Follow-On Biologics: The Law and Intellectual Property Issues

John R. Thomas
Visiting Scholar

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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.

Some commentators have also observed that, in contrast to the 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 is 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 do not comfortably apply to biologics.

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. The Food and Drug Administration (FDA) was afforded a prominent role in determining the particular standards for biosimilarity and interchangeability for individual products.

Second, the BPCIA created FDA-administered periods of regulatory exclusivity for certain brand-name drugs and follow-on 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. Finally, the BPCIA created a patent dispute resolution procedure for use by brand-name and follow-on biologic manufacturers.

A core issue concerning the BPCIA is its ability to preserve innovation while also stimulating competition in the biologics market. Some observers believe that due to the unique nature of biologics and their manufacture, the follow-on biologics market may not yield the same level of savings seen with small-molecule generic drugs. In contrast with traditional generic drugs, more clinical trials may be required, manufacturing methods may be more difficult to replicate in distinct facilities, and follow-on firms may be exposed to higher marketing costs. Whether industry will make extensive use of the BPCIA's follow-on approval pathway also is not yet certain.

Resolution of the scientific and legal issues that the BPCIA 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 not be a short-term proposition.

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Introduction

Congressional interest in the availability of lower-cost versions of biologic drugs (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 FDA-administered periods of data protection and marketing exclusivity for certain brand-name drugs and follow-on products. 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 treatments 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] Today, 20% of the drugs on the market are biologics[5] and many more new biologics reportedly are in the pipeline and/or in the approval process.[6] In 2007, "biotechs accounted for 42% of preclinical candidates and 26% of submissions for US marketing approval."[7] According to Standard & Poors, biotech drugs are two times as likely to be approved as small molecule products.[8] Projections are that by 2014, 50% of the top drugs will be the result of biotechnology.[9] EvaluatePharma argues

> that the percentage of sales from biotechnology products (bioengineered vaccines + biologics), within the world's top 100 drugs, is set to increase from 34% in 2011 to 49% in 2018. In the broader market, sales from biotechnology products are set to capture 23% of the world pharmaceutical market by 2018, versus the current share of 19% in 2011.[10]

The biologics sector is highly innovative and invests extensively in research and development (R&D) in its effort to provide products that contribute to the health and well-being of the nation. Observers agree that the biologics market is rapidly expanding by any number of 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. In particular, these medicines have added notable therapeutic options for many diseases and impacted fields such as oncology and rheumatology.[11]

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[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* (May 26, 2010), 698.

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

[4] 42 U.S.C. §262(i).

[5] Ernst & Young, *Beyond Borders, Global Biotechnology Report 2008*, 30.

[6] Kerry A. Dolan, "Biology Rising," *Forbes.com*, May 12, 2006, available at http://www.forbes.com/2006/05/12/merck-pfizer-amgen-cz_kd_0512biologics_print.html.

[7] Steven Silver, *Industry Surveys 201—Biotechnology*, Standard & Poors, August 13, 2009, 9-10.

[8] Steven Silver, *Industry Surveys 2012—Biotechnology*, Standard & Poors, August 16, 2012, 4.

[9] Ibid., 10.

[10] EvaluatePharma, *World Preview 2018, Embracing the Patent Cliff*, June 2012, 13, available at https://www.evaluatepharma.com/secure/FileResourceDownload.aspx?id=98a75eab-95f6-41d8-903f-4732848fdf78.

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

Along with their benefits, biologic drugs also have contributed to the cost of health care. Typically, biopharmaceuticals are more expensive than traditional, chemical-based drugs and while

> prescription drug spending has been a relatively small proportion of national health care spending (10% in 2006, compared to 31% for hospitals and 21% for physician services), it [prescription drug spending] has been one of the fastest growing components, until recently growing at double-digit rates compared to single-digit rates for hospital and physician services.[12]

Some biologics are particularly costly. For example, Genentech Inc. reportedly charges $4,400 for one month's treatment with Avastin®, a cancer drug.[13] The Centers for Medicare and Medicaid Services, which administers federal benefit programs for elderly and low-income citizens, reportedly spends approximately $2 billion each year on Epogen®, a treatment for anemia. 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 make them.[14] 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.[15]

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 may be readily characterized and reproduced through well-understood chemical processes.[16]

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.[17] 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.[18] 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.[19] The 111th Congress accounted for these distinctions when it enacted the BPCIA.

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[12] Kaiser Family Foundation, *Prescription Drug Trends*, September 2008, available at http://www.kff.org.

[13] Paula Tironi, "Pharmaceutical Pricing: A Review of Proposals to Improve Access and Affordability of Prescription Drugs," 19 *Annals of Health Law* (2010), 311.

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

[15] Ibid.

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

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

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

[19] Ibid.

This report reviews the BPCIA within the context of intellectual property and innovation issues. This study first provides an introduction to the biologics industry. Next, this report introduces the regulatory and intellectual property provisions of the BPCIA. This analysis then considers the potential market for biosimilars and possible industry responses that may arise in the wake of this legislation. This report closes with concluding observations.

The Biologics Industry

In the United States, 2011 revenue from the sale of biopharmaceutical products (as reported by public companies) were an estimated $58.8 billion, according to recent data.[20] The United States provides the largest market for biotech drugs; 56% of global sales in 2007 were generated in the United States.[21] During 2007, worldwide sales of biotech products totaled $75 billion, up 12.5% over 2006, a rate of growth almost twice that of world-wide pharmaceutical market.[22] Globally, 22 biotechnology products generated sales of over $1 billion in 2007 compared with six biologics in 2002.[23] Sales of biotechnology products comprised 19% of worldwide prescription and over the counter drug sales in 2011 and are expected to expand to 23% of the market by 2015.[24]

