4 42 U.S.C. § 262(l)(6)
5 42 U.S.C. § § 262(l)(7)-(8)
6 *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, 2015 WL 4430108, at *3 (Fed. Cir. July 21, 2015)
7 *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, 2015 WL 4430108, at *9 (Fed. Cir. July 21, 2015)
8 *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, 2015 WL 4430108, at *9 (Fed. Cir. July 21, 2015)
9 *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, 2015 WL 4430108, at *9 (Fed. Cir. July 21, 2015)
10 *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, 2015 WL 4430108, at *8-9 (Fed. Cir. July 21, 2015)
11 *Amgen Inc. v. Sandoz Inc.*, No. 2015-1499, 2015 WL 4430108, at *10 (Fed. Cir. July 21, 2015)
12 GBI Research, "Biosimilars – Regulatory Framework and Pipeline Analysis", http://www.prnewswire.com/news-releases/biosimilars-market-study--regulatory-framework-and-pipeline-analysis-2015-2020-market-expected-to-reach-55-billion-300117747.html
13 http://www.healthlawpolicymatters.com/2015/07/28/emerging-state-biosimilar-laws-reference-chart-and-five-issues-to-watch/?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+HealthLawPolicyMatters+%28Health+Law+%26+Policy+Matters%29
14 http://www.healthlawpolicymatters.com/files/2015/07/State-Biosimilar-Substitution-Laws-Chart-for-Blog.pdf
15 S.B. 984, 109th Gen. Assem., (Tenn. 2015) (enacted)