

Expert Analysis of Current Developments

Biosimilars in the United States: A Brief Look at Where We Are and the Road Ahead

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THE BIOLOGICS DRUG INDUSTRY has become a permanent and welcome fixture in modern medicine. The fruits of this revolution continue to improve, and save, countless lives everywhere. Unfortunately, the cost of biologics often is astronomical, at once straining the healthcare system and jeopardizing the ability of patients to obtain these much-needed drugs.

The U.S. biologics industry needs reform and now looks to the generic pharmaceutical industry's success for guidance in that regard. There are scientific complexities unique to biologics, and the drug industry in general is far more complex and sophisticated than when generics arrived more than two decades ago. Consequently, establishing a biosimilars¹ industry—no matter how badly one is needed—is truly a formidable task without a clear path forward.

This paper provides a glimpse of biologics, the generic drug industry and its origins, the legislative attempts to create a biosimilars industry, and some of the obstacles to be overcome before that goal is reached.

THE HATCH-WAXMAN ACT AND THE BIRTH OF THE GENERIC DRUG INDUSTRY

Roche v. Bolar

In 1984, the Federal Circuit case of *Roche Products, Inc. v. Bolar Pharmaceutical Co.*² illuminated the tension in the United States at that time between patent law and food and drug law. That ruling, combined with the marketing approval requirements under food and drug law, led to two distortions of the statutory patent

term. The first distortion was a shortening of the patent holder's market exclusivity period attributable to delays caused by the required approval process. That is, by the time regulatory approval was granted, little if any patent term would be left. The second distortion was that a competitor of a patent holder commencing activity for regulatory approval before patent expiration could be enjoined as an infringer.³ This gave the patent holder a *de facto* extension of the patent term. The Federal Circuit identified the need for a legislative solution to this problem,⁴ which arrived swiftly in the form of the Hatch-Waxman Act.⁵

The Hatch-Waxman Act

The Hatch-Waxman Act, passed that same year, established the generic drug industry in the U.S. Among many other things, this Act added provisions to §505 of the Food Drug and Cosmetics Act (FDCA) to create the Abbreviated New Drug Application (ANDA).⁶ In essence, an ANDA can be filed to obtain regulatory

¹ Biologics are known by various names, such as biopharmaceuticals and biologic drugs, which are used synonymously here. Likewise, biosimilars are referred to alternatively as generic biologics, follow-on biologics, and biogenerics. These terms are used synonymously here, noting that using the term "generic" in connection with biologics has, for technical reasons, been deemed by some to be inaccurate.

² 733 F.2d 858, 221 USPQ 937 (Fed. Cir. 1984).

³ John R. Thomas, PHARMACEUTICAL PATENT LAW, Chapter 1.IV.A (BNA) (2005).

⁴ *Roche v. Bolar*, 733 F.2d at 876–877.

⁵ The Drug Price Competition and Patent Term Restoration Act [Public Law No. 98-417] is commonly referred to as the Hatch-Waxman Act or the Waxman-Hatch Act.

⁶ FDCA §505(j); 21 U.S.C. §355(j). See Daniel O. Beers, GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS, Sixth Ed. (2004), §3.01, fn 1. In all, the Hatch-Waxman Act was codified in 15 USC §§68b–68c, 70b; 21 USC §§301, 355, 360cc; 28 USC §2201; and 35 USC §§156, 271, 282. See also, Thomas, PHARMACEUTICAL PATENT LAW, Chapter 1.IV.B.

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approval for a generic copy of an FDA-approved innovator drug (i.e., a “listed drug”) without the need to perform full safety and efficacy testing.⁷

A generic drug has the same active ingredient as, and is bioequivalent to, its corresponding innovator drug. Moreover, it has the same strength, dosage form and administration route, indication, and labeling.⁸ Although a generic drug has the same safety and efficacy as its corresponding innovator drug, it can cost as much as 80% less.^{9,10}

The generics industry has enjoyed exponential growth, with greater potential still. Generics now account for 56% of total U.S. prescriptions but only 13% of the dollars spent. In 2005, U.S. innovator sales amounted to \$229.5 billion, while U.S. generic sales were \$22.3 billion.¹¹ In 2006, sales by U.S. branded pharmaceutical manufacturers amounted to \$220.6 billion, while U.S. generic sales rose to \$54.1 billion.¹² Of the 11,487 innovator drugs listed by the FDA, 8,730—more than 75%—have generic counterparts.¹³

BIOLOGICS TODAY

Biologics defined

Generally, a biologic—or biologic product—is any therapeutic or diagnostic product that is, or is derived from, a living organism. According to §351 of the Public Health Service Act (PHSA), a biologic is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood component or derivative, allergenic product, or analogous product, . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”¹⁴ “Analogous” products typically include protein products (such as hormones, interferons, enzymes, and cytokines), monoclonal antibodies, and gene therapy products.

