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Follow-On Biologics: Intellectual Property Issues

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Summary

The term "biologics" refers to a category of medical preparations derived from a living organism. These medicines have added notable therapeutic options for many diseases and impacted fields such as oncology and rheumatology. The biologics industry invests extensively in R&D and contributes to a rapidly expanding market for these treatments. Biologics are often costly, however, in part due to the sophistication of the technologies and the manufacturing techniques needed to make them.

Compared to the number of generic drugs available in traditional pharmaceutical markets, few "follow-on" biologics compete with the original, brand-name product. The lack of competition in the biologics markets was perceived to be a consequence of the complexity of biologics in comparison with small-molecule, chemical-based pharmaceuticals. As a result, previously existing accelerated marketing provisions for traditional generic drugs provided under the Federal Food, Drug, and Cosmetic Act have not been as effective in accelerating biologics competition.

Congress turned to these concerns when it enacted the Biologics Price Competition and Innovation Act (BPCIA) of 2009. The BPCIA was incorporated into Title VII of the Patient Protection and Affordable Care Act. The BPCIA included three significant components. First, the BPCIA established a licensure pathway for competing versions of previously marketed biologics. In particular, the legislation established a regulatory regime for two sorts of follow-on biologics, termed "biosimilar" and "interchangeable" biologics. Second, the BPCIA created FDA-administered periods of regulatory exclusivity for certain brand-name biologics and follow-on products. No application seeking licensure of a follow-on biologic may be filed for four years from the date the referenced product was licensed. In addition, the FDA may not approve an application for a follow-on biologic for 12 years from the reference product's licensure date. The BPCIA also provides for a term of regulatory exclusivity for the applicant that is the first to establish that its product is interchangeable with the brand-name product. Finally, the BPCIA created patent dispute resolution procedures for use by brand-name and follow-on biologic manufacturers. These procedures are commonly termed the "Patent Dance," perhaps due to their complex nature.

Several intellectual property issues with respect to the BPCIA have emerged since the statute was enacted. Some have asserted that the "Patent Dance" established by the BPCIA is not obligatory and may be waived by either the brand-name or follow-on firm. Others have argued that the BPCIA does not apply to biologics approved before the passage of the law. Finally, the term of regulatory exclusivity that should be afforded to biologics within the Trans-Pacific Partnership, a proposed international trade agreement, has been subject to debate.

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Introduction

Congressional interest in the availability of lower-cost versions of biologic products (biologics) led to the 2010 enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which was incorporated as Title VII of the Patient Protection and Affordable Care Act.[1] The BPCIA included three significant components. First, the BPCIA established an expedited licensure pathway for competing versions of previously marketed biologics. The BPCIA also created periods of data protection and marketing exclusivity for certain brand-name drugs and follow-on products to be administered by the Food and Drug Administration (FDA). Finally, the BPCIA created a patent dispute resolution procedure for use by brand-name and follow-on biologic manufacturers.[2]

The term "biologics" refers to a category of medical products derived from living organisms.[3] Biologics more specifically consist of "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings."[4] The biologics market is rapidly expanding as judged by several measures, including the quantity of approved products, the size of the market, and the importance of these drugs to the health of U.S. citizens. For example, in 2010, spending on biologics was $67 billion in the United States, or approximately 20% of overall drug spending.[5] By 2013, spending on biologics in the United States increased nearly 40% to $92 billion, or approximately 28% of overall drug spending.[6] These medicines have also added notable therapeutic options for many diseases and impacted fields such as oncology and rheumatology.[7]

Along with their benefits, biologics also have contributed to the cost of health care. On average, biologics reportedly cost $45 per day per patient, as compared to $2 for traditional, small-molecule drugs.[8] Some biologics are particularly expensive. For example, the biologic Humira, which treats arthritis and other conditions, reportedly costs $50,000 per year.[9] The annual expense for the biologic Cerezyme, a treatment for Gaucher's Disease, is reportedly $200,000 per year.[10] These high costs are commonly attributed to the risks firms undertake in developing biologics, as well as the sophisticated biotechnologies and manufacturing techniques needed to

[1] P.L. 111-148, 124 Stat. 119.

[2] See James N. Czaban et al., "Panacea or Poison Pill? Making Sense of the New Biosimilars Law," 8 *BNA Pharmaceutical Law & Industry Report*, vol. 8 (May 26, 2010), p. 698.

[3] Robert N. Sahr, "The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition," *Boston College Intellectual Property & Technology Forum* (July 19, 2009), p. 070201.

[4] 42 U.S.C. §262(i).

[5] IMS Institute for Healthcare Informatics, "The Use of Medicines in the United States: Review of 2010," April 2011, http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS%20Institute/Static%20File/IHII_UseOfMed_report.pdf.

[6] Alex Brill, "The Economic Viability of a U.S. Biosimilars Industry" (February 2015), p. 4, http://www.matrixglobaladvisors.com/storage/MGA_biosimilars_2015_web.pdf.

[7] *See generally* Mary Ann Liebert, Inc., "Realizing the Promise of Pharmacogenomics: Opportunities and Challenges," *Biotechnology Law Report*, vol. 26 (June 2007), p. 261.

[8] Steve Pociask, "Lifesaving Drugs at Lower Costs," American Consumer Institute Center for Citizen Research ConsumerGram (July 22, 2014), http://www.theamericanconsumer.org/2014/07/new-consumergram-lifesavingdrugs-at-lower-costs/.

