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Follow-On Biologics: Intellectual Property and Innovation Issues

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Summary

Biologics, which are sometimes termed biopharmaceutials or biotechnology drugs, have begun to play an increasingly important role in U.S. health care. Not only are sales of biologics growing rapidly, some experts estimate that in coming years half of all newly approved drugs will result from biotechnology.

A number of patents pertaining to certain biological products will expire in the near future. Some congressional concern has been voiced over the possibility that these patent expirations may not be accompanied by the introduction of competing, lower-cost biologics in the marketplace. With respect to traditional pharmaceuticals, the Drug Price Competition and Patent Term Restoration Act of 1984, a statute commonly known as the "Hatch-Waxman Act," is widely believed to have encouraged the availability of generic substitutes for brand-name pharmaceuticals upon patent expiration. The Act in part permitted the Food and Drug Administration to expedite its marketing approval proceedings with respect to generic drugs.

Some observers believe that the Hatch-Waxman Act's accelerated marketing approval provisions do not comfortably apply to biologics, however. Biologics differ significantly from traditional small-molecule pharmaceuticals in their size, structural complexity, and method of manufacture. Competitors who wish to develop follow-on biologics may face difficult, and even insurmountable difficulties in demonstrating that their product is equivalent to a particular brand-name biologic. Other commentators assert that different kinds of biologics vary considerably in their size and structure, and believe that existing Hatch-Waxman mechanisms are appropriately applied to many biologics.

The patent system also plays a role in regulating competition in the biologics market. Patent protection is available for biologics in many circumstances, although the scope of protection may be limited by legal principles that restrict the availability of proprietary rights in naturally occurring substances.

Several bills introduced in the first session of the 110th Congress, including H.R. 1038, S. 623, H.R. 1956, S. 1505, S. 1695 (ordered to be reported, with amendments in the nature of a substitute), and H.R. 5629 would have created an expedited marketing approval pathway for follow-on biologics within the Public Health Service Act. The bills vary in important details, such as the need for the FDA to have promulgated regulatory guidance with respect to particular product classifications prior to receiving follow-on applications. Certain of these bills would establish specialized patent dispute resolution proceedings with respect to follow-on biologics. A number also created varying periods of data exclusivity for biologic products, both in favor of brand-name firms and follow-on companies.

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Follow-On Biologics: Intellectual Property and Innovation Issues

Longstanding congressional interest in the availability and cost of pharmaceuticals has focused attention upon the increasingly significant class of drugs known as "biologics."[1] 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. The Food and Drug Administration (FDA) issued marketing approval on 36 biotechnology drugs in 2002; it also approved 37 in the following year, 40 in 2004, 38 in 2005, and 36 in 2006.[2] Many more new biologics reportedly are in the approval process.[3] Today, 20% of the drugs on the market are biologics, according to Pfizer's Corey Goodman.[4] Federico Polliano, head of business development at BioGeneriX, a biotechnology company, projects that 50% of approved pharmaceuticals in 2010 will be the result of biotechnology.[5]

Dramatic growth in the number of approved drugs has been accompanied by a similar expansion in sales. IMS Health, a consulting firm, found that in 2005, the size of the U.S. biologics market was on the order of $52 billion. According to its analysis, the biologics market grew at a rate of 17%, greater than any other portion of the pharmaceutical market.[6] Some experts further project that the global biologics

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[1] The term "biologic" has been described as "poorly defined," and its precise parameters are themselves subject to debate. *See* David M. Dudzinski, "Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies," 60 *Food and Drug Law Journal* (2005), 143. The Public Health Service defines the term "biological product" to mean "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i) (2006). Biologics are also sometimes termed "biotechnology drugs" or "biopharmaceuticals." Dudzinski at 143.

[2] Biotechnology Industry Organization, available at [http://www.bio.org] and Ernst & Young, *Beyond Borders, Global Biotechnology Report 2007*, 25.

[3] 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].

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

[5] "Biogenerics: A Difficult Birth?" *IMS Global Insights*, available at [http://www.imshealth.com].

[6] Nicole Gray, "Harbingers of Change," *Pharmaceutical Executive*, May 2005, available at

(continued...)

market will expand to $67 billion by 2010.[7] Awareness of the increasing importance of biopharmaceuticals has been accompanied by an appreciation that patents covering many of these products will soon expire. Andrew Forman of WR Hambrecht concludes, for example, that $20 billion in biotech drugs worldwide will be off patent by 2010.[8]

Some commentators have expressed concerns that patent expirations may not be accompanied by the introduction of competing, lower-cost biologics in the marketplace.[9] 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 Drug Price Competition and Patent Term Restoration Act of 1984, a statute commonly known as the "Hatch-Waxman Act."[10] This legislation introduced several significant changes to both the patent law and the food and drug law. Among them were expedited marketing approval pathways that eliminated, in whole or in part, the need for firms to conduct expensive and time-consuming clinical trials when they bring generic equivalents of brand-name drugs to market.[11] The Hatch-Waxman amendments were designed to facilitate the rapid introduction of lower-cost generic drugs, while at same time promoting innovation in the pharmaceutical industry.[12]

Technical factors may limit the effectiveness of the Hatch-Waxman amendments to biologics, however. Biologics differ significantly from traditional pharmaceuticals in their complexity and method of manufacture. Typical pharmaceutical products consist of small molecules, on the order of dozens of atoms, that may be readily characterized and reproduced through well-understood chemical processes. 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.[13] As a result, the technical challenges that

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[6] (...continued)
[http://www.imshealth.com]; Nicole Gray, "Keeping Pace with the Evolving Pharmaceutical Business Model," *Pharmaceutical Executive*, May 2006, available at [http://www.imshealth.com].

[7] Ramsey Baghdadi, "Biogenerics Are Happening: Slowly, Product-By-Product," *The RPM Report*, January 2006, available at [http://www.theRPMreport.com].

[8] Aaron Smith, "Barr's Risky $2.5 Billion Bid for Biogenerics," *CNNMoney.com*, September 15, 2006. *See also* Research and Markets, "The Biogenerics Market Outlook: An Analysis of Market Dynamics, Growth Drivers and Leading Players," *Business Wire*, September 12, 2005, available at [http://www.findarticles.com/p/articles/mi_mOEIN/] is_2005_Sept_12/ai_n15382946/print.

[9] *See* Dudzinski, supra.

[10] P.L. 84-417, 98 Stat. 1585 (1984).

[11] *See* 21 U.S.C. § 355(b)(2) (2006) (with respect to § 505(b)(2) applications); *id.* § 355(j)(1) (with respect to ANDAs).

[12] *See* John R. Thomas, *Pharmaceutical Patent Law* (Bureau of National Affairs, 2005).

[13] *See* Melissa R. Leuenberger-Fisher, "The Road to Follow On Biologics: Are We There (continued...)

a competitor faces in developing a product that may be viewed as equivalent to a particular brand-name biologic product may be considerable, and in some cases perhaps even insurmountable.[14] For this reason, many experts do not describe competing biologic products as "generics," as is the case for a small-molecule pharmaceuticals; the terms "follow-on biologic" or "biosimilar" are commonly used instead.[15]

Some commentators assert that these technical challenges may also mean that the expedited approval pathways available under the Hatch-Waxman Act do not comfortably apply to biologics. Because the complexity of biologics is an order of magnitude greater than that associated with pharmaceuticals, they say, an expedited marketing approval protocol would not ensure patient safety to the degree possible with respect to traditional drugs.[16] Others observe that different kinds of biologics vary considerably in their size and structure, and believe that existing Hatch-Waxman mechanisms provide appropriate regulatory oversight for less complex biologics. These observers further explain that as scientific knowledge progresses, understanding of biologics will increase, thereby allowing expanded use of current procedures.[17] Legislation was introduced in the first session of the 110th Congress that would amend the Public Health Service Act (PHS Act)[18] to provide an expedited marketing approval pathway for follow-on biologics.[19]

FDA marketing approval is not the only gatekeeper to competition in the biologics market. The patent system also has a role to play. Although patent protection may be available for biologics in many circumstances, these patents may be limited by legal principles that restrict proprietary rights in naturally occurring substances.[20] Further, although key patents on many biologics are set to expire, other products may potentially remain protected by patents for many years to come. In recognition that the public possesses an interest in prompt challenges to drug patents that are believed to have been improvidently granted, the Hatch-Waxman Act

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[13] (...continued)
Yet?," 23 *Biotechnology Law Report* (August 2004), 389.

