Follow-on Biologics Case Study

Introduction

The rise of generic pharmaceuticals has resulted in large price reductions and numerous opportunities for large and small drug companies. Now, provisions in the new comprehensive health care law combined with a wave of patent expirations on major biologics are opening the door to companies interested in pursuing generic versions of brand-name biologics, known as follow-on biologics or biosimilars. Perhaps the best example is the case of Merck's investment in and creation of a follow-on biologics unit, Merck BioVentures.

Biologics

Most drugs fall into two categories: small molecules and large molecules.[1] Common pharmaceuticals such as Tylenol and Lipitor are small molecules: they consist of only dozens of atoms and may be reproduced exactly through well-understood chemical processes.[2] Biologics comprise the latter category. Unlike traditional pharmaceuticals, biologics are complexly structured, typically made up of millions of atoms, and are produced from living cells through biological processes.[3] Thus, generic versions of traditional pharmaceuticals are relatively easy to produce once the patent for the original drug expires. Biologics, however, face considerable, perhaps even insurmountable, technical challenges to the development of products that are truly equivalent to their brand-name counterparts. For this reason, these products are not usually referred to as "generic" biologics, but as follow-on biologics or biosimilars.[4] Apart from a description of these differences, a precise definition of the term "biologic" is hard to devise. The Public Health Service offers the following definition, albeit of "biological product" rather than "biologic": "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[5]

Despite the challenges involved in the production of follow-on biologics, the industry is expected to grow significantly in the coming years. The size of the biologics market has already been estimated to be $52 billion, with a growth rate faster than any other sector of the pharmaceuticals market.[6] Furthermore, patents on several major biologics are set to expire in the

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[1] John E. Calfee, *Follow-on biologics are not like ordinary generics, and therefore require Congress to exercise a deft regulatory hand*, AEI ONLINE, April 2007, *available at* http://www.aei.org/outlook/26010.

[2] WENDY H. SCHACHT & JOHN R. THOMAS, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 2 (Cong. Research Serv., CRS Report for Congress Order Code RL 33901, Jan. 6, 2010).

[3] *Id.* at 3.

[4] *Id.*

[5] 42 U.S.C. § 262(i) (2006).

[6] WENDY H. SCHACHT & JOHN R. THOMAS, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 1 (Cong. Research Serv., CRS Report for Congress Order Code RL 33901, Jan. 6, 2010).

next ten years, represented a market value that could be as high as $50 billion.[7] Moreover, new regulatory authority created by the Patient Protection and Affordable Care Act (PPACA) in March of 2010 allows the FDA to license follow-on biologics.[8] These favorable market and regulatory trends have led many firms to seriously consider the developing new follow-on biologics.

PPACA

For traditional pharmaceuticals, the Drug Price Competition and Patent Term Restoration Act of 1984, commonly called the Hatch-Waxman Act, governs the introduction of generic versions of off patent brand-name drugs.[9] The Hatch-Waxman Act allowed for expedited marketing approval for generics by eliminating the need for expensive and time-consuming clinical trials in most cases.[10] Two expedited approval pathways are available: section 505(j) for generic drugs with the *same* active ingredient as the brand-name drug, and section 505(b)(2) for generic drugs with a sufficiently *similar* active ingredient as the brand-name drug.[11] However, because it is nearly impossible to create biologics that are exactly the same as their brand name counterparts, and regulatory pathway for similar generics under 505(b)(2) still requires that the applying company submit additional data to demonstrate safety and effectiveness, many companies with follow-on biologics are with unable or unwilling to take advantage of these provisions.[12]

PPACA aims to allow for an analogous process in the case of follow-on biologics. The Act provides that an application provide data from clinical studies to demonstrate the safety and potency of the follow-on biologic in situations in which the brand-name drug is licensed for use.[13] However, the Secretary may waive the clinical studies requirement, along with other required elements of the application.[14] The Secretary may then designate the drug in question as either a "biosimilar" or an "interchangeable" depending on the degree of similarity.[15] The Act

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[7] *Id.* at 2; *see also* Ludwig Burger, *Battle over Biosimilar Drugs is only for the Brave*, REUTERS, July 2, 2010, *available at* http://uk.reuters.com/article/idUKLNE66102R20100702 (noting that "90 percent of today's biotechnology drugs will be off patent" by 2020.).

[8] Mari Edlin, *PPACA Creates Approval Pathway for Follow-On Biologics*, MODERN MEDICINE, Aug. 15, 2010, *available at* http://www.modernmedicine.com/modernmedicine/Chains+%26+Business/PPACA-creates-approval-pathway-for-follow-on-biolo/ArticleStandard/Article/detail/680424?contextCategoryId=40159.

[9] Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355 (2006)).

[10] *See* 21 U.S.C. § 355.

[11] JUDITH A. JOHNSON, FDA REGULATION OF FOLLOW-ON BIOLOGICS 7 (Cong. Research Serv., CRS Report for Congress Order Code RL 34045, Apr. 26, 2010).

[12] *Id.* at 8-9.

[13] *Id.* at 13.

[14] *Id.* at 13.