The U.S. biotechnology sector is highly research intensive. In 2011, public companies invested 29.3% of U.S. revenues in domestic R&D, up from 28.2% the previous year.[25] Another analysis found that "over the past 25 years, average R&D intensity (R&D spending to total firms assets) for this industry was 38 percent ... [while] over this same period average R&D intensity for all industries was only about 3 percent."[26] In comparison, research intensity in the small-molecule pharmaceutical industry was 25% over the same time period.[27] Innovative activities have resulted in a situation where "for several years in a row, biotech companies have secured more product approvals than their big pharma counterparts, even though big pharma significantly outspends the biotechnology industry on research and development."[28] One estimate is that biotechnology products comprise 25% of the total pharmaceutical pipeline.[29]

The total capitalized cost of developing a new biotechnology drug (including those that fail testing and the development time costs) is estimated at $1.2 billion, similar to small-molecule products.[30] The time it takes to develop and obtain marketing approval for a biopharmaceutical

[20] Ernst & Young, *Beyond Borders, Global Biotechnology Report 2012*, 27, available at http://www.ey.com/Publication/vwLUAssets/Beyond_borders_2012/$FILE/Beyond_borders_2012.pdf.

[21] IMS Health, *IMS Health Reports Global Biotech Sales Grew 12.5 Percent in 2007, Exceeding $75 Billion*, June 17, 2008, available at http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=bba69e392879a110VgnVCM100000ed152ca2RCRD&cpsextcurrchannel=1.

[22] Ibid.

[23] Ibid.

[24] *World Preview 2018, Embracing the Patent Cliff,* 13.

[25] *Beyond Borders, Global Biotechnology Report 2012*, 27.

[26] Joseph H. Golec and John A. Vernon, *Financial Risk in the Biotechnology Industry*, National Bureau of Economic Research, November 2007, Abstract page, available at http://www.nber.org/papers/w13604.

[27] Ibid, 4.

[28] Ernst & Young, *Beyond Borders, Global Biotechnology Report 2007,* 1.

[29] *IMS Health Reports Global Biotech Sales Grew 12.5 Percent in 2007, Exceeding $75 Billion.*

[30] Joseph A. DiMasi and Henry G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, 2007, 475, available at http://www.manhattan-institute.org/projectfda/
(continued...)

averages 97.7 months, compared to 90.3 months for chemical drugs.[31] In addition, the success rate for FDA approval of biotechnology products is 30.2% versus 21.5% for traditional drugs.[32] Biologics tend to fail most often in Phase III trials when significant funds have been expended on the development of the product.[33]

"There is no question that biotechnology is now the engine of innovation for the drug development industry," according to experts at Ernst & Young.[34] This innovation often takes place over the lifetime of the drug. According to a Boston Consulting Group study of 58 biological products licensed in the United States between 1986 and 2006, 47% had at least one additional FDA-approved indication after the initial FDA approval. Of these, "One-third of the new indications for BLAs were approved within three years of the initial indication, while another third of the new indications were approved more than seven years after the approval of the initial indication."[35] These additional clinical indications can be significant:

- Herceptin, originally approved for metastatic breast cancer, was later approved for adjuvant use in early stage cancer and may prove to be even more valuable there;
- Avastin was approved originally for colorectal cancer, and subsequently for lung cancer …;
- Some of the approved therapies for rheumatoid arthritis later proved effective against other autoimmune conditions, from Crohn's disease to psoriasis.[36]

Biologics are expensive when compared to small-molecule drugs. There are several reasons for this including the cost of manufacturing, storage and distribution considerations, and method of administration. Spending on pharmaceuticals comprises 10%-20% of total U.S. healthcare spending; 20% of the spending on pharmaceuticals is for biologics.[37]

FDA Regulation of Biologics

The FDA for the most part regulates small-molecule drugs and biologics under two different statutes. Traditional pharmaceuticals fall under the Federal Food, Drug and Cosmetic Act (FFDCA). The FFDCA in turn incorporates the Drug Price Competition and Patent Term

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wiley_interscience_cost_of_biopharm.pdf.

[31] Henry Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition," *Nature Reviews/Drug Discovery*, June 2008, 481.

[32] Tufts Center for the study of Drug Development, *Average Cost to Develop a New Biotechnology Product is $1.2 Billion*, November 9, 2006, available at http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69.

[33] *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition,* 481.

[34] *Beyond Borders, Global Biotechnology Report 2007,* 1.

[35] Maya Said, Charles-Andre Brouwers, Peter Tollman, *Continued Development of Approved Biological Drugs*, Boston Consulting Group, White Paper, December 2007, 3, available at http://www.bcg.com/documents/file15138.pdf.

[36] Henry G. Grabowski, "Data Exclusivity for Biologics: What is the Appropriate Period of Protection?" *AEI Outlook*, September 8, 2009, available at http://www.aei.org/outlook/100068.

[37] Phil Galewitz, "Checking In With Patricia Danzon on the Hot Topic of 'Biologics,'" *Kaiser Health News*, July 15, 2009, available at http://www.kaiserhealthnews.org/Checking-In-With/Biologics.aspx.

Restoration Act of 1984, which is commonly known as the Hatch-Waxman Act.[38] 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 molecule in the same strength, dosage, form, and route of administration, and the generic version is 'bioequivalent' to the original product."[39]

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.[40] Because the FDA licenses most biologics via the PHSA, rather than the FFDCA, prior to the enactment of the BPCIA no generally applicable abbreviated statutory pathway for follow-on versions of biologics existed.[41] 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.[42]

Congress intended to address these concerns with the 2010 enactment of the Biologics Price Competition and Innovation Act (BPCIA). The BPCIA is a complex statute that principally amends Section 351 of the Public Health Service Act.[43] 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 biosimilar to a brand-name product if it is deemed to be "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."[44] In order for a follow-on biologic to qualifiy 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

[38] 98th Congress, P.L. 98-417, 98 Stat. 1585.

[39] See Czaban, et al.

[40] 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).

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

[42] 21 U.S.C. §355(j)(2)(A).

[43] 42 U.S.C. §262.

[44] 42 U.S.C. §262(i)(2).