[14] *See* Dawn Willow, "The Regulation of Biologic Medicine: Innovators' Rights and Access to Healthcare," 6 *Chicago-Kent Journal of Intellectual Property* (2006), 32.

[15] *Id.*

[16] *See* Dudzinski, *supra* (noting such concerns).

[17] *See* Narinder S. Banait, *Follow-on Biological Products — Legal Issues*, 2005, available at [http://www.fenwick.com/docstore/Publications/IP/follow-on.pdf].

[18] P.L. 78-410, 58 Stat. 682 (1944).

[19] *See* H.R. 1038 and S. 623 ("Access to Life-Saving Medicine Act"); H.R. 1956 ("Patient Protection and Innovative Biologic Medicines Act of 2007"); H.R. 5629 ("Pathway for BioSimilars Act"); S. 1505 ("Affordable Biologics for Consumers Act") and S. 1695 ("Biologics Price Competition and Innovation Act of 2007").

[20] *See, e.g,* J.E.M. Ag Supply v. Pioneer Hi-Bred Int'l, Inc., 534 U.S. 124, 130 (2001) (explaining patent law principle that "products of nature" are not eligible for patenting, but that patents may be available for "human-made inventions" resulting from the use of biotechnology).

introduced incentives for firms to bring such challenges along with special procedures for resolving them in the courts.[21] The legislation introduced in the 110th Congress would account for the patent implications of follow-on biologics somewhat differently.

This report reviews doctrinal and policy issues pertaining to follow-on biologics. The report first introduces the application of federal food and drug legislation to follow-on biologics. It next turns to the patent implications of marketing follow-on biologics. Following this review of substantive law, the remainder of the report introduces innovation policy issues pertaining to follow-on biologics.

Expedited Marketing Approval Issues

Efforts to speed approval of follow-on biologics have been based upon the Hatch-Waxman Act.[22] Enacted in 1984, that statute amended the Federal Food, Drug, and Cosmetic Act (FDC Act) in part by introducing two regulatory pathways allowing for the expedited marketing approval of generic pharmaceuticals. Many policy and industry experts agree that the Hatch-Waxman Act has significantly effected the availability of generic substitutes for brand name drugs.[23] Generics are often rapidly available after patent expiration, commonly at lower prices than the brand-name original. Concurrently, given the increasing investment in research and development (R&D) and the gains in research intensity of the pharmaceutical industry, it appears that the 1984 Act has not deterred the search for, and the development of, new drugs.[24]

At issue is whether the existing Hatch-Waxman Act protocols, or a similar construct created through new legislation, could be effectively implemented for follow-on biologics. The difficulty characterizing biologics, along with the importance of manufacturing techniques to the final product, have created debate around the applicability of expedited marketing approval mechanisms for these products. This report next describes issues pertaining to the accelerated marketing approval of follow-on biologics.

Expedited Marketing Approval for Pharmaceuticals

The FDC Act has, since 1962, prohibited the marketing of a "new drug" unless that drug meets certain safety and efficacy standards. Sponsors of new drugs must submit, among other documents, a New Drug Application (NDA) demonstrating that

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[21] *See* Thomas, *supra* note 11.

[22] P.L. 84-417, 98 Stat. 1585 (1984).

[23] For additional information see CRS Report RL30756, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act")*, by Wendy H. Schacht and John R. Thomas, and CRS Report RL32377, *The Hatch-Waxman Act: Legislative Changes Affecting Pharmaceutical Patents*, by Wendy H. Schacht and John R. Thomas.

[24] *See* Thomas, *supra*.

these standards have been met in order to obtain marketing approval. A typical NDA is a complex, lengthy document that presents clinical data; chemistry, manufacturing and controls; nonclinical pharmacology and toxicology; safety update reports; and other salient information.[25] Brand-name drug companies commonly devote considerable resources, over many years, to complete the studies necessary to submit a NDA.

Prior to the passage of the Hatch-Waxman Act, the federal food and drug law contained no separate provisions addressing generic versions of drugs that had previously been approved.[26] The result was that a would-be generic drug manufacturer most often had to file its own NDA in order to market its drug.[27] Some generic manufacturers were forced to prove independently that the drugs were safe and effective, even though their products were chemically identical to those of previously approved drugs. Some commentators believed that the approval of a generic drug was a needlessly costly, duplicative, and time-consuming process prior to the Hatch-Waxman Act.[28] These observers noted that although patents on important drugs had expired, manufacturers were not moving to introduce generic equivalents for these products due to the level of resource expenditure required to obtain FDA marketing approval.[29]

In response to this concern, the Hatch-Waxman Act created two new types of applications for marketing approval of a generic pharmaceutical. One is termed an "Abbreviated New Drug Application" (ANDA).[30] An ANDA may be filed, generally speaking, if the active ingredient, route of administration, the dosage form, and the strength of the new drug are the same as those of the approved drug. An ANDA allows a generic drug manufacturer to rely upon the safety and efficacy data of the original manufacturer. The availability of an ANDA typically permits a generic manufacturer to avoid the costs and delays associated with filing a full-fledged NDA.

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[25] *See* Apotex Inc. v. FDA, 393 F.3d 210, 212 (D.C. Cir. 2004).

[26] *See* Alfred B. Engelberg, "Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness?" 39 *IDEA: J. L. & TECH.* 389, 396 (1999).

[27] *See* James J. Wheaton, "Generic Competition and Pharmaceutical Innovation: The Drug Price Competition and Patent Term Restoration Act of 1984," 34 *CATH. UNIV. L. REV.* 433, 439 (1986).

[28] *See, e.g.,* Justina A. Molzon, "The Generic Drug Approval Process," 5 *J. PHARM. & L.* 275, 276 (1996) ("The Act streamlined the approval process by eliminating the need for [generic drug] sponsors to repeat duplicative, unnecessary, expensive and ethically questionable clinical and animal research to demonstrate the safety and efficacy of the drug product.").

[29] *See* Jonathon M. Lave, "Responding to Patent Litigation Settlements: Does the FTC Have It Right Yet?" 64 *U. PITT. L. REV.* 201, 202 (2002) ("Hatch-Waxman has also increased the generic drug share of prescription drug volume by almost 130% since its enactment in 1984. Indeed, nearly 100% of the top selling drugs with expired patents have generic versions available today versus only 35% in 1983.").

[30] 21 U.S.C. § 355(j)(1) (2006).

ANDAs also allow a generic manufacturer, in many cases, to place its FDA-approved bioequivalent drug on the market as soon as any relevant patents expire.[31]

The Hatch-Waxman Act also authorized a so-called "§ 505(b)(2) application." A § 505(b)(2) application is one for which one or more of the investigations relied upon by the generic applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted...."[32] A § 505(b)(2) application differs from an ANDA in that it includes full reports of investigations concerning the safety and effectiveness of the proposed product. However, a § 505(b)(2) application is distinct from an NDA in that the § 505(b)(2) application relies upon data that the applicant did not develop.[33]

According to the FDA, a § 505(b)(2) applicant can rely upon two sources of studies "not conducted by or for the applicant and for which the applicant has not obtained a right of reference."[34] The first source consists of safety and efficacy analysis based upon data that the applicant did not originate itself and does not enjoy an express permission to access. This category of information typically consists of published scientific literature. As a result, § 505(b)(2) applications are sometimes referred to as "paper NDAs."