[9] Erwin A. Blackstone and Joseph P. Fuhr, "Innovation and Competition: Will Biosimilars Succeed?" *Biotechnology Healthcare*, vol. 9 (Spring 2012), p. 24, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3351893/.

[10] Ibid.

make them.[11] But commentators have often observed that, in contrast to the generic drugs available in traditional pharmaceutical markets, few "follow-on" biologics compete with the original, brand-name product.[12]

The lack of competition in the biologics markets is perceived to be a consequence of the distinct technical and legal aspects from the regulation of traditional, chemically based pharmaceuticals. Biologics differ significantly from traditional pharmaceuticals in their complexity and method of manufacture. Typical pharmaceutical products have a chemical origin. They consist of small molecules, on the order of dozens of atoms, which often may be readily characterized and reproduced through well-understood chemical processes.[13]

In contrast, biologics are often made up of millions of atoms, feature a more complex structure than traditional pharmaceuticals, and are manufactured from living cells through biological processes.[14] As a result, the technical challenges that a competitor faces in developing a product that may be viewed as interchangeable with a particular brand-name biologic product may be considerable, and in some cases perhaps even insurmountable.[15] For this reason, many experts do not describe competing biologic products as "generics," as is the case for small-molecule pharmaceuticals; the terms "follow-on biologic" or "biosimilar" are commonly used instead.[16] The 111th Congress accounted for these distinctions when it enacted the BPCIA.

This report reviews the intellectual property issues associated with the BPCIA. This study first introduces the regulatory and intellectual property provisions of the BPCIA. This analysis then addresses current issues that have arisen under the statute and closes with concluding observations.

FDA Regulation of Biologics

The FDA for the most part regulates small-molecule drugs and biologics under two different statutes.[17] Traditional pharmaceuticals fall under the Federal Food, Drug and Cosmetic Act (FFDCA). The FFDCA in turn incorporates the Drug Price Competition and Patent Term Restoration Act of 1984, which is commonly known as the Hatch-Waxman Act.[18] The Hatch-Waxman Act established an accelerated regulatory approval pathway for generic versions of previously approved, brand-name drugs. This approval mechanism has been described as involving "relatively simple showings that the proposed generic version uses the same active

[11] Pamela Jones Harbour, Commissioner, Federal Trade Commission, *The Competitive Implications of Generic Biologics*, June 14, 2007, http://www.ftc.gov/speeches/harbour/070614genbio.pdf.

[12] Ibid.

[13] A. Taylor Corbitt, "The Pharmaceutical Frontier: Extending Generic Possibilities to Biologic Therapies in the Biologics Price Competition and Innovation Act of 2007," *DePaul Journal of Art, Technology & Intellectual Property Law*, vol. 18 (Spring 2008), p. 365.

[14] Melissa R. Leuenberger-Fisher, "The Road to Follow On Biologics: Are We There Yet?," *Biotechnology Law Report*, August 2004, p. 389.

[15] Dawn Willow, "The Regulation of Biologic Medicine: Innovators' Rights and Access to Healthcare," *Chicago-Kent Journal of Intellectual Property*, 2006, p. 32.

[16] Ibid.

[17] See CRS Report RL34045, *FDA Regulation of Follow-On Biologics*, by Judith A. Johnson.

[18] 98th Congress, P.L. 98-417, 98 Stat. 1585.

molecule in the same strength, dosage, form, and route of administration, and the generic version is 'bioequivalent' to the original product."[19]

The great majority of biologics is instead regulated under Section 351 of the Public Health Service Act (PHSA), which has been codified at 42 U.S.C. Section 262.[20] Because the FDA licenses most biologics via the PHSA, rather than the FFDCA, prior to the enactment of the BPCIA no generally applicable expedited approval procedure for follow-on versions of biologics existed.[21] Further, because of the increased complexity of biologics in comparison with chemically based drugs, many experts believed that the expedited approval process available under the Hatch-Waxman Act could not simply be incorporated into the PHSA. In particular, some follow-on manufacturers might not be able to show that their product is the "same" as that offered by the brand-name firm, as the Hatch-Waxman Act requires.[22]

Congress intended to address these concerns with the 2010 enactment of the Biologics Price Competition and Innovation Act. The BPCIA is a complex statute that principally amends Section 351 of the Public Health Service Act.[23] The 2010 legislation establishes a regulatory regime for two sorts of follow-on biologics, termed "biosimilar" and "interchangeable" biologics respectively. The FDA is afforded a prominent role in determining the particular standards for biosimilarity and interchangeability for individual products.

Biosimilars

A follow-on biologic is deemed biosimilar to a brand-name product if it is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and "there are no clinically meaningful differences between the [biosimilar] and the reference product in terms of safety, purity, and potency of the product."[24] In order for a follow-on biologic to qualify as a biosimilar, an applicant must demonstrate to the FDA that a number of requirements are met. The BPCIA stipulates that a follow-on product is biosimilar if (1) analytical, animal, and clinical studies show that it is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; (2) the two products have the same mechanism of action; (3) the condition of use in the proposed product has been previously approved for the reference product; (4) the route of administration, dosage form, and strength of the two products are the same; and (5) the manufacturing process provides for a safe product.[25]

The FDA issued its first approval of a biosimilar in the United States under the BPCIA on March 6, 2015.[26] The agency awarded Sandoz Inc. a license to sell filgrastim-sndz under the trademark Zarxio. Zarxio is a biosimilar of Neupogen, which is sold by Amgen Inc. and consists of a man-

[19] See Czaban et al.

