P.L. 111-148: Intellectual Property Provisions for Follow-On Biologics

Wendy H. Schacht
Specialist in Science and Technology Policy

John R. Thomas
Visiting Scholar

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Summary

Congressional interest in the biotechnology industry parallels congressional attention to the availability of lower-cost pharmaceuticals. The market for biologic drugs is expanding by a number of measures including the quantity of approved products, the size of the market, and the importance of these pharmaceuticals to the health of U.S. citizens. Concurrently, patents on many biologics are expected to expire in the next few years. Some commentators have expressed concerns that patent expirations may not be accompanied by the introduction of competing, lower-cost follow-on drugs (also known as biosimilars) in the marketplace.

Biologics differ from traditional pharmaceuticals in their complexity and mode 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 intricate structure than traditional pharmaceuticals, and are manufactured from living cells through biological processes.

An expedited approval process and a patent dispute resolution procedure for traditional, small molecule pharmaceuticals was created by the Drug Price Competition and Patent Term Restoration Act of 1984, a statute commonly known as the "Hatch-Waxman Act." This law, which amended the Federal Food, Drug, and Cosmetic Act, is widely believed to have encouraged the availability of generic substitutes for many brand-name pharmaceuticals upon patent expiration. However, because biologics are typically approved under the Public Health Service Act, these mechanisms were not available for most follow-on biotechnology products.

The Patient Protection and Affordable Care Act, P.L. 111-148, offers several provisions designed to encourage innovation in biotechnology while creating an accelerated approval process for a biosimilar drug. The legislation also permits limited market exclusivity for the first follow-on biologic to be designated "interchangeable" with the reference product. At the same time, the innovator biologic is afforded a 12-year data exclusivity period during which time the Food and Drug Administration will not approve a follow-on biopharmaceutical. In addition, the legislation establishes a specialized patent dispute resolution proceeding for biologic drugs.

Some experts maintain that the intellectual property provisions of P.L. 111-148 will foster both the development of new biotechnology products and the availability of lower-cost follow-on biologics. Other commentators argue that the need for additional safety and efficacy trials to test these products, and the fact that these drugs may be similar, but not identical, may add to the prices charged for the follow-on product. High manufacturing costs associated with biopharmaceuticals also may reduce significant cost savings from biosimilars.

Contents

Contacts

Introduction

Congressional interest in the biotechnology industry parallels congressional concerns over the availability and cost of prescription drugs. The increasing significance of biologic pharmaceuticals to the health of the U.S. population has focused attention on this rapidly expanding market. Today, 20% of the available drugs are biologics[1] and some experts estimate that in the near future half of all newly approved pharmaceuticals will result from biotechnology.[2] However, biologics typically are more expensive than traditional, chemical-based drugs for multiple reasons including the high cost associated with research and development (R&D), clinical trials, and manufacturing. At the same time that these products have "contributed to increased life spans of today's population in much of the Western World," the innovations they have brought have contributed to the cost of health care.[3]

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.[4] The term "biologic" has been described as "poorly defined," and its precise parameters are themselves subject to debate.[5] 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."[6] Biologics are also sometimes termed "biotechnology drugs" or "biopharmaceuticals"[7] and typically are approved for marketing under the Public Health Service Act (PHS Act). Traditional, chemical drugs generally are approved under provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

P.L. 111-148, the Patient Protection and Affordable Care Act (H.R. 3590), provides mechanisms intended to foster innovation in biotechnology while facilitating the approval of follow-on biologic drugs, also known as "biosimilars." Congressional interest in the availability of lower-cost versions of innovative biotechnology drugs led to the creation of an accelerated approval process designed specifically for these follow-on products. The first biologic that is afforded

[1] Ernst & Young, *Beyond Boarders, Global Biotechnology Report 2008*, 30, available at http://www.ey.com/beyondborders.

[2] Herman Saftlas, "Industry Surveys, Healthcare: Pharmaceuticals," *Standard & Poor's*, June 4, 2009, 10, available at http://www.standardandpoors.com.

[3] Esther F. Schmid and Dennis A. Smith, "Pharmaceutical R&D in the Spotlight: Why is There Still Unmet Medical Need?" *Drug Discovery Today*, December 2007, 1001.

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

[5] 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," *Food and Drug Law Journal*, 2005, 143.