With respect to the second source of appropriate information, the FDA has declared that a § 505(b)(2) applicant may rely upon that agency's own finding of safety and effectiveness for an approved drug.[35] The FDA's conclusion allows applicants that wish to market a modification of an approved drug to file a § 505(b)(2) application rather than a full NDA. For example, suppose that an approved drug employed an active ingredient with a particular salt formulation. A generic firm seeks to market a generic version of the approved drug with the same active moiety, but using a different salt formulation.[36] Under these circumstances, the generic firm may be unable to file an ANDA because its proposed active ingredient is not identical to that of the approved product.[37] Due to the FDA's view, however, the generic firm could file a § 505(b)(2) application that relied upon the FDA's previous approval of the innovator drug, along with studies supporting the change in the salt

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[31] *See, e.g.,* Sarah E. Eurek, "Hatch-Waxman Reform and Accelerated Entry of Generic Drugs: Is Faster Necessarily Better?" 2003 *DUKE L. & TECH. REV.* 18 (August 13, 2003).

[32] 21 U.S.C. § 355(b)(2) (2004). The name of this application refers to its section number within the Hatch-Waxman Act itself. This provision has been codified at 21 U.S.C. § 355(b)(2), where it may be more conveniently located.

[33] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), *Guidance for Industry: Applications Covered by Section 505(b)(2)* at 2-3 (October 1999) [hereinafter "*Section 505(b)(2) Guidance*"].

[34] *Id.*

[35] *Id.*

[36] *See* Pfizer, Inc. v. Dr. Reddy's, 359 F.3d 1361, 69 USPQ2d 2016 (Fed. Cir. 2004).

[37] 37 C.F.R. § 314.93(b) (2004).

formulation from the innovator drug.[38] As may be appreciated, the availability of a § 505(b)(2) application likely leads to a substantial reduction in the costs of the generic firm in this case in comparison with the resources required to file a full NDA.

The FDA interpretation of § 505(b)(2) regarding this second source of information has been criticized. Some observers believe that under a plain reading of the Hatch-Waxman Act, a generic applicant may rely upon an innovator's proprietary data only when filing an ANDA application, not a § 505(b)(2) application. Under this view, the FDA position inappropriately expands the circumstances to which a § 505(b)(2) application applies.[39] Despite this critique, the FDA has taken the position that its "approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug."[40]

Application to Biologics

The Hatch-Waxman Act, including its expedited approval pathways, may potentially apply to biologics. This result follows because the Hatch-Waxman Act in part amended the FDC Act, which in turn applies to "drugs."[41] The Hatch-Waxman Act did not amend a distinct statute, the Public Health Service Act (PHS Act),[42] which applies specifically to biological products and contains no provisions allowing expedited marketing approval for follow-on biologics. Because the definition of "drugs" under the FDC Act is broad, however, the FDA states that "[b]iological products subject to the PHS Act also meet the definition of drugs under the Federal Food, Drug, and Cosmetic Act."[43] Under this interpretation, both expedited marketing approval pathways — the ANDA and the § 505(b)(2) application — could potentially be available for pharmaceuticals and biologics alike.[44]

Many observers believe that the possibility of employing an ANDA for a biologic is currently more theoretical than real, however, due to differences between this class of drugs and conventional pharmaceuticals. Two of the more significant differences are the increased complexity of biologics vis-à-vis pharmaceuticals, as

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[38] *Section 505(b)(2) Guidance* at 5.

[39] *See* Bruce N. Kuhlik, "The Assault on Pharmaceutical Intellectual Property," 71 *U. CHI. L. REV.* 93, 103-04 (2004).

[40] *Section 505(b)(2) Guidance* at 3.

[41] The FDC Act defines the term "drug" to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals...." 21 U.S.C. § 321(g)(1)(B).

[42] P.L. 78-410, 58 Stat. 682 (1944).

[43] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "Frequently Asked Questions About Therapeutic Biological Products"(available at [http://www.fda.gov/cder/biologics/qa.htm]).

[44] Further discussion of this issue may be found at Willow, *supra.*

well as the importance of the particular manufacturing process employed to produce a biologic. Food and drug lawyers have stated:

> Biologics differ significantly from traditional drugs in their size, complexity, structure, and method of manufacture. Drug products consist of small molecules, on the order of dozens of atoms synthesized from defined components according to a prescribed production method in an environment of manufacturing processes and controls. Biological products are much larger than drugs, made up of millions of atoms, and are manufactured from living cells through an elaborate process initiated by specifically programming a cell line to produce a certain protein in a highly controlled, sterile manufacturing environment.[45]

> Characteristic properties of biologics include a very high molecular weight and high structural complexity, a heterogeneous molecular make-up, varying levels of hard-to-remove biological impurities (bacteria, viruses and the like) and a high degree of sensitivity to environmental conditions.[46]

These traits of biologics make the manufacturing process critical to the final product. It has been argued that "[t]he production process is 90 percent of the intellectual property related to the product."[47] In contrast to traditional drugs, which are manufactured by chemical synthesis,[48] the production of biologics is more complex:

> [M]anufacturing biologics requires the nourishment and support of living host cells transfected with genetically engineered DNA to code for the desired biological protein that is expressed by the host cell. A master cell bank must be established, and host cells are cultured and fermented in large-scale bioreactors to produce commercial quantities of the desired protein.[49]

Not only are the characteristics of a biologic "clearly dependent on the process used to manufacture the product," such information is ordinarily protected via trade secrets.[50] As a result, some observers have opined that a "manufacturer would have

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[45] Gary C. Messplay and Colleen Heisey, "Follow-On Biologics: The Evolving Regulatory Landscape," *BioExecutive International*, May 2006, 43.

[46] Stephen B. Judlowe and Brian P. Murphy, *Proposed Legislation for Follow-On Biologic Pharmaceuticals in the US*, Morgan, Lewis & Backius, LLP, New York available at [http://www.buildingipvalue.com/05_NA/135_138.htm].

[47] Debra Weintraub, "Next Generation of Biopharmaceuticals," *Journal of Managed Care Medicine*, vol. 9, no. 1, 2006, available at [http://www.namcp.com/Journals /JMCM/Articles/Next%20Generation%20of%20Biopharmaceuticals.pdf].

[48] Henry Grabowski, Iain Cocburn, and Genia Long, "The Market For Follow-On Biologics: How Will It Evolve?," *Health Affairs,* September/October 2006, 1292.

[49] Judlowe & Murphy, *supra* note 44.

[50] Bruce S. Manheim Jr., Patricia Granahan, and Kenneth J. Dow, "'Follow-On Biologics': Ensuring Continued Innovation In The Biotechnology Industry," *Health Affairs*, March/April 2006, 397.

great difficulty producing a follow-on protein that is identical to the innovator product."[51]

The complexity of biological products and the importance of the particular manufacturing process used to produce them may make the showing that a follow-on product is the "same" as a previously approved biologic difficult, if not impossible.[52] Former Acting FDA Commissioner Lester Crawford has explained that "because protein drug products are large, complex molecules, derived from biological sources, generally it has not been possible to assess relative sameness with a high degree of confidence."[53] Some observers have gone further, opining that true "generic" biologics cannot exist because they cannot be judged to be the "same"as the brand-name product, a requirement that the Hatch-Waxman Act imposes with respect to an ANDA.[54]

Other commentators believe that scientific capabilities currently allow manufacturers to produce follow-on biologics that are safe and effective.[55] For example, the Generic Pharmaceutical Association (GPhA)

> strongly believes FDA's current statutory structure would permit approvals and marketing of an array of generic biopharmaceuticals (also referred to as 'biologics') with relatively low to moderate complexity, and to expand [sic] that system in the coming years to permit the approval of more complex products as the science evolves.[56]

Israel Makov, president and CEO of Teva, argues that biologic products can be adequately characterized and manufacturing processes do not necessarily affect the final drug.[57] Similarly, Patrick Vink, Global Head of Biopharmaceuticals at Sandoz, maintains both that the science is in place to assess follow-on biologics appropriately, and that unnecessary clinical trials should not be mandatory. Instead, he advocates that bioequivalence testing should be required on a case-by-case basis.[58]

In this regard, some commentators have suggested that potential manufacturers of follow-on biologics employ § 505(b)(2) applications in appropriate cases. The statutory requirements for § 505(b)(2) applications do not require that the follow-on

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[51] *Id.*

[52] *See* Weintraub, *supra* note 45.