[20] A small number of biologics have reportedly been approved as drugs under the FFDCA, including insulin, human growth hormone, and certain protein products. *See* Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States, Hearing Before H. Subcommittee on Health and the H. Comm. on Energy and Commerce, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA).

[21] Jeremiah J. Kelly, "Follow-On Biologics: Legal, Scientific, and Policy Considerations," 13 *Journal of Health Care Law and Policy*, vol. 13, 2010, p. 257.

[22] 21 U.S.C. §355(j)(2)(A).

[23] 42 U.S.C. §262.

[24] 42 U.S.C. §262(i)(2).

[25] 42 U.S.C. §262(k)(2).

[26] Letter from Ann T. Farrell, M.D., Director, Division of Hematology Products, Food and Drug Administration, to Sandoz Inc., March 6, 2015.

made form of a protein that stimulates the growth of white blood cells.[27] Cancer patients and recipients of a bone marrow transplant are among the users of these drugs. Sandoz previously marketed Zarxio outside the United States as Zarzio. As discussed subsequently in this report, however, Sandoz and Amgen are involved in ongoing litigation with respect to the marketing of Zarxio.

Interchangeable Biologics

An interchangeable biological product, in addition to meeting the biosimilarity standard, may be expected to provide the same clinical result as the reference product. If a follow-on biologic is judged by the FDA to be interchangeable with a brand-name product, then "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[28] A follow-on biologic is interchangeable if (1) it can be expected to produce the same clinical result as the reference product in any given patient and (2) the risk, in terms of safety or diminished efficacy or switching between the two products, is not greater than the use of the reference product without such alternation.[29]

The Role of the FDA

The BPCIA provides the FDA with authority to issue guidelines that implement the statutory standards of biosimilarity and interchangeability. These guidelines may be general or specific in nature, and must be issued after the public is afforded the opportunity for comment. In particular, the FDA may indicate in a guidance document that "science and experience" does not currently allow a product or product class to qualify as biosimilar or interchangeable.[30]

Pursuant to this authority, the FDA finalized three guidance documents on April 28, 2015, that it had previously issued in draft form in 2012. The three documents are

- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009;[31]
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product;[32] and
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product.[33]

The FDA also publishes a reference guide to licensed biologics products. Officially known as "Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," the text is more commonly termed the "Purple Book." As suggested by its formal title, the Purple Book consists of two separate lists: (1) the Center for

[27] Food and Drug Administration, "FDA Approves First Biosimilar Product Zarxio," press release, March 6, 2015, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm.

[28] 42 U.S.C. §262(i)(3).

[29] 42 U.S.C. §262(k)(4).

[30] 42 U.S.C. §262(k)(8).

[31] Food and Drug Administration, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," 80 *Federal Register* 24259, April 30, 2015.

[32] Food and Drug Administration, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," 80 *Federal Register* 24258, April 30, 2015.

[33] Food and Drug Administration, "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product," 80 *Federal Register* 24257, April 30, 2015.

Biologics Evaluation and Research ("CBER") List of Licensed Biological Products, along with (2) the Center for Drug Evaluation and Research ("CDER") List of Licensed Biological Products. These two information centers within the FDA each possess the authority to regulate the marketing of different sorts of biologics. The Purple Book, which may be viewed on the agency's website, includes information on whether the agency has identified a product as a biosimilar along with any relevant regulatory exclusivities.

Biosimilars and Regulatory Exclusivities

The BPCIA provides for regulatory exclusivities both for brand-name products and for first interchangeable follow-on biologics. The term "regulatory exclusivity" refers to a period of time during which the FDA protects the licensed biologic protection from competing applications for licensure. It should be appreciated that regulatory exclusivities and patent protection are separate entitlements that are administered by different federal administrative agencies and that depend upon distinct criteria. Firms in the biologics market will often possess patents in addition to the regulatory exclusivities provided by the BPCIA.

Brand-Name Products

Under the BPCIA, no application for a follow-on biologic—either biosimilar or interchangeable—may be filed with the FDA for 4 years from the date the reference product was licensed.[34] In addition, the FDA may not approve an application for a follow-on product—either biosimilar or interchangeable—for 12 years from the reference product's licensure date if the follow-on biologic relies upon data developed by the sponsor of the brand-name drug.[35]

Some authorities refer to the 4-year regulatory exclusivity as "data protection" and the 12-year regulatory exclusivity as a "marketing exclusivity."[36] Under this terminology, the BPCIA protects the brand-name firm's data package by preventing the filing of licensure applications for follow-on biologics for 4 years. Similarly, the BPCIA blocks licensure of a follow-on biologic for 12 years, thereby preserving marketing exclusivity for the brand-name firm. The BPCIA does not itself employ these terms, however, and usage by commentators may be inconsistent.