Growth of an industry

More than 250 biotechnology medicines have been approved by the FDA, including 39 biologic products in 2005 alone.¹⁵ More than 400 biologic products are in clinical and preclinical development, targeting a wide array of diseases such as cancer, AIDS, arthritis, and Alzheimer’s disease.¹⁶ Examples of the top-selling biologics are Epogen[®], Procrit[®], and Aranesp[®] for anemia and Remicade[®] for rheumatoid arthritis and other inflammatory disorders.¹⁷

Biologic products hold enormous clinical promise. Sadly, their cost to patients, employers, insurers, and government alike has reached a level virtually unheard of in the pharmaceutical industry. Vectibix[®], for metastatic colorectal cancer, costs \$4,000 per infusion and \$100,000 per year.¹⁸ Erbitux[®], for this same disease, costs \$5,000 per treatment.¹⁹ The annual cost of Elaprase[®] for treating Hunter’s syndrome is a stag-

gering \$300,000.²⁰ Indeed, four of the top-selling biologic products have a combined cost that accounted for 30% of all Medicare Part B carrier drug spending in fiscal year 2005.²¹ In short, the cost of obtaining biologic products today has become an impediment to their use by those who need them, a drain on government resources, a significant public relations problem in the biopharmaceutical industry, and a serious U.S. healthcare issue generally.

Approving biologics

In general, biological products are licensed (via biologics licenses) under §351 of the PHSA.²² In con-

⁷ See, e.g., FDCA §505(j); 21 USC §355(j).

⁸ Frequently Asked Questions, Generic Pharmaceutical Association (available online at www.gphaonline.org/Content/NavigationMenu/AboutGenerics/FAQs/default.htm) (accessed June 21, 2007).

⁹ Backgrounder on Biologics, Issues and Legislation sponsored by Rep. Henry Waxman (online at www.henrywaxman.house.gov/issues/health/generic_biologics.htm) (“Backgrounder”), citing *Generic Drugmakers Await End of Patents: The Generic Drug Industry Will Be Buoyed as 75 Brand-Name Prescription Drugs Lose Their Patent Protections*, Knight-Ridder (May 2, 2006).

¹⁰ Industry Statistics, Generic Pharmaceutical Association, June 21, 2007 (available online at www.gphaonline.org/Content/NavigationMenu/AboutGenerics/Statistics/default.htm) (accessed June 21, 2007) (“Industry Statistics”).

¹¹ Backgrounder, citing Generic Pharmaceutical Association, Statistics: Our Industry (available online at www.gphaonline.org/Content/NavigationMenu/AboutGenerics/Statistics/default.htm) (accessed February 13, 2007).

¹² Industry Statistics.

¹³ *Id.*

¹⁴ P.H.S.A. §351(i), 42 U.S.C. §262(i).

¹⁵ Backgrounder, citing Biotechnology Industry Organization, *Healthcare Overview* (available online at www.bio.org/healthcare) (accessed February 12, 2007).

¹⁶ Backgrounder, citing Pharmaceutical Research and Manufacturers of America (PhRMA), *Biotechnology Medicines in Development, 2006 Report* (online at www.phrma.org/files/Biotech%202006.pdf) (accessed February 13, 2007).

¹⁷ Backgrounder, citing *Drugmakers’ Battle for Medicare Market Share*, CQ Weekly (October 2, 2006) (citing Centers for Medicare and Medicaid Services [CMM]).

¹⁸ Gearing up for *Bio-Generics*, Signals Magazine, October 5, 2006 (available online at www.signalsmag.com/signalsmag.nsf/0/C3985651BF9C5D7E882571FE000A2575).

¹⁹ *Id.*

²⁰ *Id.*

²¹ Backgrounder, citing Kuhn, Director CMM, Testimony before the House Subcommittee on Health of the Committee on Ways and Means (July 13, 2006) (available online at <http://waysandmeans.house.gov/hearings.asp?formmode=view&id=5108>) (accessed February 13, 2007).

