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Biosimilars: Patent challenges and competitive effects

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Although it is nearly five years since enactment of the Biologics Price Competition and Innovation Act (BPCIA),[1] no biosimilars have as yet been approved for sale by the Food and Drug Administration[2] in the U.S.[3] There have, however, been several significant patent decisions narrowing the rights of biologic innovators that may affect the patent assessment and the regulatory approval pathway for marketing of biosimilars. In addition, there are already a few judicial challenges suggesting that biosimilar applicants cannot avoid the different patent review mechanisms of the BPCIA. These actions may return to innovators some of the control that has been removed by recent changes in the patent law. They also can be expected to have important consequences with respect to regulatory approval pathways for biosimilars, the timing of new product introductions, the potential for agreements between innovators and biosimilars applicants and the competitive issues that may arise, and potential pricing consequences in the event of delays in biosimilar product introductions.

As of 2013, the global biosimilars market accounts for approximately $1.3 billion in revenue. According to a recent study from Allied Marketing Research, revenue atributable to biosimilars is anticipated to increase to $35 billion by 2020 as market share for biosimilar products grow in the North American, European and Asian markets. One factor fueling the explosive growth in the biosimilars market is the "patent cliff" facing several biologics. AMR estimated that 10 biologics will lose patent protection at some point during the next four years. Revenue attributable to the biologics coming off patent is approximately $60 billion. For example, Humira, sales of which exceeded $10 billion in 2013, loses patent protection in 2016. Johnson & Johnson's Remicade, which generated close to $9 billion in sales in 2013, loses patent protection in Europe early next year, with the U.S. market opening up in 2018.[4]

Further complicating the landscape for biologics innovators is a United States Supreme Court that is increasingly active in deciding patent matters. The U.S. Supreme Court's decisions in *Association for Molecular Pathology v. Myriad Genetics*[5] last year and *Mayo v. Prometheus*[6] in 2012 held patents to isolated genes and to certain diagnostic methods, respectively, invalid for claiming laws of nature. In June 2013, the Supreme Court held that Myriad's patents on isolated DNA claimed a law of nature, which is unpatentable under Section 101 of the Patent Act. The ruling came close on the heels of the Court's March 2012 decision invalidating Prometheus' blood testing method patents, which assayed a patient's blood sample to determine the proper dosage of a therapeutic agent for autoimmune diseases, because processes merely reciting laws of nature were unpatentable. The impact of the decisions on the life sciences industry have yet to be completely absorbed or assessed, however, it is telling that the *Myriad* decision is estimated to invalidate approximately 8,000 patents with composition of matter claims directed to isolated genomic DNA. Adding to the lack of certainty for the life sciences industry, the Prometheus opinion calls into question the validity of many life sciences patents, particularly those directed to drug screening, drug mechanisms of action, and diagnostic (e.g., companion diagnostics) and treatment methods.[7]

In addition to the patent cliff and the changing and challenging patent environment for biologics companies, a recent ruling from the U.S. Court of Appeals for the Federal Circuit (which reviews patent appeals) allowing generics companies access to patented methods of analyzing their generic products, may open another avenue for biosimilar incursion into the biologics market. Patents on analytical methods for assessing biosimilarity may be of high value, particularly in a situation in which there is no practical alternative method for demonstrating biosimilarity. With a patent covering a key analytical method in hand, a biological innovator can, in principle, delay the entry of competing biosimilars into the market. The Federal Circuit has recently narrowed this promising strategy for preventing or delaying entry of generics, facilitating generic, and perhaps analogously, biosimilar incursion into the market. In the holding of a divided panel on August 3, 2012, in *Momenta Pharmaceuticals v. Amphastar Pharmaceuticals*[8] , the Court concluded that the use of Momenta's patented method to assess the similarity of samples of Lovenox (enoxaparin) by a generic manufacturer is a protected activity under the safe harbor provision of 35 USC 271(e)(1). The Supreme Court denied *certiorari* on Momenta's petition (Dkt. No. 12-1033) on June 24, 2013.