The BPCIA stipulates some circumstances where a regulatory exclusivity may not be awarded. Supplements to the reference product application; the identification of new indications, routes of administration, dosing, or delivery; and modifications to the structure of the biological product that do not result in a change in safety, purity, or potency are not eligible for these exclusivities.[37]

Both the 4-year and 12-year regulatory exclusivity periods may be extended by six months. If the FDA determines that information relating to the use of a biologic in a pediatric population may produce health benefits in that population, it may make a written request for pediatric studies. If the applicant completes the test within a timeframe established by the FDA, the regulatory exclusivity periods are extended to 4 years, 6 months; and to 12 years, 6 months, respectively.[38]

[34] 42 U.S.C. §262(k)(7)(B).

[35] 42 U.S.C. §262(k)(7)(A).

[36] See Joyce Wing Yan Tam, "Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation," vol. 98, January 2010, p. 535.

[37] 42 U.S.C. §262(k)(7)(C).

[38] 42 U.S.C. §262(m).

This additional term of protection is awarded whether or not the studies prove the product may be administered to children in a safe and effective manner.

The BPCIA recognizes the possibility that a biologic may qualify as a so-called orphan drug. This status arises under an earlier statute, the Orphan Drug Act of 1982. That legislation provided for a 7-year period of regulatory exclusivity commencing from the date the FDA allowed the orphan drug to be marketed. The orphan drug exclusivity applies to drugs that treat a rare disease or condition (1) affecting fewer than 200,000 people in the United States, or (2) affecting more than 200,000 people in the United States, but for which there is no reasonable expectation that the sales of the drug would recover the costs.[39] Orphan drug regulatory exclusivity prevents the FDA from approving another application for marketing approval for the indication for which the drug is approved, unless the original sponsor approves or the original sponsor is unable to provide sufficient quantities of the drug to the market.[40] As a result, the FDA could approve a second application for the same drug for a different use.

The BPCIA stipulates that if a brand-name biologic has been designated an orphan drug, the FDA may not approve an application for a biosimilar or interchangeable product until the later of (1) the 7-year period of orphan drug exclusivity described in the FFDCA; or (2) the 12-year regulatory exclusivity period established by this bill.[41] As a result, the Orphan Drug Act's 7-year regulatory exclusivity runs concurrently with the BPCIA's 12-year regulatory exclusivity.

First Interchangeable Products

The BPCIA also provides for a term of regulatory exclusivity for the applicant that is the first to establish that its product is interchangeable with the brand-name product for any condition of use. The period of regulatory exclusivity is the earlier of (1) one year after the first commercial marketing of the first interchangeable biologic to be approved as interchangeable with that reference product; (2) 18 months after either a final court judgment in patent infringement litigation under the PHS Act, as amended, or the dismissal of such litigation against the first applicant; (3) 42 months after the approval of the first interchangeable biologic if patent litigation under the PHS Act, as amended, remains pending; or (4) 18 months after approval of the first interchangeable biologic if the applicant has not been sued for patent infringement under the PHS Act, as amended.[42]

This regulatory exclusivity bars the FDA from making a determination of interchangeability with respect to a subsequent product for a period of time. The FDA is not prevented from making a determination of biosimilarity during this timeframe.

Patent Dispute Resolution

The BPCIA establishes specific rules for the resolution of patent disputes involving follow-on biologics.[43] These rules require the brand-name firm and the follow-on applicant to engage in a

[39] 21 U.S.C. §360bb(a)(2).

[40] 21 U.S.C. §360cc(b).

[41] BPCIA, §7002(h).

[42] 42 U.S.C. §262(k)(6).

[43] See Michael P. Dougherty, "The New Follow-On-Biologics Law: A Section by Section Analysis of the Patent Litigation Provisions in the Biologics Price Competition and Innovation Act of 2009," 65 *Food and Drug Law Journal* vol. 65, 2010, p. 231.

number of interactions prior to the commencement of litigation. Perhaps because of their complex nature, these statutory provisions are sometimes termed the "Patent Dance."[44]

In particular, the statutory steps include (1) the follow-on applicant must disclose its application to the brand-name firm; (2) each party must identify pertinent patents; (3) the parties must exchange briefings on the validity and possible infringement of those patents; (4) the parties must negotiate which patents will be subject to litigation; and (5) a simultaneous exchange of patents designated for litigation in the event the parties could not reach agreement. Each of the stages of this pre-litigation process is reviewed below. It should be appreciated from the outset that third parties cannot participate in this process, although a representative of a patent proprietor who has exclusively licensed the brand-name firm and retained a right to assert the patent or participate in litigation concerning the patent may have access to the follow-on application.[45]

Disclosure of the Follow-On Application. The BPCIA requires that the follow-on applicant, within 20 days after the FDA publishes a notice that its application has been accepted for review, must disclose to the brand-name firm the existence of the application. The applicant must provide a copy of its application along with "such other information" concerning the production of the follow-on product.[46] The applicant may also provide other information that the brand-name firm requests.[47]

Identification of Pertinent Patents. Within 60 days of the date of receipt of the application and other information from the follow-on applicant, the brand-name firm must identify patents that it deems relevant to the follow-on product. The brand-name firm may only identify patents it owns or has obtained an exclusive license. This list must include patents that the brand-name firm "believes a claim of patent infringement could reasonably be asserted [against someone] engaged in the making, using, offering to sell, selling or importing into the United States of the biological product."[48] The brand-name firm must also identify any patents on the list that it would be prepared to license to the follow-on applicant.[49]

Statement by the Follow-On Applicant. Following the receipt of the brand-name firm's patent list, the follow-on applicant must state either that it will not market its product until the relevant patents have expired, or alternatively provide its views that the patents are invalid, unenforceable, or would not be infringed by the proposed follow-on product.[50] In addition, the follow-on applicant may, at its option, provide the brand-name firm with a list of patents it believes the brand-name firm could assert against the reference product.[51] If the follow-on applicant does so, it must also state either that it will not market its product until the relevant patents have expired, or alternatively provide its views that the patents are invalid, unenforceable, or would not be infringed by the proposed follow-on product. The BPCIA allocates the follow-on applicant 60 days to provide both the mandatory and optional information.