²² Frequently Asked Questions about Therapeutic Biological Products, U.S. Food and Drug Administration, Center for Drug Evaluation and Research (online at www.fda.gov/cder/biologics/qa.htm).

trast, drugs, and on certain occasions biologics such as insulin and human growth hormone, are approved under §505 of the FDCA.²³

Existing problems

In essence, the ANDA provisions of the Hatch-Waxman Act apply only to traditional, small-molecule drugs, and no biosimilars industry exists in the U.S. Consequently, biologic innovators typically are able to continue charging monopoly prices for their products long after patent expiration absent market entry of products that are at least comparable to the innovator biologic.²⁴

The existing generic drug industry owes its robust existence in large part to the relative ease with which a generic competitor can scientifically establish sameness between its generic product and the corresponding small-molecule innovator drug, in turn demonstrating safety and efficacy. Unfortunately, the reality for would-be biosimilars companies—not to mention patients and the healthcare industry generally—is this: biologics are not small-molecule drugs.

Biologics, which typically are proteins such as antibodies and enzymes, are far more complex than classic small-molecule drugs. This added complexity is structural, chemical, and functional. In the case of protein products, for example, two products having the same amino acid sequence—the most rudimentary requirement for protein identity—nevertheless can lack sameness and even comparability²⁵ because of complexities such as differences in folding patterns, post-translational modification (via glycosylation, acetylation, and phosphorylation), and aggregation of subunits.²⁶ Not surprisingly, understanding and overcoming these anticipated difficulties in establishing sameness or even comparability between two biologic products is at the heart of creating a biosimilars industry, as determining sameness or comparability correlates with determining safety and efficacy. Even less surprisingly, this topic continues to be the focus of debate among innovator companies, generic companies, healthcare agencies, their representative organizations, and lawmakers. The economic consequences of this debate to the generic and innovator drug industries are enormous, likewise the economic and health consequences to patients in need of biologics. The competing pieces of legislation now being proposed reflect the various sides of this debate.

PROPOSED LEGISLATION

The year 2007 has ushered in competing legislative proposals for launching a biosimilars industry. By all accounts, these proposals identify drug safety and efficacy as paramount goals and acknowledge the complexities involved in making and evaluating biologics.

These proposals also reveal the broad spectrum of competing interests involved in the biosimilars debate. Some key provisions of the proposed legislation are outlined below.

Access to Life-Saving Medicine Act²⁷

Known also as the Waxman bill, the provisions of the Access to Life-Saving Medicine Act clearly favor the generics industry. This bill authorizes approval of abbreviated applications for biologic products that are “comparable” to approved innovator biologic products. As defined in the bill, “comparable” means having an “absence of clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product based upon [specified clinical and non-clinical data].”²⁸ The bill also authorizes approval of abbreviated applications for “interchangeable” biologic products. A biological product is interchangeable if it is “. . . comparable to the reference product [and] can be expected to produce the same clinical result as the reference product in any given patient.”²⁹

Approval of a comparable biologic can be based on the safety and efficacy of the brand-name product in combination with additional evidence required by the FDA to show absence of clinically meaningful differences between the comparable and innovator products. The FDA can require additional studies, most notably clinical trials, on a case-by-case basis to establish comparability or interchangeability.³⁰

Under the bill, the first applicant granted approval for an interchangeable product is awarded market exclusivity ending at the earliest of (i) 180 days after

²³ *Id.*

²⁴ *Waxman, Schumer, and Clinton Unveil Bill to Create Clear Pathway for Generic Biologic Drugs* (February 14, 2007) (online at www.henrywaxman.house.gov/pdfs/biologicspress_release_2.14.07.pdf).

²⁵ Terms such as “comparability,” “similarity,” and “interchangeability” are featured in the proposed biosimilars legislation, discussed below.

²⁶ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, Food and Drug Administration before Subcommittee on Health, Committee on Energy and Commerce, May 2, 2007. (Available online at www.fda.gov/ola/2007/policy05022007.html) (“Woodcock”).

²⁷ H.R. 1038, introduced February 14, 2007 and sponsored by Rep. Henry Waxman (available online at http://www.henrywaxman.house.gov/issues/health/generic_biologics.htm); S. 623, introduced February 15, 2007 and sponsored by Senators Hillary Clinton and Charles Schumer (available online at www.law.columbia.edu/null?&exclusive=filemgr.download&file_id=12252&rtcontentdisposition=filename%3DS%20623.pdf).