Momenta may presage the direction of future decisions on the validity and infringement of patents directed to methods for assessing biosimilarity. Though enoxaparin is not considered a biologic, it is sufficiently complex chemically to raise issues similar to those raised in demonstrating biosimilarity or interchangeability of

a biosimilar. Enoxaparin is produced by the degradation of heparin, a naturally occurring polysaccharide with molecular fractions ranging in weight from about 5 kDa to about 40 kDa. The degradation results in a chemically diverse mixture of oligosaccharide structures of varying molecular weight. Diversity also exists in the structure of the oligosaccharide units. Prior to marketing a generic version of Lovenox, FDA required that generic enoxaparin meet five criteria ("standards of identity") to demonstrate that the generic enoxaparin is has the "same active ingredient as Lovenox".[9] Due to the complexity of establishing the similarity of different samples of enoxaparin, Momenta obtained U.S. Patent Number 7,575,886 ("the '886 patent"), including claims to a method of analyzing heterogeneous populations of sulfated polysaccharides, e.g., enoxaparin.

Momenta received FDA approval to market generic enoxaparin in July 2010, rapidly generating revenue of $260 million per quarter. Two days after Amphastar received FDA approval to market its generic enoxaparin, Momenta initiated litigation, asserting that Amphastar used the patented methods of the '886 patent to manufacture enoxaparin for commercial sale. The District Court granted Momenta a preliminary injunction. The Federal Circuit vacated the preliminary injunction and the court considered the applicability of the safe harbor provision of 35 U.S.C. § 271(e)(1). The court found that: "Amphastar is required to conduct a laboratory determination of identity and strength of the active ingredient for each batch of enoxaparin. See 21 C.F.R. § 211.165(a). This test must be done according to the patented methods described in an official compendium, in this case the U.S. Pharmacopeia (USP). *See* 42 U.S.C. § 351(b). The submissions to the FDA in this case are anything but "routine"—they implicate Amphastar's very ability to continue its FDA approval for its ANDA and to continue manufacturing and marketing enoxaparin under its ANDA."[10] Thus, it appears that patented methods of analyzing biologics may be accessible to biosimilar manufacturers under the safe harbor provision of 35 U.S.C. § 271(e)(1). It is possible, therefore, that that biosimilars will be immunized against infringement of highly valuable patents directed to methods of analyzing biologics by the safe harbor provision of 35 U.S.C. § 271(e)(1).

More positively for biologics innovators, recent district court decisions have confirmed the requirement that a biosimilar manufacturer and the innovator biologic company progress through and complete the complex "patent dance" mandated by the Public Health Service Act, 42 U.S.C. §§ 351(l)(2)-(6). In November 2013, in *Sandoz, Inc. v. Amgen, Inc.*[11] , the U.S. District Court for the Northern District of California granted Amgen Inc.'s and co-defendant Hoffmann-La Roche Inc.'s Motion to Dismiss a June 2013 Complaint for Declaratory Judgment and Patent Invalidity and Non-infringement concerning two patents covering Amgen's biological product Enbrel (etanercept). According to the district court, "Sandoz does not contend, and cannot contend, it has complied with its obligations under PHS Act §§ 351(l)(2)-(6), because… it has not, to date, filed an application with the FDA."[12]

Sandoz appealed the district court decision to the Federal Circuit (Docket No. 14-1693) in March 2014. According to Sandoz Opening Brief, the district court's decision "completely deprives federal courts of jurisdiction over any declaratory judgment action implicating a biosimilar product until after the FDA had already approved the product—a serious error that undermines the BPCIA's stated purpose of advancing competition for biologic drugs." Sandoz also argued that the court had jurisdiction even though Amgen did not threaten to sue Sandoz for patent infringement under the U.S. Supreme Court's holding in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007).