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[44] Carl J. Minniti III, "*Sandoz v. Amgen*: Why Current Interpretation of the Biologic Price Competition and Innovation Act of 2009 is Flawed and Jeopardizes Future Competition," *Journal of the Patent & Trademark Office Society*, vol. 97, 2015, p. 172.

[45] 42 U.S.C. §262(l)(1)(B)(iii).

[46] 42 U.S.C. §262(l)(2)(A).

[47] 42 U.S.C. §262(l)(2)(B).

[48] 42 U.S.C. §262(l)(3)(A)(i).

[49] 42 U.S.C. §262(l)(3)(A)(ii).

[50] 42 U.S.C. §262(l)(3)(B)(ii).

[51] 42 U.S.C. §262(l)(3)(B)(i).

Statement by the Brand-Name Firm. In the event that the follow-on applicant has asserted that the patents are invalid, unenforceable, or would not be infringed by the proposed follow-on product, the brand-name firm must provide the follow-on applicant with a response within 60 days. The response must provide "the legal and factual basis of the opinion ... that such patent will be infringed by the commercial marketing" of the proposed follow-on product.[52]

Patent Resolution Negotiations. If the brand-name firm issues a statement with its detailed views that the proposed follow-on product would infringe valid and enforceable patents, then the parties are required to engage in good faith negotiations. The purpose of the negotiation is to identify which previously identified patents will be the subject of a patent infringement action.[53] If the parties agree on the patents to be litigated, the brand-name firm must bring an action for patent infringement within 30 days.[54]

Simultaneous Exchange of Patents. If those negotiations do not result in an agreement within 15 days, then the follow-on applicant must notify the brand-name firm of how many patents (but not the identity of those patents) that it wishes to litigate.[55] Within five days, the parties are then required to exchange lists identifying the patents to be litigated.[56] The number of patents identified by the brand-name firm may not exceed the number provided by the follow-on applicant. However, if the follow-on applicant previously indicated that no patents should be litigated, then the brand-name firm may identify one patent.[57]

Commencement of Patent Litigation. The brand-name firm may then commence patent infringement litigation within 30 days. That litigation will involve "each patent that is included on such lists"—in other words, all of the patents on the brand-name firm's list and all of the patents on the follow-on applicant's list.[58] The follow-on applicant must then notify the FDA of the litigation. The FDA must then publish a notice of the litigation in the *Federal Register*.[59]

Notice of Commercial Marketing. The BPCIA requires the follow-on applicant to provide notice to the brand-name firm 180 days in advance of its first commercial marketing of its proposed follow-on biologic.[60] The brand-name firm is allowed to seek a preliminary injunction blocking such marketing based upon any patents that either party had preliminarily identified, but were not subject to the initial phase of patent litigation.[61] The litigants are required to "reasonably cooperate to expedite such further discovery as is needed" with respect to the preliminary injunction motion.[62]

The BPCIA stipulates a number of other important features of this unique patent dispute resolution system. First, the BPCIA provides for relevant patents that are issued to the brand-name firm, or for which the brand-name firm obtains an exclusive license, after the brand-name

[52] 42 U.S.C. §262(l)(3)(C).
[53] 42 U.S.C. §262(l)(4)(A).
[54] 42 U.S.C. §262(l)(6)(A).
[55] 42 U.S.C. §262(l)(5)(A).
[56] 42 U.S.C. §262(l)(5)(B)(i).
[57] 42 U.S.C. §262(l)(5)(B)(ii).
[58] 42 U.S.C. §262(l)(6)(B).
[59] 42 U.S.C. §262(l)(6)(C).
[60] 42 U.S.C. §262(l)(8)(A).
[61] 42 U.S.C. §262(l)(8)(B).
[62] 42 U.S.C. §262(l)(8)(C).

firm has provided its initial list of relevant patents to the follow-on applicant.[63] In such circumstances the brand-name firm must provide the follow-on applicant with a supplement that identifies the patent within 30 days of its issuance of licensing.[64] The follow-on applicant is then afforded 30 days to provide either (1) a detailed explanation of why the applicant believes that the patent is invalid, unenforceable, or not infringed; or (2) a statement that the applicant does not intend to market the product commercially until the patent expires.[65] Such a patent is to the "notice of commercial marketing" provision, in that the brand-name firm may move for a preliminary injunction following notification that the follow-on applicant intends to market its proposed product.[66]