[53] Judlowe & Murphy, *supra*.

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

[55] Judlowe & Murphy, *supra*.

[56] Generic Pharmaceutical Association, *Generic Biopharmaceuticals*, available at [http://www.gphaonline.org]

[57] Selena Class, "Biogenerics: Waiting for the Green Light," *IMS Global Insights*, October 28, 2004 (available at [http://www.imshealth.com]).

[58] *Id.*

product be the "same" as the approved product. Rather, the applicant must provide clinical data demonstrating the follow-on product to be safe and effective, but may rely upon data generated by the brand-name firm itself, or by third parties.[59] The applicant must substantiate the "relevance and applicability" of previous findings to the follow-on product, however, and may need to supply clinical data to describe any relevant distinctions between the brand-name biologic and the follow-on product.[60]

It should be appreciated that some observers believe that § 505(b)(2) applications are inappropriate for biologics, however. For example, the Biotechnology Industry Organization (BIO) has asserted that:

> Approval of follow-on biotechnology products must be based on the same rigorous standards applied by the FDA for the approval of pioneer biotechnology products.... Currently, the science does not exist to provide an alternative to a full complement of data, including clinical evidence, to demonstrate safety and effectiveness for follow-on biotechnology products.... Therefore, in the current state of scientific knowledge and technique, a clinical trial remains a fundamental principle for evaluating the safety and effectiveness of a follow-on biotechnology product.[61]

Proposed Legislation

Legislation proposed in the 110th Congress would have amended the Public Health Service Act in order to provide an expedited marketing approval pathway for biologics that are "comparable" to previously approved brand-name products. The Access to Life-Saving Medicine Act, introduced as H.R. 1038 and S. 623, would grant the Secretary of Health and Human Services (HHS) certain discretion to determine, on a case-by-case basis, what studies were necessary to establish comparability. A comparable biologic would be required to have comparable principal structural features with the corresponding brand-name product; the same mechanism of action, if known; and the same route of administration, dosage form, and strength, among other factors.[62]

Under these bills, an applicant for a comparable biological product would be allowed optionally to elect to establish "interchangeability" with the brand-name product.[63] If the follow-on applicant's product was expected to produce the same clinical result as the brand-name product, then the follow-on product could be labeled as such.

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[59] Narinder S. Banait, "Follow-on Biological Products — Legal Issues" (2005) (available at [http://www.fenwick.com]).

[60] 21 U.S.C. § 355(b)(2) (2006).

[61] Biotechnology Industry Organization, *Follow-on Biotechnology Products* (available at [http://www.bio.org/healthcare/followon/]).

[62] H.R. 1038 at § 3; S. 623 at § 3.

[63] H.R. 1038 at § 3; S. 623 at § 3.

Two other bills, H.R. 1956, the Patient Protection and Innovative Biologic Medicines Act of 2007, and S. 1505, the Affordable Biologics for Consumers Act, instead call for the Secretary of Health and Human Services initially to publish a number of individual guidance documents, each relating to a particular class of biological products. That "product-class specific guidance" would stipulate the particular data and information required to file a marketing approval application for products within that category. Interested parties would then be permitted to file applications for similar biological products within that category at a certain date, generally not less than 12 years after approval or licensing of the reference product.

S. 1695, the Biologics Price Competition and Innovation Act of 2007, and H.R. 5629 take another approach. Under these bills, a follow-on biologic may be designated as either a "biosimilar" or an "interchangeable" product. In general, 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 have been previously approved for the reference product, and (4) the route of administration, dosage form, and strength of the two products are the same. A follow-on product is interchangeable if (1) it can be expected to product 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.[64]

Intellectual Property Issues

Patent Protection for Biologics

As with pharmaceuticals, biologics may be subject to patent protection provided certain conditions are met.[65] An award of marketing approval by the FDA and the grant of a patent by the U.S. Patent and Trademark Office (USPTO) are distinct events that depend upon different criteria. FDA procedures determine whether the drug is sufficiently safe and effective to be marketed. In contrast, the USPTO grants patents on inventions that fulfill requirements established by the Patent Act of 1952, including utility, novelty, and nonobviousness.[66] Because patent proprietors may be able to block competitors during the term of the patent,[67] these intellectual property rights also play a role in the marketplace availability of follow-on biologics.

Although a complete review of the patent system exceeds the scope of this report, its basic contours may be concisely stated. The Patent Act allows inventors

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[64] For additional information, see CRS Report RL34045, *FDA Regulation of Follow-On Biologics*, by Judith A. Johnson.

[65] *See* CRS Report RL30648, *An Examination of the Issues Surrounding Biotechnology Patenting and Its Effect on Entrepreneurial Companies*, by John R. Thomas.

[66] *See* 35 U.S.C. §§ 101, 102, 103 (2006).

[67] 35 U.S.C. § 271(2006).

to obtain patents on processes, machines, manufactures, and compositions of matter that are useful, novel and nonobvious.[68] An invention is judged as useful if it is minimally operable towards some practical purpose.[69] To be considered novel within the patent law, an invention must differ from existing references that disclose the state of the art, such as publications and other patents.[70] The nonobviousness requirement is met if the invention is beyond the ordinary abilities of a skilled artisan knowledgeable in the appropriate field.[71]

In order to receive a patent, an inventor must file a patent application with the USPTO.[72] Patent applications must include a specification that so completely describes the invention that skilled artisans are enabled to practice it without undue experimentation.[73] The patent application must also contain distinct, definite claims that set out the proprietary interest asserted by the inventor.[74]

Trained personnel at the USPTO, known as examiners, review all applications to ensure that the invention described and claimed in the application fulfills the pertinent requirements of the patent law. If the USPTO believes that the application fulfills the statutory requirements, it will allow the application to issue as a granted patent.[75] Each patent ordinarily enjoys a term of twenty years commencing from the date the patent application was filed.[76] If the patent proprietor was unable to market its product for a period of the patent term due to lack of approval by the FDA, the term may be extended by a portion of the regulatory review period in some circumstances.[77]

Granted patents give the patentee the right to exclude others from making, using, selling, offering to sell, or importing into the United States the patented invention.[78] Parties who engage in those acts without the permission of the patent proprietor during the term of the patent can be held liable for infringement. The patentee may file a civil suit in federal court in order to enjoin infringers and obtain monetary remedies.[79] Although issued patents enjoy a presumption of validity,

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[68] 35 U.S.C. §§ 101, 102, 103 (2006).

[69] *See* Brenner v. Manson, 383 U.S. 519, 86 S.Ct. 1033, 16 L.Ed.2d 69 (1966).

[70] 35 U.S.C. § 102 (2006).

[71] 35 U.S.C. § 103(a) (2006).

[72] 35 U.S.C. § 111 (2006).

[73] 35 U.S.C. § 112 (2006).

[74] 35 U.S.C. § 112 (2006).

[75] 35 U.S.C. § 151 (2006).

[76] 35 U.S.C. § 154 (2006).

[77] 35 U.S.C. § 156 (2006).

[78] 35 U.S.C. § 271(a) (2006).