²⁸ H.R. 1038, §2(a)(4).

²⁹ *Id.* at §2(a)(5).

³⁰ *See, e.g., id.* at §2(a)(4)(B).

marketing; (ii) one year after a final favorable court decision or dismissal of patent litigation; (iii) 36 months after approval if litigation is still unresolved; and (iv) one year after approval if there is no litigation.³¹

An applicant for a comparable biologic product may ask the holder of the reference product for a list of patents relating to the product. The patent holder must disclose these patents, and the applicant can then challenge one or more of them. In response, the patent holder must either bring an infringement suit within 45 days of notice of challenge or lose the right to obtain certain remedies in court beyond reasonable royalties later.³²

Many provisions in this bill parallel those in the Hatch-Waxman Act. Notable differences exist, however. Unlike the Hatch-Waxman Act, which awards innovator market exclusivities for new chemical entities, products, and product uses, to name a few, the Waxman bill awards no such exclusivities. In addition, this proposed legislation permits, but does not mandate, certifying to invalidity, non-infringement, or unenforceability regarding unexpired brand-name patents on applying for regulatory approval.³³

*Patient Protection and Innovative Biologic Medicines Act of 2007*³⁴

By all indications, the Patient Protection and Innovative Biologic Medicines Act—also referred to as the Inslee bill—favors the brand-name biologics industry and addresses provisions of the Waxman bill that clearly would be repugnant to innovator companies. The Inslee bill provides the right to apply for a biologics license for a biological product claimed to be “similar” to a reference product.³⁵ Notably, the bill requires post-market safety monitoring of the approved product. The bill also requires the use of a “proper name” unique to each manufacturer’s protein product and labels warning against substitution without express authorization by a physician. Finally, this bill awards to innovators market exclusivity periods ranging from 12 to 15 years, depending on the circumstances. These exclusivity periods exceed by as much as several-fold those awarded under the Hatch-Waxman Act.³⁶

*Biologics Price Competition and Innovation Act of 2007*³⁷

The bipartisan Biologics Price Competition and Innovation Act, referred to here as the Kennedy bill, appears intended to strike a compromise between the Waxman and Inslee bills. The Kennedy bill amends §351 of the PHSA to provide an approval pathway for safe biosimilar and interchangeable biological products.³⁸ A biological product is “biosimilar” to a refer-

ence product if there are “no clinically meaningful differences between [the two] in terms of . . . safety, purity, and potency. . . .”³⁹ A biological product is “interchangeable” with a reference product if it “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”⁴⁰

To demonstrate biosimilarity, an applicant must provide, among other things, data from one or more human clinical studies⁴¹ absent the FDA’s determination that such data are unnecessary.⁴² A showing of interchangeability requires evidence that the biologic product is biosimilar to the reference product and “can be expected to produce the same clinical result as the reference product in any given patient.”⁴³

Importantly, the Kennedy bill provides innovator market exclusivity, the absence of which would be unthinkable for the brand-name industry. However, the market—or data—exclusivity granted brand-name companies is 12 years,⁴⁴ a period vastly exceeding the exclusivity granted for the first interchangeable biologic product.⁴⁵ This 12-year exclusivity grant is on par with that provided by the Inslee bill. Not surprisingly, the Generic Pharmaceutical Association has deemed the exclusivity period “arbitrary,” “excessive,” “unprecedented,” and “unwarranted.”⁴⁶

Finally, this bill provides a multi-step process for identifying and resolving patents that may be infringed by the biosimilar product. This process involves a series of informational exchanges and negotiations be-

³¹ *Id.* at §3(a)(10).

³² *Id.* at §3(a)(17), (b)(1).

³³ *Id.* at §3(a)(17)(B).

³⁴ H.R. 1956, introduced April 19, 2007, and sponsored by Reps. Jay Inslee, Gene Green, and Tammy Baldwin (available online at www.house.gov/inslee/docs/pdfs/biologics_bill_april_2007.pdf).

³⁵ H.R. 1956, §2(a)(2), which adds §(k)(1)(A) to the PHSA.

³⁶ *Id.* at §2(a)(2), which adds §(k)(3)(A)–(C) to the PHSA.

³⁷ S. 1695, introduced June 27, 2007 and sponsored by Senators Edward Kennedy, Hillary Rodham Clinton, Michael Enzi, and Orrin Hatch (available online at <http://thomass.loc.gov/cgi-bin/query/C?c110:/temp/~c110X9tE3E>).