Another notable feature is the BPCIA's stipulation of which individuals may receive the information that the follow-on applicant provides to the brand-name firm during the patent dispute resolution process.[67] The recipients of the follow-on application and manufacturing data are limited to one in-house counsel employed by the brand-name firm and one or more of the brand-name firm's outside counsel.[68] Each of these individuals must abide by a number of confidentiality requirements stipulated by the BPCIA. In particular, the application and manufacturing data may not be disclosed to outside individuals without the permission of the follow-on applicant.[69] Further, the application and manufacturing data are to be used for the sole and exclusive purpose of resolving the patent dispute.[70]

In addition, the BPCIA places some restrictions upon the ability of both the follow-on applicant and brand-name firm to bring an action for declaratory judgment concerning the validity, enforceability, or infringement of a patent. If the follow-on applicant does not provide its application and manufacturing data within 20 days after being notified that the FDA has accepted its application for filing,[71] then the brand-name firm may bring a declaratory judgment action on any patent that claims the biologic or its use.[72] If the follow-on applicant does provide its application and manufacturing data within the 20-day timeframe,[73] then neither party may bring an action for declaratory judgment regarding any subsequently identified patent prior to the follow-on applicant's notice that commercial marketing may begin in 180 days.[74] Further, if the follow-on applicant initially provides its application and manufacturing data, but subsequently fails to provide patent-related data as stipulated by the BPCIA, the reference product sponsor may seek a declaratory judgment based upon the patents it identified.[75]

Finally, the infringement remedies that brand-name firms may obtain are limited if they fail to identify a patent or to commence patent litigation within the time limits established by the BPCIA. If a brand-name firm does not bring a patent infringement action in the courts within the

[63] The brand-name firm provides this initial list under 42 U.S.C. §262(l)(3)(A)(i).

[64] 42 U.S.C. §262(l)(7).

[65] 42 U.S.C. §262(l)(3)(B).

[66] 42 U.S.C. §262(l)(8)(B).

[67] 42 U.S.C. §262(l)(1).

[68] 42 U.S.C. §262(l)(1)(B)(ii).

[69] 42 U.S.C. §262(l)(1)(C).

[70] 42 U.S.C. §262(l)(1)(D).

[71] 42 U.S.C. §262(l)(2)(A).

[72] 42 U.S.C. §262(l)(9)(C).

[73] 42 U.S.C. §262(l)(2)(A).

[74] 42 U.S.C. §262(l)(9)(A).

[75] 42 U.S.C. §262(l)(9)(B.

statutory 30-day time period,[76] then a court may only award a reasonable royalty as relief for infringement of a patent named in that suit.[77] If the brand-name firm does not identify in a timely manner a patent in response to receipt of the follow-on application and manufacturing data, then it may not assert the patent at all.[78] A later-acquired patent may also not be asserted if it is not identified within 30 days of its acquisition or exclusive licensing.

Current Issues

Is the "Patent Dance" Optional?

Disagreement over whether the patent dispute resolution procedures of the BPCIA are permissive or obligatory has led to litigation. As discussed above, the BPCIA includes elaborate provisions calling for the follow-on biologic manufacturer to share with the brand-name firm such information as manufacturing methods, patent contentions, and a notice of imminent launch. However, the first recipient of a follow-on biologic license, Sandoz Inc. for Zarxio® (filgrastim-sndz), declined to follow the "Patent Dance" procedures with Amgen Inc., the manufacturer of the brand-name biologic Neupogen®. In so doing, Sandoz took the position that the BPCIA's complex "Patent Dance" procedures were optional. Amgen disagreed. Litigation commenced by Amgen resulted in the decision in *Amgen Inc. v. Sandoz Inc.*,[79] where a divided panel of the U.S. Court of Appeals for the Federal Circuit concluded that a follow-on biologics manufacturer may opt out of the "Patent Dance"—subject to the statutory consequences.

The Federal Circuit released its decisions in *Amgen v. Sandoz* on July 21, 2015, with each member of the three-judge panel issuing an opinion expressing distinct views. Writing for the majority, Judge Lourie initially observed that the BPCIA frequently uses the term "shall" when it describes the various obligations of the follow-on firms.[80] Although Judge Lourie explained that the term "shall" often implies a mandatory obligation, he further observed that the BPCIA explicitly contemplates the consequence for failing to meet the statutory deadline: the brand-name firm may immediately bring an infringement action against the follow-on firm.[81] As a result, Judge Lourie concluded that when the BPCIA uses the term "shall," the statute merely states a condition that the follow-on applicant must fulfill in order to receive a benefit stipulated by the statute. Put differently, in the view of Judge Lourie, the follow-on applicant need not comply with the "Patent Dance" if it is willing to face a lawsuit for infringement immediately.[82]

However, Judge Lourie read 42 U.S.C. §262(l)(8)(A) differently. That provision provides, with emphases added, that the follow-on applicant "*shall* provide notice to the [brand-name firm] not later than 180 days before the date of the first commercial marketing of the biological product *licensed* under subsection (k)." According to Judge Lourie, 42 U.S.C. §262(l)(8)(A) was a standalone provision that was distinct from the remainder of the "Patent Dance" procedures. Further, this provision was mandatory because the BPCIA did not specify the consequences of not

[76] 42 U.S.C. §262(l)(6)(A).

[77] 35 U.S.C. §271(e)(6)(B).

[78] 35 U.S.C. §271(e)(6)(C).

[79] Case No. 2015-1499 (Fed. Cir. July 21, 2015). Citations are to the slip opinion, which is available at the U.S. Court of Appeals for the Federal Circuit.