[79] 35 U.S.C. § 281 (2006).

accused infringers may assert that the patent is invalid or unenforceable on a number of grounds.[80]

A few patent law principles have particular impact upon biologics. First, the courts have generally concluded that novel and nonobvious products and processes of biotechnology may be patented, notwithstanding the fact that the invention derives from the field of biochemistry or is itself a "living invention." In *Diamond v. Chakrabarty*,[81] for example, the Supreme Court held a genetically modified bacterium was patentable. The Court explained that the inventor's "claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter — a product of human ingenuity 'having a distinctive name, character [and] use.'"[82]

Biotechnology firms may at times confront the longstanding patent law principle that a naturally occurring substance may not be patented as such.[83] For example, a scientist could not obtain a patent on a previously unknown plant that she discovered growing in the wild. A patent may be obtained once significant artificial changes are made to that natural substance, however. For example, a biological substance that is discovered in nature and isolated from its source may be subject to patent protection. Amgen's Epogen®, a genetically engineered form of erythropoietin that combats anemia by encouraging the production of red blood cells, provides one example of a patented biologic.[84]

In addition, a patent may be available for a new process used to manufacture a known biologic.[85] Suppose, for example, that a naturally occurring biological agent and its activity are already known to the state of the art. The contribution of the biotechnology firm is to develop a manufacturing process that allows for widespread, commercial use of that agent. In this scenario, the biotechnology firm may obtain a patent on the manufacturing process, but not upon the biological agent itself. It should be appreciated that the value of such a process patent will depend upon whether competitors will be able to employ a distinct manufacturing process in order to create a comparable final product. Because of the potential ability of competitors to design around process patents, some observers believe that process patents may

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[80] 35 U.S.C. § 282 (2006).

[81] 473 U.S. 303 (1980).

[82] *Id.* at 309-10.

[83] *See* Diamond v. Diehr, 450 U.S. 175, 185 (1980) ("Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas.").

[84] U.S. Patent No. 5,955,422 (claiming in part "[a] pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture."). *See also* Amgen, Inc. v. Hoechst Marion Roussel, Inc., 457 F.3d 1293 (Fed. Cir. 2006).

[85] *See* Alix Weisfeld, "How Much Intellectual Property Protection Do the Newest (and Coolest) Biotechnologies Get Internationally?," 6 *Chicago Journal of International Law* (2006), 833.

be of less significance in the marketplace than patents directed towards the final product itself.[86]

The Hatch-Waxman Act, Intellectual Property, and Biologics

In addition to creating expedited marketing approval pathways for generic drugs, the Hatch-Waxman Act incorporated numerous additional provisions pertaining to intellectual property.[87] Among these provisions are a statutory exemption from claims of patent infringement based on acts reasonably related to seeking FDA approval (commonly know as the "safe harbor"); patent term extension for a portion of the time spent seeking marketing approval; special provisions for challenging the enforceability, validity, or infringement of approved drug patents; data exclusivities for brand-name firms; and a reward for challenging patent enforceability, validity, or infringement consisting of 180 days of generic exclusivity to the first generic applicant to file a patent challenge against any approved drug.[88]

The applicability of the intellectual property provisions of the Hatch-Waxman Act to biologics presents complex issues. Some of the provisions of the Hatch-Waxman Act plainly apply to biologics, whether they were approved under the FDC Act or the PHS Act. In particular, the patent term extension and "safe harbor" provisions found in Title II of the Hatch-Waxman Act were enacted as general amendments to the Patent Act (Title 35 of the U.S. Code). The patent term extension statute, codified at 35 U.S.C. § 156, specifically accounts for the possibility of a "human biological product" approved under the Public Health Service Act. The "safe harbor" provision, found at 35 U.S.C. § 271(e)(1), has been construed to apply to biologics as well.[89]

Congress framed the remaining intellectual property provisions of the Hatch-Waxman Act, including those establishing data exclusivities and specialized dispute resolution proceedings, as specific amendments to the FDC Act.[90] These provisions

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[86] *See* Dennis J. Karjala, "Biotech Patents and Indigenous Peoples," 7 *Minnesota Journal of Law, Science, and Technology* (2006), 483.

[87] P.L. 84-417, 98 Stat. 1585 (1984).

[88] A more detailed discussion of the Hatch-Waxman Act is found at CRS Report RL30756, *Patent Law and Its Application to the Pharmaceutical Industry: An Examination of the Drug Price Competition and Patent Term Restoration Act of 1984 ("The Hatch-Waxman Act")*, by Wendy H. Schacht and John R. Thomas.

[89] *See* Patent Fairness Act of 1999: Hearing on H.R. 1598 Before the House Comm. on the Judiciary, 106th Cong. 94 (1999) (statement of Hon. Henry A. Waxman, Member, House Comm. on Government Reform) (available at [http://commdocs.house.gov/committees/judiciary/hju62499.000/hju62499_0f.htm]).

[90] The term "data exclusivity" refers to a period of time during which an applicant for FDA marketing approval may not rely upon the preclinical, clinical, or other data developed and submitted by another firm. Data exclusivity does not preclude the FDA from approving an application for marketing approval when the applicant has itself conducted, or has a right of access to, preclinical, clinical, or other data generated by another company. Some

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would therefore apply to biologics only to the extent they were governed by the FDC Act. To the extent that a particular biologic is approved under the auspices of the PHS Act, however, these provisions would be inapplicable.[91]

Should the FDC Act apply to a particular biologic, one of its more notable intellectual property provisions relates to so-called marketing exclusivities. The term "marketing exclusivity" refers to a period of time during which the FDA affords an approved drug protection from competing applications for marketing approval. Among the marketing exclusivities is a five-year period available for drugs that qualify as new chemical entities. Should the drug's sponsor submit new clinical studies in support, that sponsor may obtain a three-year period of data exclusivity that applies to the use of the product that was supported by the new clinical study.

Proposed Legislation

Certain legislation introduced in the 110th Congress would amend the Public Health Service Act in order to provide patent dispute resolution proceedings for biologics. The proposed regimes would act differently than the existing Hatch-Waxman framework. Under the two bills titled the Access to Life-Saving Medicine Act, H.R. 1038 and S. 623, follow-on or prospective follow-on applicants are allowed to request identification of all relevant patents from the holder of the reference product. The brand-name firm would then be required to respond to such a request within 60 days, and may demand payment of up to $1,000 in exchange for this service. The reference product holder would further be required to update this list for a period of two years.[92]

The follow-on applicant would be able to challenge any identified patent by providing the basis for the challenge to the patent proprietor and holder of the reference product.[93] The patent proprietor would be required to bring a patent infringement suit within 45 days of notice of a challenge or lose the right to certain remedies in court. Patent holders would be unable to seek declaratory judgment with respect to patents not subject to notice by the follow-on applicant.[94]

Under S. 1505, the Affordable Biologics for Consumers Act, a Federal Register notice would announce the filing of an application for a biosimilar. The sponsor of the reference product would be permitted to request information about the biosimilar for purposes of determining infringement issues, identifying patents that may be infringed by the biosimilar, and indicating whether its patents are available for

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[90] (...continued)
sources refer to data exclusivity as "marketing exclusivity" or "data protection." *See* Thomas, supra, at 349.

[91] *See* Terry Mahn and Margo Furman, *The Role of Patent and Non-Patent Exclusivity Under the Hatch-Waxman Act* (2005), 19-20 (available at [http://www.fr.com/practice/pdf/05-16-05%20_PatentandNon-PatentExclusivity.pdf]).

[92] H.R. 1038 and S. 623 at § 3(a).

[93] *Id.*

[94] *Id.*

licensing. The biosimilar applicant is required to provide a written explanation to the patent owner of why the identified patents are invalid or would not be infringed by the proposed product.[95]

S. 1505 renders the filing of the biosimilar applicant's written explanation to be an act of patent infringement that the sponsor of the reference product may pursue in federal court.[96] That bill further stipulates that a patent designated to be available for licensing by the sponsor of the reference product may not be the subject of a declaratory judgment action prior to the approval of the application for a biosimilar.[97] Otherwise the biosimilar applicant is barred from commencing a declaratory judgment action at a time later than 18 months of the application's filing date, or at a time later than 60 days of its explanation of its patent position to the reference product sponsor provided that explanation took place within 18 months of the application's filing date.