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.[45]

Interchangeable Biologics

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."[46] 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.[47]

The Role of the FDA

The BPCIA provides the FDA with the 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. The FDA is specifically allowed to indicate in a guidance document that "the science and experience" does not currently allow a product or product class to qualify as biosimilar or interchangeable.[48]

Regulatory Exclusivities

The BPCIA provides for regulatory exclusivities for both brand-name products and the first interchangeable follow-on biologic. With respect to brand-name products, the BPCIA offers two sorts of regulatory exclusivity, one with a duration of 4 years, and the other 12 years. The BPCIA specifically provides:

> (7) EXCLUSIVITY FOR REFERENCE PRODUCT.—
>
> (A) EFFECTIVE DATE OF BIOSIMILAR APPLICATION APPROVAL.—Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a).
>
> '(B) FILING PERIOD.—An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a).[49]

Some discussion has occurred about whether the 12-year regulatory exclusivity period identified in the statute operates as "data protection" or as a "marketing exclusivity." In the FDA's public

[45] 42 U.S.C.§262(k)(2).

[46] 42 U.S.C. §262(i)(3).

[47] 42 U.S.C. §262(k)(4).

[48] 42 U.S.C. §262(k)(8).

[49] 42 U.S.C. § 262(k)(7).

hearing notice, the agency referred to a "12-year period of marketing exclusivity."[50] Several Members of Congress drafted letters to the FDA explaining that the 12-year period instead acted as a data exclusivity. One letter explained:

> The Act does not provide market exclusivity for innovator products. It provides data exclusivity, which prohibits FDA from allowing another manufacturer of a highly similar biologic to rely on the Agency's prior finding of safety, purity and potency for the innovator product for a limited period of time. It does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a full biologics license application rather than an abbreviated application that relies on the prior approval of a reference product.[51]

Similarly, other Members of Congress explained that the 12-year regulatory exclusivity acts as data exclusivity that "only protects the FDA from allowing another manufacturer to rely on the data of an innovator to support another product. Importantly, it does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a similar of competitive product."[52] A third letter from Members of Congress stated their belief that "the statute is clear that the FDA can begin reviewing biogeneric applications during the 12 year exclusivity period."[53] The FDA subsequently issued a draft guidance document that appeared to align the agency's view with that of the congressional correspondents.[54]

The BPCIA stipulates some circumstances where 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 this proprietary interest.[55]

Both the 4-year and 12-year protection periods may be extended by 6 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, each term of regulatory exclusivity may be extended by 6 months.[56] 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.

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[50] Dept. Health & Human Servs., FDA, "Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments," 75 *Federal Register* (Oct. 5, 2010), 61497.

[51] Letter of January 7, 2011, from Senator Michael Enzi et al., to Dr. Margaret Hamburg, Commissioner, FDA (available at http://www.hpm.com/pdf/1-7-11%20Senate%20Biologics%20letter%20to%20FDA.pdf) (signed by Senators Enzi, Hagan, Hatch, and Kerry).

[52] See Letter of December 21, 2010, from Representative Anna G. Eshoo, et al., to FDA (available at http://patentdocs.typepad.com/files/letter-to-fda.pdf) (signed by Representatives Barton, Eshoo, and Inslee).

[53] See Letter of January 24, 2011, from Senator Sherrod Brown, et al., to Dr. Margaret Hamburg, Commissioner, FDA (available at http://patentdocs.typepad.com/files/senator-letters-exclusivity.pdf) (signed by Senators Brown, Harkin, McCain, and Schumer).

[54] FDA, Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Feb. 2012), 3.

[55] 42 U.S.C. §262(k)(7)(C).

[56] 42 U.S.C. §262(m).

In enacting the BPCIA, Congress recognized 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 seven-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 less 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.[57] Orphan drug exclusivity prevents the FDA from approving another application for marketing approval for the indication for which the drug is approved. As a result, the FDA could approve a second application for the same drug for a different use. The FDA cannot approve the same drug made by another manufacturer for the same use, however, unless the original sponsor approves or the original sponsor is unable to provide sufficient quantities of the drug to the market.[58]

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 protection period established by this bill.[59] As a result, the Orphan Drug Act's 7-year exclusivity period runs concurrently with the BPCIA's 12-year exclusivity period.

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.[60]

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.[61] These rules require the brand-name firm and the follow-on applicant to engage in a

[57] 21 U.S.C. §360bb(a)(2).

[58] 21 U.S.C. §360cc(b).

[59] BPCIA, §7002(h).

[60] 42 U.S.C. §262(k)(6).

[61] 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* (continued...)

number of interactions prior to the commencement of litigation. These interactions 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.[62]

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.[63] The applicant may also provide other information that the brand-name firm requests.[64]

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. To be capable of identification, the patents must be owned or subject to an exclusive license by the brand-name firm. 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."[65] The brand-name firm must also identify any patents on the list that it would be prepared to license to the follow-on applicant.[66]

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.[67] 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.[68] 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.

(...continued)

(2010), no. 2 at 231.

[62] 42 U.S.C. §262(l)(1)(B)(iii).

[63] 42 U.S.C. §262(l)(2)(A).

[64] 42 U.S.C. §262(l)(2)(B).

[65] 42 U.S.C. §262(l)(3)(A)(i).

[66] 42 U.S.C. §262(l)(3)(A)(ii).

[67] 42 U.S.C. §262(l)(3)(B)(ii).