³⁸ *See, e.g.*, S. 1695, §2(a).

³⁹ S. 1695, §2(b)(3)(2).

⁴⁰ *Id.* at §2(b)(3)(3).

⁴¹ *Id.* at §2(a)(k)(2)(A)(i)(I)(aa)–(cc).

⁴² *Id.* at §2(a)(k)(2)(A)(ii).

⁴³ *Id.* at §2(a)(k)(4)(A)(i) and (ii).

⁴⁴ *Id.* at §2(a)(k)(7)(A).

⁴⁵ *See, e.g.*, S. 1695, §2(a)(k)(6)(A)–(C), setting forth the exclusivity period granted for a first interchangeable biological product.

⁴⁶ GPhA Statement on Sens. Kennedy–Enzi–Clinton–Hatch Biogenerics Legislation, Generic Pharmaceutical Association, June 27, 2007 (available online at www.gphaonline.org/AM/Template.cfm?Section=Press_Releases&TEMPLATE=/CM/HTMLDisp lay.cfm&ContentID=3560).

tween the biosimilar applicant and the innovator company, starting with the applicant's confidential disclosure to the brand-name company of its application and information about its manufacturing process.⁴⁷ The purpose of this and following exchanges is to arrive either at an agreed-on list identifying patents to be litigated or at an exchange of patent lists when no agreement can be reached.⁴⁸ Regardless of whether agreement is reached, the brand-name company then has 30 days to sue the biosimilar applicant in order to assert its patents.⁴⁹

Separately, the biosimilar applicant must notify the brand-name company 180 days prior to its intended product launch.⁵⁰ The latter may then seek to preliminarily enjoin the product launch using any patent previously identified as relevant to the biosimilar product but not included in the initial litigation.⁵¹

It remains to be seen whether the Kennedy bill will be joined by still more competing bills falling elsewhere along the innovator/generic spectrum of interests.

THE ROAD AHEAD

Establishing an approval pathway for biosimilars is long overdue, as lawmakers themselves have conceded.⁵² Yet simplicity is not the motif characterizing the path to that end. The scientific complexities of establishing comparability, similarity, or interchangeability for biologics are realities that must be—and are being—addressed by all sides.⁵³ These complexities are the subject of heated debate, as are the ways to best ensure the safety and efficacy of biologics, the intellectual property and commercial interests of innovator and generic companies alike, and the accessibility of biologics for the patients who need them.

Muddying the waters even further is the presumption that cost savings for biosimilars will be less than those enjoyed for traditional generic drugs.⁵⁴ In fact, it has been proposed by some that biosimilars are unlikely to offer *any* significant savings.⁵⁵

To say the least, it remains unclear which of the existing bills will prevail, in what form, when, and to what effect.⁵⁶ However this process moves forward, we can only hope that the outcome will provide at least some measure of relief and fairness where it is needed.

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⁴⁷ S. 1695, §2(a)(1)(2)(A).

⁴⁸ *Id.* at §2(a)(1)(3)–(5).

⁴⁹ *Id.* at §2(a)(1)(6)(A) and (B).

⁵⁰ *Id.* at §2(a)(1)(8)(A).

⁵¹ *Id.* at §2(a)(1)(8)(B). As used in this context, a patent that is “relevant” to the biosimilar product is one that is listed pursuant to S. 1695, §2(a)(1)(3)(A) or (B).

⁵² See, e.g., *The Future of Biologics – Examining Market Competition, Innovation and Patient Safety*, Remarks by Sen. Orrin G. Hatch before the U.S. Chamber of Commerce (April 25, 2007) (available online at http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.View&PressRelease_id=1796 (“Hatch”).

⁵³ See, e.g., Woodcock and Hatch.

⁵⁴ *Generic Biologic Drugs Unlikely to Offer Significant Savings*, Medical News Today (May 6, 2007) (available online at <http://www.medicalnewstoday.com/printerfriendlynews?newsid=69584>) (accessed May 23, 2007).

⁵⁵ *Id.*

⁵⁶ June 5, 2007 personal communication with Congressional Staffer. See, also, *Hopes for Speedy Action on Generic Biologics Bill Fade in Senate*, Biologic Drug Report (April 16, 2007) (available online at <http://www.biologicdrugreport/News/news-041607.htm>) (accessed June 8, 2007).