The Biologics Price Competition and Innovation Act of 2007, S. 1695, also included specialized patent dispute resolution procedures. Under S. 1695, the follow-on applicant must provide attorneys for the owner of the reference product with confidential information relevant to a patent infringement determination within 20 days after the Secretary publishes a notice that an application has been accepted for review. Within 60 days of the date of receipt of that information, the reference product sponsor is then required to identify patents that it deems relevant to the biosimilar or interchangeable product. The reference product sponsor is required to update this list with any patents it subsequently acquires. The biosimilar or interchangeable product applicant is then allowed 60 days to provide the reference product sponsor with a list of patents it deems relevant to the reference product. The biosimilar or interchangeable product applicant 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 or would not be infringed. In the latter case, the reference product sponsor or interested third party must provide the biosimilar or interchangeable product applicant with a response concerning the infringement and validity of those patents within 60 days. The parties are then required to engage in good faith negotiations to agree on which patents will be the subject of a patent infringement action. If those negotiations do not result in an agreement within 15 days, the parties will exchange lists of relevant patents to be litigated, with at least one patent identified by the reference product sponsor being subject to litigation. The reference product sponsor may then commence patent infringement litigation within 30 days. The biosimilar or interchangeable product applicant must notify the reference product sponsor at least 180 days before it commences commercial

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[95] S. 1505 at § 2(a).

[96] *Id.* at § 2(c).

[97] A declaratory judgment action is provided by a "federal or state law permitting parties to bring an action to determine their legal rights and positions regarding a controversy not yet ripe for adjudication...." *Black's Law Dictionary* (8th ed. 2004). In the context of patents, an action for declaratory judgment potentially would allow a biosimilar applicant to "clear the air by suing for a judgment that would settle the conflict of interests" with the owner of the reference product. *Arrowhead Indus. Water, Inc. v. Ecolochem, Inc.*, 846 F.2d 731, 735 (Fed. Cir. 1988).

marketing, and the reference product sponsor is allowed to seek a preliminary injunction at that time. Declaratory judgments are prohibited for either party unless the biosimilar or interchangeable product applicant fails to provide product and patent application as required, at which time the reference product sponsor may seek a declaratory judgment.

H.R. 5629, the Pathway for Biosimilars Act, requires that within 30 days of the filing of a biosimilar application, the Secretary will publish a notice of the application, and the follow-on applicant will provide the reference product owner with information concerning the biosimilar product and its production. Within 60 days of the receipt of this information, the reference product sponsor is required to identify patents that it deems relevant to the biosimilar product. The reference product sponsor is required to update this list with any patents it subsequently acquires. In addition, "interested third parties" may inform the biosimilar applicant of one of its relevant patents at any time, and then be entitled to obtain information concerning the follow-on product and its production. The interested third party is then provided 90 days to identify further relevant patents; as with the reference product sponsor, the interested third party must update this list with subsequently acquired patents. Reference product sponsors and interested third parties must additionally state why they believe the biosimilar product would infringe their patents. The biosimilar applicant is then allowed 45 days to 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 or would not be infringed. In the latter case, the reference product owner of the interested third party may commence a patent infringement lawsuit against the biosimilar applicant within 60 days. Follow-on applicants would be unable to seek declaratory judgment with respect to patents that are subject to notice and explanation by their owners until the later of 120 days after the explanation is provided, or 3 years prior to the expiration of marketing exclusivity.

In addition to patent dispute resolution proceedings, several of the bills provide for data exclusivities that would be awarded to brand-name firms. These data exclusivities would prevent the FDA from approving a follow-on version of the brand-name firm's product until a certain period of time had elapsed. Under S. 1695, a brand-name product would receive 12 years of exclusive data rights, at which time the FDA would be permitted to approve a follow-on biologic. H.R. 1956 also calls for 12 years of data exclusivity, although this period may be extended to 15 years if the reference product obtains further marketing approval for a new indication and "provides a significant clinical benefit in comparison with existing therapies." The proposal of S. 1505 is similar to that of H.R. 1956, although S. 1505 calls for a period of 16 (rather than 15) years in the event of approval of new indication with a significant clinical benefit.

H.R. 5629 would not allow the approval of an application for a follow-on biologic until at least 12 years after licensing of the reference product. For pediatric applications, the approval would not become effective until 12 years and 6 months after approval of the reference product. Pediatric exclusivity must be determined by the FDA no later than 9 months prior to the expiration of the initial marketing exclusivity period or no additional pediatric exclusivity will be awarded. In addition, the data exclusivity period is extended to 14 years if, during the 8-year period

following licensing of the reference product, approval of a new indication which would provide significant improvement in treatment, diagnosis, or prevention. For pediatric applications, approval of the follow-on biologic application would not become effective until 14 years and 6 months after approval of the reference product provided that the pediatric exclusivity is determined by FDA no later than 9 months prior to the end of the initial marketing exclusivity period.

Several of the bills also propose the creation of a marketing exclusivity that would be awarded to the sponsor of a particular follow-on biologic that was the first to obtain FDA marketing approval. Under S. 1695, following the award of marketing approval to the first *interchangeable* product, the FDA is prevented from approving additional interchangeable products for the shortest of (1) one year after it is marketed, (2) 18 months after a litigation outcome favorable to the first approved interchangeable product applicant, (3) 18 months after marketing approval if the first approved interchangeable product applicant is not sued for patent infringement, or (4) 42 months after marketing approval if the first approved interchangeable product applicant has been sued and the litigation is ongoing. In contrast, H.R. 1038 and S. 623 would allow the first interchangeable biological product to enjoy a marketing exclusivity period equal to the shortest of (1) 180 days after it is marketed, (2) one year after a litigation outcome favorable to the first approved interchangeable product applicant, (3) one year after marketing approval if the first approved interchangeable product applicant is not sued for patent infringement, or (4) 36 months after marketing approval if the first approved interchangeable product applicant has been sued and the litigation is ongoing. H.R. 5629 would permit the first interchangeable follow-on biologic a marketing exclusivity period of 24 months after the latter of either the date of the first commercial marketing of the interchangeable product, or, if marketed before interchangeability is determined, the date that the product is determined to be interchangeable.

Innovation Issues

Patents have been particularly significant to the pharmaceutical industry. Creation of an expedited approval process for generic versions of traditional chemical drugs that have come off patent has been deemed very successful in bringing lower-cost versions of innovator products to the marketplace. However, while many biopharmaceuticals are now poised to lose, or recently have lost, patent protection, additional considerations not associated with typical chemical drugs may be brought into play in determining the success of efforts to bring similar, less expensive biotechnologies to the marketplace. Questions for policymakers remain as to whether or not an expedited approval process for biopharmaceuticals will result in a competitive market for these products similar to that created by the Hatch-Waxman Act for chemical drugs. The high costs associated with manufacturing biologics, the scale of additional clinical trials required for FDA marketing approval, and other marketing considerations may affect the availability of lower-cost versions of these products. The section below discusses the role of patents in innovation and the particular situation in the pharmaceutical industry. It then explores some of the unique issues associated with the manufacture and marketing of follow-on biologics to provide a context within which to assess various legislative options.

Patents and Innovation

Patent ownership is perceived to be an incentive to innovation, the basis for the technological advancement that contributes to economic growth. Article I, Section 8, Clause 8 of the U.S. Constitution states: "The Congress Shall Have Power... To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries...." Although not without question, patents are widely thought to encourage innovation by simultaneously protecting the inventor and fostering competition. They provide the inventor with a right to exclude others, temporarily, from use of the invention without compensation. Patents generally give the owner an exclusive right for 20 years (from date of filing) to further develop the idea, commercialize a product or process, and potentially realize a return on the initial investment. Concurrently, the process of obtaining a patent places the concept in the public arena. As a disclosure system, the patent can, and often does, stimulate other firms or individuals to invent "around" existing patents to provide for parallel technical developments or meet similar market needs.

The grant of a patent does not necessarily provide the owner with an affirmative right to market the patented invention. Pharmaceutical products are also subject to marketing approval by the Food and Drug Administration. Federal laws typically require that pharmaceutical manufacturers demonstrate that their products are safe and effective in order to bring these drugs to the marketplace. Issuance of a patent by the U.S. Patent and Trademark Office and FDA marketing consent are distinct events that depend upon different criteria.