[68] 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.[69]

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.[70] If the parties agree on the patents to be litigated, the brand-name firm must bring an action for patent infringement within 30 days.[71]

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.[72] Within five days, the parties are then required to exchange lists identifying the patents to be litigated.[73] 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.[74]

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.[75] 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*.[76]

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.[77] 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.[78] The litigants are required to "reasonably cooperate to expedite such further discovery as is needed" with respect to the preliminary injunction motion.[79]

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-

[69] 42 U.S.C. §262(l)(3)(C).
[70] 42 U.S.C. §262(l)(4)(A).
[71] 42 U.S.C. §262(l)(6)(A).
[72] 42 U.S.C. §262(l)(5)(A).
[73] 42 U.S.C. §262(l)(5)(B)(i).
[74] 42 U.S.C. §262(l)(5)(B)(ii).
[75] 42 U.S.C. §262(l)(6)(B).
[76] 42 U.S.C. §262(l)(6)(C).
[77] 42 U.S.C. §262(l)(8)(A).
[78] 42 U.S.C. §262(l)(8)(B).
[79] 42 U.S.C. §262(l)(8)(C).

name firm, or for which the brand-name firm obtains an exclusive license, after the brand-name firm has provided its initial list of relevant patents to the follow-on applicant.[80] 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.[81] 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.[82] 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.[83]

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.[84] 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.[85] 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.[86] Further, the application and manufacturing data are to be used for the sole and exclusive purpose of resolving the patent dispute.[87]

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,[88] then the brand-name firm may bring a declaratory judgment action on any patent that claims the biologic or its use.[89] If the follow-on applicant does provide its application and manufacturing data within the 20-day timeframe,[90] 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.[91] 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.[92]

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

[81] 42 U.S.C. §262(l)(7).

[82] 42 U.S.C. §262(l)(3)(B).

[83] 42 U.S.C. §262(l)(8)(B).

[84] 42 U.S.C. §262(l)(1).

[85] 42 U.S.C. §262(l)(1)(B)(ii).

[86] 42 U.S.C. §262(l)(1)(C).

[87] 42 U.S.C. §262(l)(1)(D).

[88] 42 U.S.C. §262(l)(2)(A).

[89] 42 U.S.C. §262(l)(9)(C).

[90] 42 U.S.C. §262(l)(2)(A).

[91] 42 U.S.C. §262(l)(9)(A).

[92] 42 U.S.C. §262(l)(9)(B.

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 statutory 30-day time period,[93] then a court may only award a reasonable royalty as relief for infringement of a patent named in that suit.[94] 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.[95] A later-acquired patent may also not be asserted if it is not identified within 30 days of its acquisition or exclusive licensing.

The Potential Market for Follow-On Biologics

A core issue concerning the BPCIA is its ability to preserve innovation while also stimulating competition in the biologics market. Many experts agree that the Hatch-Waxman Act has had a significant effect on the availability of small-molecule, generic substitutes for brand-name drugs.[96] Prior to the enactment of the Hatch-Waxman Act, 35% of top-selling drugs had generic competitors after patent expiration; now almost all do.[97] Concurrently, the time to market for these generic products has decreased substantially. According to the Congressional Budget Office (CBO), prior to passage of the act in 1984, the average time between the expiration of a brand-name patent and the availability of a generic was three years. Today, upon FDA approval a generic may be introduced immediately after patents on the innovator drug expire as companies are permitted to undertake clinical testing during the time period associated patents are in force. "By streamlining the approval process for a generic drug form, the Hatch-Waxman Act reduced the average delay between patent expiration and generic entry into the consumer market from *greater* than three *years* to *less* than three *months* for top-selling drugs."[98] In cases where the generic manufacturer is the patent holder, a substitute drug may be brought to market before the patent expires.

In the absence of the research, development, and testing performed by the brand-name pharmaceutical companies, generic drugs as we know them today would not exist. The provisions of the Hatch-Waxman Act permit the generic industry to rely on information generated and financed by the brand-name companies to obtain approval for their product by the FDA. However, the pharmaceutical industry today differs from what it was in the early 1980s. The cost of developing a drug has doubled[99] to where it now takes over $1 billion to bring a new drug to market.[100] Typically, the cost of developing a generic is between $1 million and $5 million.[101] The

[93] 42 U.S.C. §262(l)(6)(A).

[94] 35 U.S.C. §271(e)(6)(B).

[95] 35 U.S.C. §271(e)(6)(C).

[96] For a detailed discussion on the results of the Hatch-Waxman Act see CRS Report R41114, *The Hatch-Waxman Act: Over a Quarter Century Later*, by Wendy H. Schacht and John R. Thomas, *The Hatch-Waxman Act: A Quarter Century Later*, by Wendy H. Schacht and John R. Thomas.

[97] Michael A. O'Shea and Christopher M. Mikson, "The Hatch-Waxman Act: Still Critical, Still in Flux," *The National Law Journal*, January 23, 2006.

[98]David A. Holdford and Bryan A. Liang, *The Growing Influence of Generic Drugs: What it Means to Pharmacists and Physicians*, Power-Pak C.E., December 2006, available at http://www.centad.org/seminar/4.%20Generics/GrowingInfluencePowewrPak2006.pdf.

[99] *The Hatch-Waxman Act: Still Critical, Still in Flux.*

[100] Christopher Paul Adams and Van Vu Brantner, "Spending on New Drug Development," *Health Economics*, (published online 26 Feb.2009) Epub ahead of print.

number of clinical trials necessary to file a new drug application has doubled since 1980 and the number of participants in these trials has tripled.[102] Thus, the rate of return from investment in a new drug has dropped by 12% over this time period.[103] Concurrently, companies appear to be moving away from the development of drugs that address large patient populations, but for which they cannot charge high prices, toward more specialized medicines, primarily biologics, that may be used by fewer patients, but for which high prices can be secured. In 2007, 55 blockbuster drugs were considered specialized products, up from 12 in 2001.[104]

While in the traditional pharmaceutical market, generic substitutes commonly become available to consumers as patents on brand-name drugs expire due to the provisions of the Hatch-Waxman Act, the loss of patent protection for biologics has not and is not expected to generate similar results. As discussed previously, biologics differ significantly from traditional pharmaceuticals in their complexity and method of manufacture.[105] The unique nature of biologics and their manufacture may militate against the type of savings generated by small-molecule generics. It remains uncertain whether or not there will be a significant market for follow-on biologics and what cost-savings may or may not be generated. According to some experts:

> The economics of the small-molecule generics market likely will not be transferrable to the follow-on biologics market. High barriers to entry, high fixed costs of manufacturing, and marketing expenses will more likely manifest themselves in a market that has a small number of firms with relatively small price drops upon introduction of follow-on therapies.[106]

While analysts argue that "The capital and expertise required to develop, scale up, and achieve yields competitive with experienced innovators, combined with the added uncertainty around gaining regulatory approval, may make entry of biosimilars in the markets less financially attractive,"[107] other commentators maintain that over time a competitive market will emerge and "flourish" although the "field of play will be narrower than previously thought."[108] The producers of follow-on biologics are expected to be led by a small group of companies including those already in the established generic market such as Teva, Sandoz, Cangene, Biocon, and Dr. Reddy's.[109]

(...continued)

[101] Federal Trade Commission, *Emerging Health Care Issues: Follow-on Biologic Drug Competition*, June 2009, iii, available at http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.

[102] Gregory J. Glover, "The Influence of Market Exclusivity on Drug Availability and Medical Innovations," *The AAPS Journal*, August 3, 2007, E313.

[103] *The Hatch-Waxman Act: Still Critical, Still in Flux.*

[104] PriceWaterhouseCoopers, *Pharma 2020: Marketing the Future,* February 2009, 13, available at http://www.pwc.com/pharma.

[105] Ibid.

[106] Ian Evans, "Follow-on Biologics: A New Play for Big Pharma," *Yale Journal of Biology and Medicine*, June 2010, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892764/.

[107] Dean & Company, *The U.S. Biosimilars Market, Threats and Opportunities*, April 4, 2010, 4, available at http://www.dean.com/expertise/biosimilars.pdf.

[108] Bruce Carlson, "Biosimilar Market Fails to Meet Projections," Genetic Engineering & Biotechnology News, October 1, 2009, available at http://www.genengnews.com/keywordsandtools/print/1/12970/.

[109] Ibid.

In Europe, where biosimilars have been approved since June 2003, there has been little penetration of the market by follow-on biologics. Laws prohibiting automatic substitution of follow-on drugs and safety concerns have inhibited widespread use of biosimilars.[110] According to a report by Dean & Company, "A combination of safety concerns, brand loyalty, and aggressive pricing strategies by branded manufactures have contributed to their lack of traction in spite of their lower price."[111] Sales of Omnitrope, the first FDA approved biosimilar, are only 1% of the $831 million European human growth hormone market, due in part to doctors unwilling to change products, delivery mechanism issues, and prices that are only 20%-25% below innovator.[112] In the United States, to date, there has been only "tepid demand" for Omnitrope.[113]

Several specific issues that may affect the market for follow-on biologics are discussed below.

Clinical Trials

Currently, there is uncertainty over the biosimilar approval process that will be required by the FDA; however, all experts agree that, at least initially, clinical trials of the follow-on product likely will be necessary. The scale and extent of clinical trials are expected to factor into whether or not this industry will provide the cost savings needed to be viable.[114] The varied characteristics of individual biologic products may make it likely that regulatory and developmental requirements for follow-on products will need to reflect each individual situation.[115] Innovator and generic manufacturers appear to agree that "unlike small-molecule copycats, for biogenerics [sic], the nature and extent of the data needed will also depend very much on the product involved: regulatory guidelines must be defined product by product."[116]

The number and extent of clinical trials that may be required for approval of a biosimilar is reflective of the general nature of biologics that has resulted in longer mean clinical development time for these products when compared with traditional drugs.[117] The number of clinical trials necessary to file a new drug application has doubled since 1980 and the number of participants in these trials has tripled.[118] If additional clinical trials are necessary to demonstrate "sameness," effectiveness, and safety, estimates are that it may take twice the time to develop a follow-on biopharmaceutical than a chemical generic with a cost that some expect to be 8-100 times higher than that associated with a traditional generic product.[119] Phase III trials are the most expensive of

[110] Bain & Company, *Biosimilars: A Marathon, Not a Sprint*, December 16, 2009, 2, available at http://www.bain.com/bainweb/PDFs/cms/Public/2009_BB_Biosimilars.pdf.

[111] *The U.S. Biosimilars Market, Threats and Opportunities,* 6.

[112] Laura A. Carpenter, "Generic Substitution and Biopharmaceuticals: Where Are All the Follow-on Biologics: And, How Much Money Will They Save?" *The National Law Review*, January 1, 2010, available at http://www.natlawreview.com/article/generic-substitution-and-biopharmaceuticals-where-are-all-follow-bi.

[113] *Biosimilars: A Marathon, Not a Sprint,* 3.

[114] "Delay in U.S. Regulatory Approval Significantly Lowers Forecast for BioGenerics Market to $2.3 Billion," *Business Wire*, November 22, 2005.

[115] John Ansell, "Biogenerics Part I: Set to Make Real Inroads or Not?," *PharmaWeek*, January 26, 2006, available at http://www.pharmaweek.com?Exclusive_Content/1_26.asp.

[116] Ibid.

[117] *The Market For Follow-On Biologics: How Will It Evolve?*, 1293.

[118] Gregory J. Glover, "The Influence of Market Exclusivity on Drug Availability and Medical Innovations," *The AAPS Journal*, August 3, 2007, E313.