[6] 42 U.S.C. § 262(i) (2006)

[7] *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 143.

"interchangeable" status with the reference drug is provided limited market exclusivity. Concurrently, the legislation furnishes the innovator biologic a 12-year data exclusivity period during which time the Food and Drug Administration (FDA) will not approve a follow-on product using safety and efficacy information provided by the original drug's sponsor. A specialized patent dispute resolution procedure is also established. This paper offers an overview of these provisions. For more detailed discussion on follow-on biologics see CRS Report RL33901, *Follow-On Biologics: Intellectual Property and Innovation Issues*, and CRS Report RL34045, *FDA Regulation of Follow-On Biologics*.

Expedited Marketing Approval

The marketing of a new drug is prohibited unless that product meets certain safety and efficacy standards. Sponsors of new drugs must submit documentation demonstrating that these standards have been met in order to obtain marketing approval. Typically, this is a complex, lengthy document that presents clinical data; chemistry, manufacturing and controls; nonclinical pharmacology and toxicology; safety update reports; and other salient information.[8] Brand-name drug companies commonly devote considerable resources, over many years, to complete the studies necessary to submit an application for a new pharmaceutical.

P.L. 111-148 creates an expedited approval process for follow-on biologics that are not able to utilize the accelerated approval mechanism established for traditional chemical drugs by the Hatch-Waxman Act.[9] Under the Hatch-Waxman Act, the manufacturer of a potential generic chemical drug may submit an Abbreviated New Drug Application (ANDA) to the FDA for approval if, generally speaking, 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 New Drug Application. ANDAs also may allow a generic manufacturer to place its FDA-approved bioequivalent drug on the market as soon as relevant patents expire.[10]

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 pharmaceutical is the "same" as a previously approved biologic—as required under the Hatch-Waxman Act—difficult, if not impossible.[11] Therefore, a somewhat different approach is taken in P.L. 111-148. This legislation creates a two-tiered expedited approval process based upon FDA determination of the type and breadth of studies necessary to determine whether a follow-on biologic is "biosimilar" or "interchangeable." Information provided to the FDA on the approval application must demonstrate that the follow-on biologic is *similar* to the reference product based on data from a clinical study or studies to demonstrate safety, purity, and potency for one or more appropriate conditions of use for which the reference product is licensed. In addition, the Secretary of Health

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

[9] 21 U.S.C. sec. 355 and following.

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

[11] Debra Weintraub, "Next Generation of Biopharmaceuticals," *Journal of Managed Care Medicine*, 2006, available at http://www.namcp.com/Journals/JMCM/Articles/Next%20Generation%20of%20Biopharmaceuticals.pdf.

and Human Services may determine that elements in the application, such as clinical studies, may be unnecessary.

The Secretary of Health and Human Services is to determine what data are to be provided in the application for licensing a follow-on biologic. A follow-on product may be designated as "biosimilar" if (1) analytical, animal, and clinical studies show that it is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, (2) the two products have the same mechanism of action, (3) the condition of use in the proposed product has been previously approved for the reference product, (4) the route of administration, dosage form, and strength of the two products are the same, and (5) the manufacturing process provides for a safe product.

The Secretary may also designate a follow-on biologic as "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.

It is expected that the information required for a follow-on product approval will be less costly and take less time to generate than for the innovator drug.

Data Exclusivity

In an expedited approval process, the follow-on product is permitted to rely on the safety and efficacy data generated by the innovator drug (although only the FDA has actual access to the information). The Hatch-Waxman Act established a "data exclusivity" period during which the FDA will not consider competing applications for marketing approval of generic chemical drugs. Among the existing data exclusivities contained in this act is a five-year period available for drugs that qualify as new chemical entities. Should the original 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.

At 12 years, P.L. 111-148 provides a more robust data exclusivity period for innovator biologics; no application for a biosimilar product may be approved for 12 years from the reference product's licensure date. No application for a follow-on biologic may be filed with the FDA for four years from the date the reference product was licensed. However, exclusivity will not be awarded for (1) supplements to the reference product application; (2) the identification of new indications, routes of administration, dosing, or delivery; or (3) modifications to the structure of the biological product that do not result in a change in safety, purity, or potency.