Sandoz argues that "the district court's contrary ruling defies both the plain text and very purpose of the BPCIA. The BPCIA contains no provision depriving courts of jurisdiction to resolve patent disputes where jurisdiction already existed, as here, before an FDA filing. While the BPCIA does contain certain limitations on declaratory judgment actions after a biosimilar application is submitted, those limitations do not apply to Sandoz's complaint, which was filed before any FDA application. The district court was not at liberty to impose a jurisdictional bar that does not exist in the statute's text, and its decision to create such a bar — without briefing on the issue, no less — was pure error."[13]

The district court compounded this error by misinterpreting the BPCIA's provisions. According to the district court, "neither a reference product sponsor, such as Amgen, nor an applicant, such as Sandoz, may file a lawsuit unless and until they have engaged in a series of statutorily-mandated exchanges of information." But those patent exchanges serve only as a prelude for an action for a patent owner's infringement lawsuit under § 271(e)(2)(C), not a declaratory judgment. The statute allows either party to file for declaratory judgment once a biosimilar applicant gives notice of its intention to market its product. Thus, even if the BPCIA applied, as the district court found, its provisions would expressly permit Sandoz's action here because Sandoz provided Amgen notice of its intention to commercially market its product before bringing this case.

The district court's judgment also seriously disrupts the exclusivity structure of the BPCIA. According to the statute, the biosimilar applicant must give at least six months' notice before launching its product. If a biosimilar applicant is forbidden from providing this notice before its approval—as the district court now holds—then applicants will be forbidden from launching biosimilar products until six months after obtaining final FDA authority to do so, in all cases, and regardless of any existing patent coverage or the expiry of the 12-year data exclusivity period. The court's erroneous construction thereby guarantees every biosimilar product must uselessly wait to launch for six months after the FDA provides formal approval to launch, creating an extra-statutory period of product exclusivity that Congress never intended in drafting the BPCIA.

Ever since the BPCIA was enacted in 2010, attorneys have evaluated the patent litigation provisions of the Act for guidance on which strategies to pursue. The Federal Circuit's interpretation of the Act in this case is significant -- particularly since it is the first. In March of 2014, Celltrion Healthcare Co. filed a Complaint for Declaratory Judgment in the U.S. District Court for the District of Massachusetts seeking a judgment with respect to certain patents allegedly covering Janssen Biotech's biological product Remicade. The Complaint initiates the

second lawsuit that requires judicial interpretation of the complex patent resolution provisions added to the PHS Act by the BPCIA.

The *Sandoz* and *Celltrion* cases are worthy of close attention. It is likely that the decisions in these cases will influence the interpretation and the implementation of the BPCIA for years to come, and thereby the pace and scope of biosimilars applications.

Although the creation of a regulatory approval pathway in the BPCIA was one of several cost-containment and reduction mechanisms included in the Patient Protection and Affordable Care Act (PPACA)[14], no biosimilars have yet been approved by the FDA. On July 24, 2014, Novartis' affiliate Sandoz announced that its Section 351 (k) application for filgrastim was accepted by FDA, the first biosimilar to be accepted by the Agency under the BPCIA.[15]

The BPCIA amended Section 351 (k) of the Public Health Service Act to create an abbreviated licensure pathway for biological products that are "biosimilar" to or "interchangeable" with licensed biological products. The Biosimilar User Fee Act of 2012[16] was enacted subsequently to fund the Agency's evaluations of Section 351 (k) applications. The BCPIA abbreviated approval pathway is similar in purpose to the Abbreviated New Drug Application (ANDA) pathway established by the Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act for generic versions of conventional drug products. The patent notification and challenge process is, however, significantly different for biosimilars. The initial patent challenges under the BPCIA noted above, and the resultant uncertainty they can be expected to cause, may result in further delays with respect to applications and approvals for many potential biosimilars.