[119] IMS Health, "Biogenerics: A Difficult Birth?," May 18, 2004 available at http://www.imshealth.com/web/content/
(continued...)

the required trials and any additional requirements for follow-on biologics likely would increase the cost to the public.[120]

Manufacturing Considerations

Biotechnology drugs are characterized by their manufacturing process such that:

> The manufacturing process for each biologic defines, to a significant extent, the product because biologics are based on living cells or organisms whose metabolisms are inherently variable. Moreover, apparently small differences between manufacturing processes can cause significant differences in the clinical properties of the resulting products.[121]

Manufacture of biologics will therefore tend to be significantly more expensive than traditional chemically synthesized drugs.[122] It has been estimated that each large U.S.-based biologic "manufacturing facility costs between $200 and $400 million to build, and takes four years before gaining approval by the US Food and Drug Administration."[123] In addition, the cost of materials to manufacture biologics may be 20 to 100 times more than chemical drugs.[124] The production process for biologics typically takes longer than traditional drugs and may take eight to nine months.[125]

The FDA is required to inspect the manufacturing facilities and processes involved in the production of biologics: "Unlike small-molecule manufacturing, biomanufacturers get approval for both the drug and the process used to make it, and that approval can take years."[126] Therefore, these facilities must be built and operational prior to the FDA approval process. According to FDA guidelines, "Issuance of a biologics license is a determination that the product, *the manufacturing process, and the manufacturing facilities* [emphasis added] meet applicable requirements to ensure the continued safety, purity and potency of the product."[127]

When the manufacturing process is altered in any way, the FDA typically requires that this validation be repeated.[128] Such manipulation may alter the nature of the product that is

(...continued)

0,3148,64576068_63872702_70261000_71026746,00.html.

[120] Ernst & Young, "Coming of Age," *Beyond Boarders*, 2005, available at http://www.ey.com/beyondboarders.

[121] Christopher Webster et al., "Biologics: Can There Be Abbreviated Applications, Generics, or Follow-On Products?," *International BioPharm*, July 1, 2003, available at http:P//www.biopharm-mag.com/biopharm/article/articleDetail.jsp?id=73785.

[122] Henry Grabowski, Iain Cockburn, and Genia Long, "The Market For Follow-On Biologics: How Will It Evolve?," *Health Affairs,* September/October 2006, 1293 and Linda Hull Felcone, "The Long and Winding Road to Biologic Follow-ons," *Biotechnology Healthcare*, May 2004, 24, available at http://www.biotechnologyhealthcare.com/journal/fulltext/1/2/BH0102020.pdf.

[123] Alison McCook, "Manufacturing on a Grand Scale," *The Scientist*, February 14, 2005, available at http://www.thescientist.com.

[124] *The Market For Follow-On Biologics: How Will It Evolve?,* 1293.

[125] *The Long and Winding Road to Biologic Follow-ons*, 24.

[126] Alison McCook, "Manufacturing on a Grand Scale," *The Scientist*, February 14, 2005, available at http://www.thescientist.com.

[127] U.S. Food and Drug Administration, *Frequently Asked Questions About Therapeutic Biological Products*, July 26, 2006, available at http://www.fda.gov/cder/biologics/qa.htm.

[128] *Manufacturing on a Grand Scale*.

produced.[129] One commentator stated: "It's hard to predict how process variations will change a product's safety or effectiveness."[130] This can be a result of the incidence of impurities arising from changes in the method of production and the increased opportunity of adverse immune reactions.[131] Finding and identifying impurities in biologics may be difficult as, to date, simple tests do not exist. Thus, additional costs may be associated with preventing impurities from entering into the production process.[132]

The manner in which a follow-on biologic is made may have significant impact on the composition of the final product and its cost. Experts maintain that the manufacturing process is "far more difficult to perfect and replicate from one facility to another."[133] The number of firms able to produce a biosimilar may therefore be limited,[134] while making the product relatively more expensive than a small-molecule generic pharmaceutical:

> the ability of biosimilars manufacturer to increase market share through low pricing will be dictated not only by varying up-front development requirements, but also by its relative manufacturing costs, which are more significant for biologics compared with small-molecule drugs. The ability of a biosimilars manufacturer to achieve a favorable cost position will be dictated by factors such as scale, location of capacity and efficiency (i.e., yields) in protein expression and purification.[135]

Sales and Marketing

Several commentators have suggested that marketing costs associated with follow-on biologics will be higher than with traditional generics because of the need to convince doctors that these products generate similar results.[136] If the follow-on biopharmaceutical cannot be termed equivalent to the brand-name drug, doctors and pharmacists may not be willing to readily substitute the biosimilar. Therefore, it may be expected that:

> Marketing and patient support are more important for biosimilars, favouring companies with significant financial resources and who have had experience in marketing branded products. The generics market has historically used prices to secure market share, so it is important for biosimilar developers to understand and act on these factors. Early-stage success in the

[129] Ingrid Kaldre, "The Future of Generic Biologics: Should the United States 'Follow-On' the European Pathway?" *Duke Law and Technology Review*, November 6, 2008, available at http://www.law.duke.edu/journals/dltr/articles/pdf/2008dltr0009.pdf.

[130] William Alpert, "Biotech's Next Challenge," *SmartMoney.com*, May 22, 2006, available at http://www.smartmoney.com/barrons/index.cfm?story=20060522.

[131] Joshua W. Devine, Richard R. Cline, and Joel F. Farley, "Follow-on Biologics: Competition in the Biopharmaceutical Marketplace," *Journal of the American Pharmacists Association*, March/April 2006, 194.

[132] Gurdeep Singh Shah, "The Current Market for Generic Biologics," International Biopharmaceutical Association, June 2006, available at http://www.ibpassociation.org/IBPA_articles/jun2006issue/The_Current_Market_for_Generic_Biologics.htm.

[133] Michael S. Labson and Krista Hessler Carver, "Follow-on Biologics Proposals v. Hatch-Waxman: What the FOB Market Might Look Like," *Covington & Burling RA Focus*, January 2008, 17, available at http://www.cov.com/files/Publication/43b1a21b-04e0-4f78-bb72-035bfa1cc014/Presentation/PublicationAttachment/5f154780-4212-48dc-b0d2-10664710e51a/Follow-on%20Biologics%20Proposals%20v.%20Hatch-Waxman%20-%20What%20the%20FOB%20Market%20Mig.pdf.

[134] Ibid., 17.

[135] *Biosimilars: A Marathon, Not a Sprint,* 4.

[136] *The Long and Winding Road to Biologic Follow-ons*, 24.