[15] WENDY H. SCHACHT & JOHN R. THOMAS, PL 111-148: INTELLECTUAL PROPERTY PROVISIONS FOR FOLLOW-ON BIOLOGICS 3 (Cong. Research Serv., CRS Report for Congress Order Code R 41270, May 25, 2010).

also provides 12 years of data exclusivity, during which no application for a follow-on biologic will be approved after the brand-name drug's licensure date.[16]

The Act, however, does not remedy all challenges facing the development of follow-on biologics. For example, rather than developing new follow-on biologics, firms might try to create new biologics by making small modifications to the manufacturing process for existing biologics, thereby receiving an additional 12 years of data exclusivity.[17] Furthermore, some industry leaders see 12 years as an insufficient time period to incentivize research and development.[18] Finally, cost may bar all but the largest firms from developing follow-on biologics. According to the Federal Trade Commission, follow-on biologics are expected to take between 8 to 10 years to develop and to cost between $100 million and $200 million, while small-molecule generic development typically costs between $1 million and $5 million.[19]

Merck

Merck's plans for follow-on biologics provide a prime example of a large, established biotechnology company taking advantage of the opportunities provided by the changes in the biologics market. In 2008, Merck announced plans to launch a new unit, Merck BioVentures, dedicated to developing follow-on biologics.[20] Dick Clark, Merck's CEO, believes that the company "can become the leading provider of high quality, competitively priced follow-on biologics."[21] At a 2008 business briefing, the company indicated that it planned to spend $1.5 billion in order to reach its goal of producing six new follow-on biologics by 2012.[22] Merck's announcement stood in contrast to that of its big pharma brethren, of whom only Novartis and Teva Pharmaceuticals had created divisions aimed at follow-on biologics.[23]

A key step in the advancement of Merck's follow-on biologics program was the acquisition of Insmed for $130 million in 2009.[24] A developer of follow-on biologics focused on niche markets, Insmed's 50,000 square-feet based in Boulder, Colorado and staff of 70 protein

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[16] *Id.*
[17] Edlin, *supra* note 8.
[18] *Id.*
[19] FEDERAL TRADE COMMISSION, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 14 (2009), available at http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.
[20] Ed Silverman, *Merck Wants To Develop Follow-On Biologics*, PHARMALOT, Dec. 9, 2008, available at http://www.pharmalot.com/2008/12/merck-wants-to-develop-follow-on-biologics/.
[21] *Id.*
[22] Ellen Foster Licking, *Merck's Ambitious Plans for Follow-On Biologics*, BIOPHARMA TODAY, Dec. 18, 2008, *available at* http://www.biopharmatoday.com/2008/12/mercks-ambitious-plans-for-follow-on-biologics.html.
[23] *Id.*
[24] Press Release, Insmed, Inc., Insmed Sells Follow-on Biologics Platform to Merck & Co., Inc. for Gross Proceeds of $130 Million (Feb. 12, 2009), *available at* http://investor.insmed.com/releasedetail.cfm?ReleaseID=364842.

experts[25] are expected to benefit Merck substantially. Interestingly, Insmed's acquisition was the result of a unique viral marketing campaign[26] that saw Insmed's scientists appear on Youtube to tout the benefits of follow-on biologics. In Merck had also boosted its follow-on biologics program in 2006, when it acquired Glycofi, a biotechnology company based in New Hampshire.[27]

However, Merck's BioVentures program also suffered a setback in 2009 when it announced the cancellation of a much-publicized follow-on biologic for Amgen's Aranesp, an anti-anemia drug, due to lengthy and expensive safety testing.[28] At the time, Merck's head of research and development maintained that the company had two other follow-on biologics in clinical development and expected about five to be in the final stages of testing by 2012.[29] Merck also gained competition in the follow-on biologics market from Pfizer, who is planning to launch two follow-on biologics in the next four or five years and ultimately plans to have 10-15 available.[30]

Merck's foresight has placed it in a position to be a leader of the follow-on biologics industry. Indeed, it appears that the current status of the follow-on biologics industry can be described as a "two-horse race" between Merck and Israeli pharmaceuticals giant Teva for market dominance.[31] The competition between these two companies also demonstrates the high barriers to entry that characterize the follow-on biologics market. In the words of William Marth, president and CEO of Teva's North American branch, "[w]hat you need to invest to get into that market [is] $100 million to $150 million per product entry, and . . . eight to 10 of them in your basket in order to come to the market with a really powerful offering."[32]

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[25] *See* Posting of Ellen Licking to The In Vivo Blog, http://invivoblog.blogspot.com/2009/02/dotw-evolution.html (Feb. 13, 2009, 19:30).
[26] *See* Posting of Kate Rawson to The In Vivo Blog, http://invivoblog.blogspot.com/2008/02/starring-role-for-follow-on-biologics.html (Feb. 11, 2008, 16:19).
[27] Press Release, Merck & Co., Inc., Merck & Co., Inc. to Acquire GlycoFi, Inc. (May 9, 2006), *available at* http://www.glycofi.com/news/050906.html.
[28] Posting of Jonathan D. Rockoff to Wall Street Journal Health Blog, http://blogs.wsj.com/health/2010/05/11/merck-scraps-once-promising-follow-on-biologic-for-anemia/ (May 11, 2010, 10:50 ET).
[29] *Id.*
[30] Cynthia Challener, *Follow-On Biologics Present Opportunity to Big Pharma*, ICIS.COM, Feb. 10, 2010, *available at* http://www.icis.com/Articles/2010/02/15/9333235/follow-on-biologics-present-opportunity-to-big-pharma.html.
[31] *See* Ellen Foster Licking and Joseph Haas, *A Two-Pharma Horse Race in Follow-on Biologics*, IN VIVO: THE BUSINESS & MEDICINE REPORT, Feb. 2009, at 19.
[32] Ellen Foster Licking and Joseph Haas, *A Two-Pharma Horse Race in Follow-on Biologics*, IN VIVO: THE BUSINESS & MEDICINE REPORT, Feb. 2009, at 19.