[80] Amgen v. Sandoz, slip op. at 12.

[81] 42 U.S.C. §262(l)(9)(C).

[82] Amgen v. Sandoz, slip op. at 15.

complying with it.[83] Under this ruling, no follow-on biologic may be sold until 180 days after notice has been given to the brand-name firm, regardless of whether the "Patent Dance" is followed or not.

With respect to 42 U.S.C. §262(l)(8)(A), Judge Lourie further concluded that FDA licensure of the follow-on product was a predicate to the statutory notice requirement. Put differently, providing notice to the brand-name firm prior to FDA approval of the follow-on product was insufficient. The follow-on firm must first obtain agency approval and then provide notice at least 180 days before marketing—a period of time that would presumably allow to consider its business and legal options.[84]

Judge Newman wrote an opinion concurring in part and dissenting in part. In her view, the "Patent Dance" forms an essential part of the balance achieved by the BPCIA. She did not believe that a follow-on firm should be able to obtain the benefits of the brand-name firm's package of pre-clinical and clinical data without respecting the statutory patent dispute resolution procedures. However, she agreed with Judge Lourie's conclusion that 42 U.S.C. §262(l)(8)(A), the provision governing first notice of commercial marketing, was mandatory and not permissive.

Finally, Judge Chen wrote an opinion dissenting in part. Like Judge Lourie, he agreed that the "Patent Dance" was optional. But he also believed that the 180-day notice of first commercial marketing was part and parcel of the entirety of the statutory scheme. As a result, in the view of Judge Chen, once a follow-on firm faltered on any of its statutory patent dispute resolution obligations, the entirety of the "Patent Dance" scheme should be considered to have collapsed. Under this view, the 180-day notice of first commercial marketing would also be optional for follow-on firms.

Tallying the votes of the three judges, the holding of *Amgen v. Sandoz* is: (1) follow-on applicants may optionally engage in the structured "Patent Dance," with the alternative of facing an immediate charge of infringement by the brand-name firm (Judges Lourie and Chen); (2) follow-on applicants are required to provide notice to brand-name firms at least 180 days before first commercial marketing (Judges Lourie and Newman); and (3) the 180-day notice must be provided following FDA licensure of the follow-on product, and not at some earlier date (all three judges agreed). These rulings are now the law of the United States with respect to the BPCIA, unless the Federal Circuit agrees to rehear the matter or the Supreme Court reviews the Federal Circuit's decision. Although Federal Circuit rehearing or the grant of certiorari are, as a statistical matter, relatively rare events, the significance of the *Amgen v. Sandoz* rulings may make further judicial proceedings more probable. This report will be updated to reflect any future developments.

Retroactive Effect of the BPCIA

Another dispute has arisen over whether the BPCIA operates with respect to biologics that the FDA reviewed prior to the enactment of that statute. A 2012 "Citizen Petition"[85] filed by Abbott Laboratories ("Abbott") to the FDA asserted that the BPCIA should not apply to biologics that were the subject of licensure applications prior to March 23, 2010, the date the statute was signed

[83] Id. at 20.

[84] Id. at 16.

[85] See 21 C.F.R. §§10.30. "Citizen petitions allow anyone to file a petition with the FDA regarding the Agency's rulemaking activities or, more importantly, its administrative actions." Matthew Avery, William Newsom, and Brian Hahn, "The Antitrust Implications of Filing 'Sham' Citizens Petitions with the FDA," *Hastings Law Journal*, vol. 65, December 2013, p. 113.

into law.[86] Abbott explained that a biologics licensure application includes considerable analytical, preclinical, and clinical data, along with manufacturing information, most of which qualifies as a trade secret. In the view of Abbott, allowing another firm to rely upon those trade secrets in support of their applications for follow-on licensure would constitute a taking under the Fifth Amendment of the U.S. Constitution.[87] As a result, Abbott advised the FDA not to interpret the BPCIA to apply prospectively only so as to avoid a constitutional violation.

Others disagree with this interpretation. For example, Representative Anna G. Eshoo wrote to the FDA asserting that the "BPCIA clearly states" that the 12-year regulatory exclusivity "applies to all biologics and the expiration clock is retroactive...."[88] Representative Eshoo further observed that "Congressional intent [was] for the new pathway to apply to biologics approved before and after the passage of the Affordable Care Act."[89]

This dispute has not yet been resolved. However, FDA actions allow the inference that the agency believes that the BPCIA applies to all biologics regardless of their date of licensure. For example, the agency's Purple Book identifies the biologic Neupogen (filgrastim) as having a licensure date of February 20, 1991, and a regulatory exclusivity expiration date of February 20, 2003—more than seven years prior to the 2010 effective date of the BPCIA. This Purple Book listing suggests that the FDA believes that the 12-year regulatory exclusivity period, along with the remainder of the BPCIA, applies to all licensed biologics.

The President's Annual Budget

The President's Annual Budget has for several years suggested that Congress reduce the term of regulatory exclusivity for brand-name biologics from 12 to 7 years. Most recently, the 2016 Budget proposes that in order to "increase access to ... biologics" brand-name biologic firms should receive "seven years of exclusivity, rather than 12 years under current law...."[90] Representatives of brand-name biologics firms have reportedly reacted negatively to this proposal, explaining that the BPCIA enjoyed bipartisan support in Congress and that the 12-year period will encourage investment in innovation.[91]

The Trans-Pacific Partnership

The Trans-Pacific Partnership (TPP) is a proposed regional free trade agreement being negotiated between the United States and 11 other nations.[92] Intellectual property law is among the numerous issues addressed by the TPP. With respect to biologics, the United States reportedly

[86] Citizen Petition from Abbott Laboratories to Division of Docket Management, Food and Drug Administration, April 2, 2012.

