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INNOVATORS AND IMITATORS: AN ANALYSIS OF PROPOSED LEGISLATION IMPLEMENTING AN ABBREVIATED APPROVAL PATHWAY FOR FOLLOW-ON BIOLOGICS IN THE UNITED STATES

DONNA M. GITTER*

ABSTRACT

Biopharmaceuticals, also called biologics, account for nearly one out of eight prescriptions written worldwide. One source estimates that more than $10 billion worth of biologics will come off patent by 2016. Few generic competitors are likely to enter this market, however, in light of the fact that no abbreviated approval pathway presently exists for generic biologics, also called follow-on protein products. Without such a system in place, generic manufacturers must perform a full complement of lengthy and costly clinical trials in order to receive approval from the U.S. Food and Drug Administration to market their follow-on biologics. Congress is presently considering legislation, titled the Access to Life-Saving Medicine Act, which would permit expedited approval of certain off-patent biologics. This legislation is modeled upon the Hatch-Waxman Act of 1984, which facilitates abbreviated approval of generic versions of traditional pharmaceuticals.

This Article analyzes the legal and policy implications of an abbreviated approval pathway for follow-on biologics, focusing on three salient aspects of this issue. First, the Article examines the effect of the Hatch-Waxman Act on the market for conventional drugs and concludes that legislative enactment of an abbreviated approval pathway for follow-on protein products will have a similar salutary effect on the market for these biological products. Second, the Article considers the current state of scientific knowledge regarding biologics and determines that an abbreviated approval framework for biologics is feasible, at least for simpler molecules. Third, the Article analyzes the intellectual property implications of an abbreviated approval pathway for follow-on protein products. The Article offers some recommendations for amending the Access to Life-Saving Medicine Act so as to maximize pioneer firms' incentives to innovate while simultaneously encouraging competition from follow-on manufacturers.

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I. INTRODUCTION

Biopharmaceuticals, also called biological products or, simply, biologics,[1] now account for approximately one out of eight prescriptions written worldwide.[2] These products, which have proven particularly effective in treating certain chronic conditions, such as rheumatoid arthritis, multiple sclerosis, cancer, and diabetes,[3] are also quite expensive relative to nonbiologic pharmaceuticals, costing as much as twenty times more annually.[4] Although one source estimates that more than $10 billion worth of biopharmaceutical drugs will come off patent by 2016,[5] few generic competitors will find it worthwhile to enter the market upon the expiry of these patents in light of the fact that no abbreviated approval pathway[6] presently exists for generic biologics.[7] Without such a system in place, generic manufacturers

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1. *See* Ronald A. Rader, *What Is a Biopharmaceutical?*, BIOEXECUTIVE INT'L, Mar. 2005, at 60, 61, *available at* http://www.bioexecutiveintl.com/content/articles/frame.asp?ck=true&issue=0305&article=11 (noting the multifarious definitions of the term "biopharmaceutical" and offering the following definition: "noun: a pharmaceutical product manufactured by biotechnology methods (involving live organisms; bioprocessing)").

2. N. LEE RUCKER, AARP PUBLIC POLICY INSTITUTE, BIOLOGICS IN PERSPECTIVE: EXPANDED CLINICAL OPTIONS AMID GREATER COST SCRUTINY 1 (2007), *available at* http://assets.aarp.org/rgcenter/health/fs136_biologics.pdf.

3. *Id.*

4. Press Release, Express Scripts, Inc., Biotech Drug Spending Increases 21 Percent Even as Growth in Rx Expenditure Slows (Apr. 25, 2007), http://phx.corporate-ir.net/phoenix.zhtml?c=69641&p=irol-newsArticle&ID=989907&highlight=. One source states that annual treatment cost per patient for biologics can total tens of thousands of dollars per year and in some cases may exceed $100,000 annually. REP. HENRY WAXMAN, BACKGROUNDER ON BIOLOGICS 2, http://www.house.gov/waxman/pdfs/biologicsbackground_2.14.07.pdf (last visited June 23, 2008).

5. ENGEL & NOVITT, LLP, POTENTIAL SAVINGS THAT MIGHT BE REALIZED BY THE MEDICARE PROGRAM FROM ENACTMENT OF LEGISLATION SUCH AS THE *ACCESS TO LIFE-SAVING MEDICINE ACT* (H.R. 6257/S. 4016) THAT ESTABLISHES A NEW CBLA PATHWAY FOR FOLLOW-ON BIOLOGICS 12, tbl.4a, (2007) [hereinafter ENGEL & NOVITT].

6. The U.S. Food and Drug Administration (FDA) defines an abbreviated application as one that relies, to at least some extent, on the Agency's conclusions regarding the safety and effectiveness (or safety, purity, and potency) of an approved product and also contains additional data necessary, other than the underlying clinical data supporting the approved product, to establish that the follow-on product is safe and effective. *Safe and Affordable Biotech Drugs—The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 5 (2007) [hereinafter *Hearing on Biotech Drugs*] (statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, FDA), *available at* http://oversight.house.gov/documents/20070326104056-22106.pdf. For a discussion of the abbreviated approval scheme for nonbiologic generic drugs, see *infra* Part III.B.

7. It should be noted that the terms "generic biologic" and "biogeneric" are contentious ones, as the branded pharmaceutical industry contends that generic biologics do not truly exist, given that biologics are so strongly affected by the manufacturing process. These firms prefer the term "off-patent biologic" or "follow-on biologic" (FOB). *See* Biotechnology Indus. Org. (BIO), BIO Citizen Petition to the FDA: Follow-On Therapeutic Proteins 9 (Apr. 23, 2003) [hereinafter BIO Petition], *available at* http://www.bio.org/healthcare/followon/BIO_CP--FINAL_DRAFT_4_22_03.pdf (describing a follow-on therapeutic protein as a product that does not "contain a full complement of original non-clinical and clinical data and that relies on any data or information contained

must perform a full complement of lengthy and costly clinical trials in order to receive approval from the U.S. Food and Drug Administration (FDA) to market their follow-on biologics.