The patent system has dual policy goals — providing incentives for inventors to invent and encouraging inventors to disclose technical information.[98] Disclosure requirements are factors in achieving a balance between current and future innovation through the patent process, as are limitations on scope, novelty mandates, and nonobviousness considerations.[99] Many observers believe that patents give rise to an environment of competitiveness with multiple sources of innovation, which is viewed by some experts as the basis for technological progress. This may be important because, as Professors Robert Merges and Richard Nelson found in their studies, in a situation where only "a few organizations controlled the development of a technology, technical advance appeared sluggish."[100]

Not everyone agrees that the patent system is a particularly effective means to stimulate innovation. Critics argue that patents provide a monopoly that induces

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[98] Robert P. Merges, "Commercial Success and Patent Standards: Economic Perspectives on Innovation," *California Law Review*, July 1988, 876.

[99] Keneth W. Dam, "The Economic Underpinnings of Patent Law," *Journal of Legal Studies*, January 1994, 266-267. Scope is determined by the breath of the claims made in a patent. Claims are the technical descriptions associated with the invention. In order for an idea to receive a patent, the law requires that it be "new, useful [novel], and nonobvious to a person of ordinary skill in the art to which the invention pertains."

[100] Robert P. Merges and Richard R. Nelson, "On the Complex Economics of Patent Scope," *Columbia Law Review*, May 1990, 908.

additional social costs. Some observers believe that the patent system encourages industry concentration and presents a barrier to entry in some markets.[101] Others believe that the patent system too frequently attracts speculators who prefer to acquire and enforce patents rather than engage in socially productive activity.[102] Still other commentators suggest that the patent system often converts pioneering inventors into technological suppressors, who use their patents to block subsequent improvements and thereby impede technological progress.[103]

Role of Patents in Pharmaceutical R&D

The utility of patents to companies varies among industrial sectors. Patents are perceived by pharmaceutical companies as critical to the drug industry. That may reflect the nature of R&D performed in this sector, where the resulting patents are more detailed in their claims and therefore easier to defend.[104] In contrast, one study found that in the aircraft and semiconductor industries patents are not the most successful mechanism for capturing the benefits of investments. Instead, lead time and the strength of the learning curve were determined to be more important.[105] Research undertaken by Professor Wesley Cohen and his colleagues demonstrated that patents were considered the most effective method to protect inventions in the drug industry when biotechnology is included.[106]

The high cost of drug development and the concomitant uncertainty associated with clinical trials necessary for marketing approval lends significance to patents in the pharmaceutical arena. Studies by Joseph DiMasi of Tufts University and others published in 2003 estimated that the capitalized cost of bringing a new drug (defined as a "new molecular entity" rather than a new formulation of an existing pharmaceutical product) to the point of marketing approval was $802 million (2000 dollars).[107] Additional research done by Federal Trade Commission analysts found

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[101] *See* John R. Thomas, "Collusion and Collective Action in the Patent System: A Proposal for Patent Bounties," *University of Illinois Law Review*, 2001, 305.

[102] *Id.*

[103] *On the Complex Economics of Patent Scope*, 839.

[104] *Id.*, 255 and 257. *See also*: Edwin Mansfield, "Intellectual Property Rights, Technological Change, and Economic Growth," in *Intellectual Property Rights and Capital Formation in the Next Decade*, eds. Charles E. Walker and Mark A. Bloomfield (New York: University Press of American, 1988), 12 and 13.

[105] Richard C. Levin, Alvin K. Klevorick, Richard R. Nelson, and Sidney G. Winter. "Appropriating the Returns for Industrial Research and Development," *Brookings Papers on Economic Activity*, 1987, in *The Economics of Technical Change*, eds. Edwin Mansfield and Elizabeth Mansfield (Vermont, Edward Elgar Publishing Co., 1993), 253.

[106] Wesley M. Cohen, Richard R. Nelson, and John P. Walsh, *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)*, NBER Working Paper 7552, Cambridge, National Bureau of Economic Research, February 2000, available at [http://www.nber.org/papers/w7552].

[107] Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs," 22 *Journal of Health Economics,*

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the costs to be even higher; between $839 million and $868 million (2000 dollars).[108] At the same time, the total capitalized costs appear to be growing at an annual rate of 7.4% above general price inflation.[109]

A large portion of new drug costs (in terms of money and time) is associated with the size and breath of clinical trials necessary to obtain FDA marketing approval. According to a study supported by the Federal Reserve of Boston, only 10% of potential drug candidates reach the human trial phase and only a small portion of these actually reach the market.[110] In research presented at a conference sponsored by the Federal Reserve Bank of Dallas, Duke University's Henry Grabowski found that only 1% of drug compounds reach the human trial stage and 22% of those entering clinical trials receive FDA approval.[111] Professor Iain Cockburn notes that "as drug discovery became more science-intensive, ... it became not just more expensive but also more difficult to manage."[112] Furthermore, returns to new drug introductions vary widely and some experts have found that the median new drug does not bring in sufficient profits to cover the costs of bringing the product to the marketplace.[113] According to research by Professors Grabowski, John Vernon, and DiMasi, only 34% of new drugs (new chemical entities) introduced generated profits that equaled the industry average R&D cost.[114]

The degree to which industry perceives patents as effective has been characterized as "positively correlated with the increase in duplication costs and time associated with patents."[115] In certain industries, patents significantly raise the costs incurred by nonpatent holders wishing to use the idea or invent around the patent —

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[107] (...continued)
2003. Capitalized cost includes the "time cost" associated with an investment and the cost of testing drug products that fail.

[108] Christopher P. Adams and Van V. Brantner, *Estimating the Costs of New Drug Development: Is it Really $802m?*, Federal Trade Commission, December 2004, available at [http://media.romanvenable.net/images/drugCost.pdf].

[109] *The Price of Innovation: New Estimates of Drug Development Costs*, 180.

[110] Carrie Conway, "The Pros and Cons of Pharmaceutical Patents," *Regional Review*, Federal Reserve Bank of Boston, March, 2003, available at [http://www.findarticles.com].

[111] Henry G. Grabowski, "Patents, Innovation, and Access to New Pharmaceuticals," *Journal of International Economic Law,* 2002, 851.

[112] Iain Cockburn, "The Changing Structure of the Pharmaceutical Industry," *Health Affairs*, January/February 2004, 15.

[113] Henry G. Grabowski, "Patents and New Product Development in the Pharmaceutical and Biotechnology Industries," *Science and Cents: Exploring the Economics of Biotechnology*, Proceedings of a 2002 Conference, Federal Reserve Bank of Dallas, 95-96 available at [http://www.dallasfed.org/research/pubs/science/grabowski.pdf]; and Henry Grabowski, John Vernon, and Joseph A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," 20 *Pharmacoeconomics*, 2002.

[114] Henry Grabowski, John Vernon, and Joseph A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," 20 *Pharmacoeconomics*, 2002, 23.

[115] *Appropriating the Returns for Industrial Research and Development*, 269.

an estimated 40% in the pharmaceutical sector, 30% for major new chemical products, and 25% for typical chemical goods — and are thus viewed as significant. However, in other industries, patents have much smaller impact on the costs associated with imitation (e.g., in the 7%-15% range for electronics), and may be considered less successful in protecting resource investments.[116]

The significant costs of pharmaceutical R&D, coupled with the uncertainty of the clinical trial process, lend consequence to patents in this area because "the disparity between the investments of innovators and those of imitators is particularly large in pharmaceuticals — almost as large as when software pirates simply copy the diskettes of an innovator."[117] While the capitalized cost of developing a new drug to the point of market approval is estimated at over $800 million, it takes only between $1 million and $2 million to obtain approval for a generic version of the chemically synthesized pharmaceutical.[118] This difference is a result of the costs associated with clinical trials needed to demonstrate the safety and efficacy of a new drug, data that could be utilized by generic companies if not protected by a patent.[119]

Manufacturing Considerations

As discussed above, 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.[120]

This insures that the manufacture of biologics will tend to be significantly more expensive than traditional chemically synthesized drugs.[121] 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."[122] Therefore, these facilities must be built and operational prior to the FDA approval

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[116] Edwin Mansfield, Mark Schwartz, and Samuel Wagner. "Imitation Costs and Patents: An Empirical Study," *The Economic Journal*, December 1981, in *The Economics of Technical Change*, 270. *See also*: *Appropriating the Returns for Industrial Research and Development*.