Biosimilars present unique challenges for FDA review and approval because biological products, and the processes to create them, are typically more difficult and complex than those for small molecule traditional drug products. The BPCIA defined "biosimilarity" as "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components."[17] For a conclusion of biosimilarity, however, the BPCIA requires that there are "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency."[18] "Interchangeability" is a higher standard than biosimilarity, requiring a showing that the proposed biosimilar may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.[19]

The scientific and procedural complexity of establishing the application and review process for biosimilars has been quite difficult for FDA, which has had to consider widely-varying interpretations and suggestions from different aspects of the industry, including biopharma, healthcare providers, and insurers.[20] Over the past few years, the Agency has developed several draft guidance documents to set out proposals as to what data will be needed for Section 351 (k) applications and the types of meetings that will be available with the Agency by applicants at various points along the application process.[21] Many contentious issues remain to be addressed, however, including: (1) whether there should be distinctive nomenclature for the biosimilars, to enable tracking of them for safety and liability purposes;[22] (2) whether there should be labeling requirements specific to the biosimilars, to clarify that they may not be interchangeable and/or are limited to only certain of the indications for which the reference product was approved; and (3) the standards under which a proposed biosimilar will be considered to be concluded to be interchangeable by the Agency, and thus eligible for certain types of federal and state reimbursement, including potentially the automatic substitution laws for generic drug products of certain states.

As noted above, the patent and exclusivity provisions of the BPCIA differ significantly from those for generic drugs under the Hatch-Waxman Amendments. Under the BPCIA, a reference biological product receives a 12-year exclusivity period from biosimilar marketing.[23] A Section 351 (k) application may not be submitted until four years after the licensure of the reference product.[24] The six-month additional pediatric exclusivity period of the FDCA for drug products also applies to biological drug products under the BPCIA.[25] The BPCIA also establishes unique patent dispute resolution procedures for Section 351 (k) applications, which differ significantly from those applicable to generic drugs.[26] These include a required negotiation between the biosimilar applicant and the reference product sponsor and the confidential exchange of information regarding relevant patent rights. This required information includes a copy of the application, the manufacturing process proposed to be used in the production of the biosimilar, and certain additional information that may be requested by the reference product sponsor. The reference product sponsor must provide a list of patents on which the sponsor believes a claim of infringement could reasonably be made, including potentially patents containing claims directed to methods of manufacture, which are uniquely important with respect to biologics from both a production and regulatory standpoint, as well as a list of patents the sponsor would be prepared to license to the applicant.

The radically different nature of this process from that for ANDA products under the Hatch-Waxman Amendments also has raised concerns by the Federal Trade Commission that the required information exchanges by competitors may present potential anticompetitive issues.[27] In addition, the FTC can be expected to scrutinize any agreements between biosimilar applicants and the reference product sponsor to delay marketing of the biosimilar in return for payments, similar to the Commission's opposition to what it refers to as "pay for delay" agreements in the conventional drug context.[28]

The delays and uncertainties resulting from these initial challenges to the patent provisions of the BPCIA, and from the continued uncertainties regarding the scope and type of data that will be required by FDA to support biosimilars applications, can consequently be expected to result in continued difficulties for applicants in successfully introducing biosimilars, notwithstanding the significant market demands for their introduction.[29]

1 Pub.L. 111-148, Title VII, Subtitle A (2010), 124 Stat. 804-821, 42 U.S.C. § 262.

2 For a general overview of the BPCIA, *see* Stephen Paul Mahinka and Kathleen M. Sanzo, An Overview and Update on Biosimilars, *LMG Life Sciences Guide 2012*, 15 (2012).

3 For contrasting experience in the EU, *see* Francis Megerlin, et al, Biosimilars and the European Experience: Implications for the United States, 32 *Health Affairs* 1803 (Oct. 2013).

4 Global Biosimilars/Follow-on-Biologics Market (Technology, Types, Applications, Services and Geography) - Size, Share, Global Trends, Company Profiles, Demand, Insights, Analysis, Research, Report, Opportunities, Segmentation and Forecast, 2013 – 2020 (July 2014).

5 *Association for Molecular Pathology v. Myriad Genetics*, 569 U.S. 12-398 (2013).