The 12-year exclusivity period is designed to address concerns that patents on biologics do not provide as potent a scope of proprietary rights as patents on small molecule drugs. Follow-on biologics cannot be the "same" as the reference product because they are made by different cell lines under different manufacturing processes. Thus, a firm utilizing an expedited approval process for a biosimilar drug based on the Hatch-Waxman Act would have access to the health, safety, and efficacy data of the innovator product but would be able to "design around" the reference drug without infringing the existing patents. Data exclusivity serves as an incentive to additional costly development and encourages venture capital investments necessary for continued R&D, testing, and commercialization. Proponents maintain that data exclusivity provides certainty in the process of developing a biologic which patents do not. This certainty

generates competition in the marketplace where without significant data exclusivity for biotechnology products the venture capital sector is expected to invest elsewhere. In addition, commentators point out that data exclusivity does not prevent the introduction of a follow-on biologic product based on that company's own testing.

Market Exclusivity for First Interchangeable Product

Market exclusivity is awarded to the applicant that is the first to establish that its product is "interchangeable" with the reference product for any condition of use and is approved for use by the FDA. During this time, the FDA will not approve another follow-on product. The period of marketing exclusivity is the earlier of: (1) one year after the first commercial marketing of the first interchangeable biosimilar product to be approved as interchangeable with that reference product; (2) 18 months after either a final court judgment in patent infringement litigation under the Public Health Service (PHS) Act, as amended, or the dismissal of such litigation against the first applicant; (3) 42 months after the approval of the first interchangeable biosimilar biological product if patent litigation under the PHS Act, as amended, remains pending; or (4) 18 months after approval of the first interchangeable biosimilar product if the applicant has not been sued for patent infringement under the PHS Act, as amended.

Patent Dispute Resolution

In addition to creating expedited marketing approval pathways for generic drugs, the Hatch-Waxman Act incorporates numerous additional provisions pertaining to intellectual property.[12] 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; and special provisions for challenging the enforceability, validity, or infringement of approved drug patents.[13]

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 apply to biologics, whether they were approved under the FD&C 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.[14]

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

[13] A more detailed discussion of the Hatch-Waxman Act is found in CRS Report R41114, *The Hatch-Waxman Act: A Quarter Century Later*, by Wendy H. Schacht and John R. Thomas andRL30756, 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.

[14] *Patent Fairness Act of 1999: Hearing on H.R. 1598*, 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.

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 FD&C Act. These terms would therefore apply to biologics only to the extent they were governed by the FD&C Act. If a particular biologic is approved under the auspices of the PHS Act, however, these provisions are not applicable.[15]

To address patent infringement issues for biologic drugs approved under the PHS Act, P.L. 111-148 establishes a specialized patent dispute resolution proceeding that differs from the Hatch-Waxman framework. The legislation requires that within 20 days after the Secretary of Health and Human Services publishes a notice that its application has been accepted for review, the biosimilar or interchangeable product applicant will provide the reference product sponsor with details concerning the product and its production. 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 also 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 or would not be infringed. In the latter case, the reference product sponsor or interested third party is to provide the biosimilar or interchangeable product applicant with a response concerning the infringement and validity of those patents within 60 days.

The parties are 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 is to notify the reference product sponsor at least 180 days before it commences commercial 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 a product and patent application as required, at which time the reference product sponsor may seek a declaratory judgment.

Observations

Observers agree that the market for biologic pharmaceuticals is expanding by a 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. Patents on many biologics are expected to expire in the next few years; however, some commentators have expressed concerns that patent expirations may not be accompanied by the introduction of competing, lower-cost follow-on drugs in the marketplace. The intellectual property provisions of P.L. 111-148 are designed to address these concerns by establishing an accelerated approval process for follow-on products and creating a specialized patent dispute resolution mechanism. However, it remains to be determined if the cost

[15] 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.

savings will be as substantial as those generated by generic chemical drugs. The need for additional safety and efficacy trials to test these products, and the fact that these drugs may be similar, but not identical, may add to the prices charged for the follow-on product. Other factors may also affect the availability of biosimilars including high manufacturing costs and the rapid rate of innovation in the biotechnology sector. As the provisions of the new legislation become operable, experts will be better able to assess if the law has a significant effect on the availability of follow-on biologics while at the same time ensuring that innovation in the biotechnology arena continues.

Author Contact Information

Wendy H. Schacht
Specialist in Science and Technology Policy
wschacht@crs.loc.gov, 7-7066

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

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