[117] Federic M. Scherer, "The Economics of Human Gene Patents," 77 *Academic Medicine*, December 2002, 1352.

[118] *Patents, Innovation, and Access to New Pharmaceuticals*, 852.

[119] *The Economics of Human Gene Patents*, 1352.

[120] *Biologics: Can There Be Abbreviated Applications, Generics, or Follow-On Products*?

[121] *The Market For Follow-On Biologics: How Will It Evolve?*, 1293; and *The Long and Winding Road to Biologic Follow-ons*, 24.

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

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."[123]

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."[124] In addition, the cost of materials to manufacture biologics may be 20 to 100 times more than chemical drugs.[125] The production process for biologics typically takes longer than traditional drugs and may take eight to nine months.[126]

Altering the manufacturing process in any way tends to require that validation be repeated.[127] One commentator stated: "It's hard to predict how process variations will change a product's safety or effectiveness."[128] This is a result of the incidence of impurities arising from changes in the method of production and the increased opportunity of adverse immune reactions.[129] It is difficult to find and identify impurities in biologics as, to date, simple tests do not exist. Thus, there are often additional costs associated with preventing impurities from entering into the production process.[130] Some experts argue that there is also a need for additional clinical (human) trials to insure that any changes to the production process do not result in impurities that are harmful.[131] However, generic manufacturers assert that they can maintain high standards in the manufacturing process to insure similar products that are safe and effective.[132]

Clinical Trials

The scale and extent of clinical trials necessary to approve follow-on biologics is expected to factor into whether or not this industry will provide the cost savings

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[123] 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].

[124] *Manufacturing on a Grand Scale.*

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

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

[127] *Manufacturing on a Grand Scale*.

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

[129] 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.

[130] 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].

[131] *Biologics: Can There Be Abbreviated Applications, Generics, or Follow-On Products?*

[132] *Proposed Legislation for Follow-On Biologic Pharmaceuticals in the US.*

needed to be viable.[133] 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.[134] Innovator and generic manufacturers appear to agree that "Unlike small-molecule copycats, for biogenerics, 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."[135]

Generic biotechnology manufacturers assert that extensive new clinical trials would not be necessary in an expedited approval process but should be considered on a case-by-case basis, as discussed previously. Innovator companies dispute this. The nature of biologics has resulted in longer mean clinical development time for these products when compared with traditional drugs.[136] 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.[137] Phase III trials are the most expensive of the required trials and any additional requirements for follow-on biologics likely would increase the cost to the public.[138]

Marketing Concerns

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.[139] If the follow-on biopharmaceutical cannot be termed equivalent to the brand name drug, doctors and pharmacists may not be able to readily substitute:

> 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

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

[134] 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].

[135] *Id.*

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

[137] IMS Health, "Biogenerics: A Difficult Birth?," May 18, 2004 available at [http://www.imshealth.com/web/content/0,3148,64576068_63872702_70261000_71026746,00.html].

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

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

and act on these factors. Early-stage success in the biosimilars market, however, is more dependent on the speed to market and successful marketing strategies.[140]

The greater the number of generic alternatives, the less the cost. 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 higher prices and generate more profits than the typical generic firm.[141] In addition, "Financial and scientific barriers might prevent the cutthroat price wars fought in the traditional generic market."[142] 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.[143] A Merrill Lynch analysis[144] estimated prices 20%-30% below the brand biologic for the first biosimilar to be marketed while a report by Citizens Against Government Waste[145] 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.

Additional Observations

If alternative mechanisms for accelerated approval of follow-on biologics are legislated, many experts argue that the cost savings will not be as substantial as those generated by typical generic drugs. High manufacturing costs, the need for additional safety and efficacy trials to test these products, and augmented marketing efforts directed at doctors and patients to encourage the use of similar, but not identical drugs, are expected to add to the prices associated with the follow-on product. The differences between biologics and other drugs

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[140] 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].

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

[142] *Id.*

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

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

[145] 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.

> in turn lead to important differences in the economics of discovery, development, manufacturing, and distribution for drugs and biologics. Consequently, this could lead to different economic outcomes in terms of average prices, number of competitors, returns on spending for research and development (R&D), and other market measures.[146]

Some commentators are concerned that an expedited generic approval process similar to that established in the Hatch-Waxman Act may raise issues associated with the affect of patent challenges on biotechnology companies, many of which do not make a profit. How might this impact upon innovation in this sector? It has been argued that "[n]inety percent of biotech companies are surviving on venture capital, do not yet have a single product on the market, and are working hard to move products through preclinical discovery and chemistry to clinical investigation and then through FDA approval."[147] Often, a firm's intellectual property is its primary asset, particularly through the drug development stage, and typically is utilized to raise funds for additional R&D. Thus, several experts maintain that defending patents may divert support from on-going innovation, especially in small companies that make up a significant portion of the biotechnology sector.

Other experts argue that "[o]pening up biotech drugs to the prospect of generic competition *after* [emphasis added] patents expire may even spark innovation — forcing biotech companies to come up with improved versions of existing drugs that perhaps require less-frequent dosing, have fewer side effects or hang around the body longer, making them more effective."[148] However, the ability of brand name companies to bring out improved versions of their initial biologic may dampen development of follow-on products.[149] Because biotechnology is advancing so quickly, improvements in existing products may dissuade generic firms from making follow-on products that require large investments in manufacturing plants and clinical trials.[150] Patients may just switch to the next generation brand name drug.

A question remains whether or not multiple companies will invest the time and money necessary to develop follow-on biologics:

> The scope of the requirements means that, in organizational terms, the development of biogenerics demands a culture and mentality closer to that of proprietary pharmaceutical developers than to that of conventional generics firms.... If regulatory demands for biogenerics prove exacting, then [established pharmaceutical] companies are probably better off developing entirely novel biotech products instead. The regulatory requirements for these products are

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[146] *The Market For Follow-On Biologics: How Will It Evolve?*, 1292.

[147] *See* Weintraub, *supra.*

[148] Scott Gottlieb, *Biologics Warfare*, May 6, 2005, available at [http://www.aei.org/publication22467].

[149] *Biopharmaceuticals.*

[150] *Id.*

> usually much clearer, and in most cases, companies will stand to make far better commercial returns by taking this road.[151]

On the other hand,

> One reason generics companies are dropping out of the race is the sheer scope of demands these projects require.... Generic companies also tend to be much less tolerant of delays and setbacks.... Given these circumstances, most generics companies will have a hard time coming to grips with the demands of biogenerics.[152]

If fewer companies chose to make follow-on products, there would be less competition in the marketplace resulting in reduced cost savings. This raises the issue of whether there are other, or additional mechanisms to encourage firms to produce lower cost follow-on biologics.

In accessing any potential legislative activity in this area, it might be important to consider how to facilitate follow-on products after patent expiration while continuing to encourage innovation in the brand name biopharmaceutical sector. The Hatch-Waxman Act attempted to build just such a balance between the introduction of widely available generic drugs with adequate incentives for investment in the development of new pharmaceuticals. Many policy and industry experts agree that the Hatch-Waxman Act has had a significant effect on the availability of generic substitutes for brand name drugs while investment in the development of new pharmaceuticals has continued. At issue is whether or not it is desirable to pursue, and possible to achieve, a similar balance of interests in the biopharmaceutical industry.

http://www.crsdocuments.com

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[151] *Biogenerics Part I: Set to Make Real Inroads or Not?*

[152] *Id.*