> biosimilars market, however, is more dependent on the speed to market and successful marketing strategies.[137]

Many experts argue that a strong sales and marketing force is needed to "educate" doctors and consumers even if the price of the biosimilar is 20%-30% lower than the brand-name drug.[138] This effort may require a new sales force and added investment on behalf of the company producing a biosimilar.[139] Due to the particular issues associated with follow-on biologics, successful commercialization may "require a field sales force outside of the traditional skills of the wholesale-driven generics industry."[140] Because providers may not be comfortable with substitution of products that are not identical to the innovator drug, there is expected to be a steep learning curve, less competition, and higher prices.[141]

The greater the number of small-molecule generic alternatives, the lower the cost. "For example, the average price reduction for a generic that has been granted 180-day exclusivity is only 30%, as compared to a 70% amount for multi-source generics."[142] However, biologics may not generate multiple follow-on products for the same brand-name biopharmaceutical because of the higher costs associated with bringing these drugs to the marketplace. Price differentials associated with follow-on products may not be as great as with other generics because of the large initial costs related to establishing manufacturing facilities and performing any additional clinical studies necessary for FDA approval. Therefore, the makers of follow-on products would be expected to charge prices that, while lower than the brand biologic, would be relatively higher than those charged for typical small-molecule drugs.[143] In addition, "Financial and scientific barriers might prevent the cutthroat price wars fought in the traditional generic market."[144]

A study by Kalorama Information (*The Market for Generic Biologics: Issues, Trends, and Market Potential*, June 1, 2005) estimated that follow-on products will sell for only 10%-20% less than the brand-name biologic, not the 40%-80% reduction in price generally seen with chemical drug generics.[145] A Merrill Lynch analysis[146] estimated prices 20%-30% below the brand biologic for the first biosimilar to be marketed while a report by Citizens Against Government Waste[147] estimated savings of 10%-25% over the brand biologic price in the first year and 25%-47% by the fifth year after introduction of a follow-on drug. The Federal Trade Commission issued a report in

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[137] Mark J. Belsey, Laura M. Harris, Romita R. Das, and Joanna Chertkow, "Biosimilars: Initial Excitement Gives Way to Reality," *Nature Reviews Drug Discovery*, July 2006, available at http://www.nature.com/nrd/journal/v5/n7/full/nrd2093.html.

[138] Cynthia Challener, "Big Pharma's Edge in Biosimilars," *ICIS Chemical Business,* February 10, 2010, available at http://www.icis.com/Articles/2010/02/15/9333235/Follow-on-biologics-present-opportunity-to-big-pharma.html.

[139] Mari Edlin, "PPACA Creates Approval Pathway for Follow-On Biologics," *Drug Topics,* August 15, 2010, available at http://license.icopyright.net/user/viewFreeUse.act?fuid=OTg5NTgyMQ%3D%3D.

[140] *The U.S. Biosimilars Market, Threats and Opportunities,* 5.

[141] *Biosimilars: A Marathon, Not a Sprint,* 3-4.

[142] *Generic Substitution and Biopharmaceuticals: Where Are All the Follow-on Biologics: And, How Much Money Will They Save?*

[143] William Alpert, "Biotech's Next Challenge," *SmartMoney.com*, May 22, 2006, available at http://smartmoney.com/print/index.cfm?printcontent=/barrons/index.cfmstory=20060522.

[144] Ibid.

[145] Susan J. Ainsworth, "Biopharmaceuticals," *Chemical and Engineering News*, June 6, 2005, 21-29.

[146] Merrill Lynch, *Biogenerics: Big Opportunities, Small Threat*, September 6, 2006.

[147] Everett Ehrlich and Elizabeth L. Wright, "Biogenerics: What They Are, Why They Are Important, and Their Economic Value to Taxpayers and Consumers," *Citizens Against Government Waste*, May 2, 2007.

June 2009 stating that follow-on companies "are likely to introduce their drug products at price discounts between 10 and 30 percent of the pioneer products' price to the most price-sensitive customers."[148] Duke University Professor Henry Grabowski and his colleagues reached similar findings.[149] Additional analysis by University of North Carolina Professor John Vernon and others found that biosimilars will generate prices between 10% and 25% less than the innovator product.[150] A study prepared for the Department of Health and Human Services states that price discounts for follow-on products are expected to be in the 10%-20% range.[151]

Potential Industry Responses

New Biologic License Applications (BLAs)

Companies possess various options in bringing follow-on products to the marketplace. Several firms, including the largest generic drug producer Teva, plan to continue using the established biologics approval process.[152] Companies may choose to make a new innovator biologic for the same medical condition rather than a follow-on drug if the required clinical trials are parallel to those associated with the standard approval process, a biologic license application. "Only a small tweak in the manufacturing process for an already-marketed biologic could offer another 12 years of exclusivity to its owner," rather than any limited exclusivity provided by a designation of "interchangeability."[153]

Collaborative Work with Big Pharma

An accelerated approval process for follow-on biologics may facilitate cooperative efforts between traditional, small-molecule generic drug companies and large pharmaceutical firms ("Big Pharma"). As discussed previously, significant barriers may block the development and commercialization of biosimilars because of the technical challenges associated with manufacturing and the number and breadth of required clinical trials.[154] Additionally, many generic firms may not possess the marketing capabilities that may be necessary to convince

[148] *Emerging Health Care Issues: Follow-on Biologic Drug Competition*, 23.

[149] Henry Grabowski, Iain Cockburn, Genia Long, Richard Mortimer, and Scott Johnson, The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions, August 2007, 2, available at http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

[150] John A. Vernon, Alan Bennet, and Joseph H. Golec, "Exploration of Potential Economics of Follow-On Biologics and Implications for Data Exclusivity Periods for Biologics," *Boston University School of Law, Journal of Science and Technology Law*, 2010, 69, available at http://www.bu.edu/law/central/jd/organizations/journals/scitech/volume161/documents/Vernon_WEB.pdf.