6 *Mayo Collaborative Services, DBA Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012.

7 E. Coe, *Myriad, Prometheus* Pushing Life Sciences Cos. to Licensing, *Law360* (June 3, 2014).

8 *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, Nos. 12-1062, -1103, -1104 (Fed. Cir. Aug. 3, 2012)

9 FDA Letter, J.A. 286, 295.

10 *Momenta*, pp. 18-19.

11 *Sandoz, Inc. v. Amgen, Inc.* and Hoffman-La Roche, Inc., Docket No. C-13-2904 (N.D. Cal. Nov. 12, 2013).

12 The reference to PHS Act 42 U.S.C. §§ 351(l)(2)-(6) is to the BPCIA's multi-step "patent dance" procedures: Step 1 – Transmission of Biosimilar Application; Step 2 – Reference Product Sponsor's Paragraph 3(A) Patent List; Step 3 – Biosimilar Applicant's Paragraph 3(B) Patent List; Step 4 – Reference Product Sponsor's Response; Step 5 – Patent Resolution Negotiations; Step 6 – Patent Resolution If No Agreement; and Step 7 – Filing of the Patent Infringement Action

13 *Sandoz*, Docket No. 14-1693, Document 29 (March 14, 2014), at p. 14.

14 Pub.L. 111-148, (2010), 124 Stat. 804-821, 42 U.S.C. § 262.

15 Novartis Press Release, FDA Accepts Sandoz Application for Biosimilar Filgrastim (July 24, 2014). For initial reaction, see J. Overley, Biosimilars Clarity Coming as FDA Eyes Sandoz Application, *Law360* (July 25, 2014).

16 Enacted as part of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), Pub.L. 112-144, 126 Stat. 1026-1039.

17 42 U.S.C. § 262(i)(2)(A).

18 42 U.S.C. § 262(i)(2)(B).

19 42 U.S.C. § 262(i)(3).

20 A Citizen Petition to FDA by Abbott Laboratories [now on behalf of its successor AbbVie, Inc.] (April 2, 2012) requested that FDA not approve a biosimilar of its drug product Humira on the basis that to do so would necessarily and unlawfully require disclosure of the reference product's trade secrets.

21 See FDA Draft Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (May 2014); FDA, Draft Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Product Sponsors or Applicants (March 2013); FDA Draft Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act (Feb. 2012); FDA Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Feb. 2012); FDA Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb. 2012).

22 The FDA is considering Citizen Petitions on both sides of this issue. *Compare, e.g.*, Citizen Petition to FDA of Novartis Group (October 28, 2013), requesting that biosimilars be identified by the same international nonproprietary names as the reference products, *with* Citizen Petition to FDA of Amgen, Inc. (Dec. 20, 2013), requesting that biosimilars should have unique names.

23 42 U.S.C. § 262(k)(7)(A). The FDA recently issued draft guidance requesting scientific and structural information from biosimilars applicants regarding determining the date of first licensure of the reference biologic product, and indicated it would making information publicly available regarding reference product exclusivity and dates of first licensure, see FDA Draft Guidance for Industry, Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (August 2014).

24 42 U.S.C. § 262(k)(7)(B).

25 42 U.S.C. § 262(m)(1).

26 42 U.S.C. § 262(l).

27 See Remarks of S. Munck, FTC Chief Intellectual Property Counsel, quoted in *Pink Sheet* at p. 1 (May 7, 2012).

28 See *FTC v. Actavis, Inc.*, 133 S. Ct. 2223 (2013) (FTC antitrust challenge to agreement between pioneer and generics drug manufacturers to delay introduction of a generic version of the pioneer conventional drug held to be subject to evaluation under the antitrust rule of reason as to its potential competitive effects).

29 For a detailed discussion, see Henry G. Grabowski, et al., Regulatory and Cost Barriers Are Likely to Limit Biosimilar Development and Expected Savings in the Near Future, 33 *Health Affairs* 1048 (June 2014).