[87] The Fifth Amendment of the U.S. Constitution provides in part: "nor shall private property be taken for public use, without just compensation." See generally CRS Report 97-122, *Takings Decisions of the U.S. Supreme Court: A Chronology*, by Robert Meltz.

[88] Letter from Anna G. Eshoo, Member of Congress, to The Honorable Margaret Hamburg, M.D., Commissioner, Food and Drug Administration, April 20, 2012.

[89] Ibid.

[90] Office of Management and Budget, *Fiscal Year 2016 Budget of the U.S. Government*, February 2, 2015, p. 63.

[91] SCRIP Intelligence, "Obama Reignites 7-year Biosimilar Exclusion and Inflames 'Innovators,'" *PharmaShare*, April 10, 2011, http://www.pharma-share.com/author/scrip-intelligence.

[92] See CRS Report R42694, *The Trans-Pacific Partnership (TPP) Negotiations and Issues for Congress*, coordinated by Ian F. Fergusson.

seeks to include a requirement that TPP member states adhere to a 12-year period of regulatory exclusivity, in line with the period established by the BPCIA.[93]

However, as noted, the President's proposed annual budget has recently recommended that the period of regulatory exclusivity be reduced to seven years.[94] Some have asserted that the TPP should reflect this seven-year period as well in order to reduce health care costs and prevent the United States from being "locked in" to the existing 12-year period of protection. In addition, former Representative Waxman explained that a seven-year period of biologics exclusivity within the TPP will "ensure that developing countries are not left behind in this agreement."[95]

On the other hand, other members of Congress have expressed distinct views. Senators Patty Murray and Maria Cantwell wrote on July 12, 2012, that "it is vitally important that U.S. negotiators propose robust intellectual property rights for biologics...."[96] Eight members of the Massachusetts delegation explained the next day that an "agreement that reflects U.S. law on biologics exclusivity standards will help Massachusetts companies continue to expand and compete in the global economy."[97] Senator Claire McCaskill (D-MO) subsequently wrote that TPP negotiations "in the emerging field of biological medical products, it is especially important that the negotiations protect the 12 years of exclusivity that U.S. law now provides...."[98]

Concluding Observations

This overview suggests that the BPCIA is a complex and novel statute. Resolution of the scientific and legal issues that this legislation raises will likely engage the courts and the FDA for many years to come. It may also take some time for members of the biologics industry to develop a working familiarity and appropriate strategies within the BPCIA framework. As a result, marketplace availability of significant numbers of follow-on biologics may well be a long-term proposition.[99]

Notably, the BPCIA does not employ the same framework as the patent dispute resolution proceedings that have been available under the Hatch-Waxman Act for more than a quarter century. In particular, unlike the Hatch-Waxman Act, the BPCIA does not require brand-name firms to identify relevant patents in advance of generic competition. Because the FDA publishes a list of relevant patents in a publication informally known as the "Orange Book," generic drug companies possess some ability to assess the patent positions of brand-name pharmaceutical firms. The lack of an Orange Book may place follow-on biologic applicants as a comparative disadvantage.[100]

On the other hand, some commentators believe that follow-on applicants possess a number of advantages over the brand-name firm. Follow-on applicants may control the number of patents to

[93] See U.S. Trade Representative, *2014 Special 301 Report*, pp. 16-18, http://www.ustr.gov/sites/default/files/USTR%202014%20Special%20301%20Report%20to%20Congress%20FINAL.pdf.

[94] Office of Management and Budget, *Fiscal Year 2016 Budget of the U.S. Government*, February 2, 2015, p. 63.

[95] Letter from Henry Waxman, Member of Congress, to Ambassador Michael Froman, USTR, December 6, 2013.

[96] Letter from Patty Murray, United States Senator, and Maria Cantwell, United States Senator, to President Barack Obama, July 12, 2012.

[97] Letter from Edward J. Markey, Member of Congress, to the President, July 13, 2012.

[98] Letter from Claire McCaskill, United States Senator, to President Barack Obama, August 6, 2012.

[99] See Czaban, supra.

[100] Ibid.

be litigated, at least initially.[101] The failure of brand-name firms to act within tight statutory deadlines may result in substantial patent enforcement penalties.[102] And, unlike the Hatch-Waxman Act, the BPCIA does not tightly link FDA approval with patent rights. Brand-name firms must wholly rely upon the judiciary to stay the release of follow-on biologics into the marketplace.[103]

The adoption of a patent dispute resolution system that is distinct from the procedures of the Hatch-Waxman Act may also suggest congressional dissatisfaction with that regime and a desire to attempt new approaches. As is always the case in this field of endeavor, individuals interested in the intellectual property issues surrounding biologics would be wise to remain vigilant concerning developments to the new law of follow-on biologics in coming years.

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[101] 42 U.S.C. §262(l)(5)(A).

[102] 35 U.S.C. §271(e)(6)(B).

[103] See Dougherty, supra.