[151] The Lewin Goup and i3 Innovus, *Economic Analysis of Availability of Follow-on Protein Products*, prepared for the Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, July 2009, 54, available at http://aspe.hhs.gov/sp/reports/2009/fopps/report.pdf.

[152] Thomas Gryta, "Biosimilar Development Progresses, Without FDA Guidelines," *SmartMoney*, September 14, 2010, available at http:www.smartmoney.com/news/on/?story=on-20100816-000267 and Lewis Krauskopf, "Interview-Teva Sees Flawed U.S. Biosimilars Process, *Forexpros.com*, June 23, 2010, available at http://www.forexpros.com/news/general-news/interview-teva-sees-flawed-u.s.-biosimilars-process-144818

[153] *PPACA Creates Approval Pathway for Follow-On Biologics*.

[154] *Follow-on Biologics: A New Play for Big Pharma*.

doctors and other providers to use biosimilars. Thus, these companies may partner with the large pharmaceutical firms that have the expertise necessary to penetrate the follow-on market: "With access to financing, well-established sales and marketing, and in some cases existing biotechnology capabilities, these [large] companies may have a real advantage."[155] The extensive workforce of Big Pharma, and the existing relationships with doctors and hospitals, can influence decisions concerning follow-on products which can benefit the generic manufacturer.[156]

Concurrently, large pharmaceutical companies may be interested in collaborating with traditional generic manufacturers to develop follow-on products as an alternative source of revenue.[157] As patents on small-molecule pharmaceuticals expire and drug approvals lag despite increased R&D, some large firms will look to joint efforts to augment the products in their pipeline.[158] Follow-on biologics may look attractive because they "command high prices, will likely have fewer entrants than generics due to high barriers to entry, and play to the existing strengths of big pharma firms."[159]

Biobetters

Another approach to the biologics market is the development of what are termed "biobetters,"

> a drug that is in the same class as an existing biopharmaceutical but is not identical. While a biosimilar should perform as well as the original, a bio-better is expected to have certain advantages, such as improved safety and efficacy.[160]

If the cost to bring a biosimilar to the marketplace is between $100 million to $200 million dollars,[161] it may be more profitable for a firm to develop a biobetter that can compete with the innovator product, establish market share, and obtain 12 years of data exclusivity. Companies producing biobetters will have to use the traditional biologic approval process; however, the risk of failure may be diminished because the innovator product already has been shown to be safe, effective, and commercially successful.[162]

> Generics companies have more than one option: Instead of advancing biosimilars, they can out-compete the pioneer products, increase market share, and avoid start-up costs, building overall profits…. A company starts with a validated drug target, established market, and a proven clinical development approach, but incorporates a simple change in the development process or design of the drug molecule that could drastically improve the product offering. By modifying the pioneer product, a biobetter developer can cut the clinical development

[155] *Big Pharma's Edge in Biosimilars*.

[156] *Follow-on Biologics: A New Play for Big Pharma*.

[157] *Big Pharma's Edge in Biosimilars*.

[158] *Follow-on Biologics: A New Play for Big Pharma*.

[159] Ibid.

[160] Brian Bormley, "A Race To Develop Better-Perfoming Biopharmaceuticals," *Wall Street Journal Blog*, August 10, 2010, available at http://blogs.wsj.com/venturecapital/2010/08/10/a-race-to-develop-better-performing-biopharmaceuticals/.

[161] *Emerging Health Care Issues: Follow-on Biologic Drug Competition*, iii.

[162] Jonathan D. Rockoff, "Merck Scraps One-Promising Follow-On Biologic for Anemia," *Wall Street Journal Health Blog*, May 11, 2010, available at http://blogs.wsj.com/health/2010/05/11/merck-scraps-once-promising-follow-on-biologic-for-anemia/.

> risk associated with an entirely new molecule, and still compete with the originator's product.[163]

Similarly, innovator biologic firms may develop biobetters as a means to bring to market new versions of their existing biopharmaceuticals or to create competing products. For example, MedImmune (acquired by AstraZeneca in 2007) does not plan to enter the follow-on biologics market, but instead will undertake development of biobetters.[164] The intent is to improve the original biologic and use this to achieve a market advantage.[165] "Superior product will give pharmaceutical companies the edge to offset competition from an FOB [sic] that has no distinct advantage over the first-generation product."[166]

Concluding Observations

This overview of the new legislation 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.[167]

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.[168]

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 be litigated, at least initially.[169] The failure of brand-name firms to act within tight statutory deadlines may result in substantial patent enforcement penalties.[170] And, unlike the Hatch-Waxman Act, the BPCIA does not tightly link FDA approval with patent rights. Brand-name

[163] Bassil Dahiyat, "Innovation Over Imitation," *PharmExec.com*, November 4, 2009, available at http://license.icopyright.net/user/viewFreeUse.act?fuid=MTAxODg3NDg%3D.

[164] Laura Bush, "MedImmune's Greenleaf on Biopharmaceutical Innovation and Biobetters," BioPharmInternational.com, May 19, 2010, available at http://biopharminternational.findpharma.com/biopharm/News/MedImmunes-Greenleaf-on-Biopharmaceutical-Innovati/ArticleStandard/Article/detail/670622.

[165] David E. Szymkowski, "True Biosimilars Do Not Offer a Compelling Business Case," *PharmTech.com*, August 1, 2010, available at http://pharmtech.findpharma.com/xencor.

[166] *Innovation Over Imitation*.

[167] See Czaban, *supra*.

[168] Ibid.

[169] 42 U.S.C. §262(l)(5)(A).

[170] 35 U.S.C. §271(e)(6)(B).

firms must wholly rely upon the judiciary to stay the release of follow-on biologics into the marketplace.[171]

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 pharmaceutical patent law would be wise to remain vigilant concerning developments to the new law of follow-on biologics in coming years.

Author Contact Information

John R. Thomas
Visiting Scholar
jrthomas@crs.loc.gov, 7-0975

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[171] See Dougherty, *supra*.