After many years of debate about this issue among numerous stakeholders, including the branded pharmaceutical industry, generic pharmaceutical firms, scientific researchers, government officials, employers facing rising health care costs, pharmacy benefits managers, and patient groups, as well as academics, Congress is presently considering legislation, titled the Access to Life-Saving Medicine Act,[8] that would permit expedited FDA approval of certain off-patent biologics. This legislation is modeled on the Hatch-Waxman Act of 1984 (HWA),[9] which facilitates abbreviated approval of generic versions of conventional pharmaceuticals. In light of the unique nature and variability of each biological product, the Access to Life-Saving Medicine Act would allow the FDA to consider each biological product on a case-by-case basis.

This Article analyzes the legal and policy implications of implementing an abbreviated approval pathway for follow-on biologics. Part II of this Article offers a brief primer on biologics, describing both their scientific characteristics as well as their significance in the marketplace. Part III examines the current regulatory scheme for FDA approval of conventional pharmaceuticals, both branded and generic, and for biologics as well, noting that, while the HWA furnishes an abbreviated approval pathway for generic drugs, there is no analogous expedited approval pathway for follow-on biologics. Part IV explores the recent decision in *Sandoz, Inc. v. Leavitt*,[10] in which the United States District Court for the District of Columbia required the FDA to take action on an abbreviated application for a follow-on biologic product. The Access to Life-Saving Medicine Act, a

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in another product's application" (emphasis omitted)); *see also* Andrew Wasson, Comment, *Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biological Products*, 2005 DUKE L. & TECH. REV. 0004, ¶ 4 n.16 (2005), http://www.law.duke.edu/journals/dltr/articles/pdf/2005dltr0004.pdf (noting that brand name firms prefer the term "off-patent"). The generic pharmaceutical industry, however, maintains that the terms "generic biologic" and "biogeneric" are indeed appropriate. *See id.* This Article uses the terms "follow-on biologic" or "follow-on protein product," which are terms employed by the FDA as well. *See* FDA, Regulatory and Scientific Issues Related to Developing Follow-On Protein Products, http://www.fda.gov/cder/regulatory/follow_on/default.htm (last visited June 23, 2008) ("We use the informal term *follow-on protein products* generally to refer to proteins and peptides that are intended to be sufficiently similar to a product already approved under the Federal Food, Drug, and Cosmetic Act or licensed under the Public Health Service Act to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product.").

8. Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007). The Senate companion bill is S. 623, 110th Cong. (2007).

9. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 35, and 42 U.S.C.).

10. 427 F. Supp. 2d 29 (D.D.C. 2006).

pending congressional bill proposing an abbreviated approval pathway for follow-on biologics, is the subject of Part V. Part VI analyzes the legal and policy implications of an abbreviated approval pathway for follow-on biologics, focusing on three distinct aspects of this issue. First, drawing upon legal and economic literature, this Part examines the effect of the Hatch-Waxman Act on the market for conventional drugs and concludes that legislative enactment of an abbreviated approval pathway for follow-on protein products will have a similar, though not identical, salutary effect on the market for these biological products. Second, Part VI considers whether it is feasible, given the current state of scientific knowledge, to approve follow-on biologics in the absence of a full array of clinical trials. A comprehensive analysis of legal and scientific scholarship, as well as of legislative testimony, reveals that scientific knowledge presently permits an abbreviated approval pathway for follow-on biologics, at least for simpler molecules. Third, this Part also considers the intellectual property implications of an abbreviated approval pathway for follow-on protein products and offers recommendations for structuring intellectual property protection so as to maximize pioneer firms' incentives to innovate while simultaneously encouraging competition from follow-on manufacturers. Part VII examines the recently established approval framework for follow-on protein products in the European Union. Ultimately, the enactment of U.S. legislation creating an abbreviated approval pathway for follow-on biologics will prove essential because of the potential it offers for dramatic savings for the health care system. The proposed legislation properly entrusts the scientific aspects of the approval process to the FDA, the body that the U.S. public currently charges with such decisions. In terms of intellectual property protection, with certain modifications, the proposed bill can, with certain modifications, effectively preserve incentives for innovation.

II. A PRIMER ON BIOLOGICS

A. Biologics Defined

A biological product, or biologic, is "a product that is derived from a living organism and used in the prevention, treatment, or cure" of human disease.[11] As explained by one source, biologics "include vac-

11. *Primer on Generic Biologics*, HEALTH CARE ADVISORY (Alston & Bird, LLP, Atlanta, Ga.), Nov. 20, 2006, at 1 [hereinafter Alston & Bird], *available at* http://www.alston.com/files/Publication/ef5353ff-48a3-4718-ad12-5b184143070d/Presentation/PublicationAttachment/cdf245bf-896b-4a94-a364-06d3b18d13a7/Biogenerics%20Primer%20FDA%20Advisory.pdf; *see also* 42 U.S.C. § 262(i) (2000) ("[T]he term 'biological product' means 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

cines, hormones, human growth factors, enzymes, clotting and anti-clotting factors, and recombinant protein products."[12]

According to the FDA, "[b]iologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues," and "are isolated from a variety of natural sources—human, animal, or microorganism—and may be produced by biotechnology methods and other cutting-edge technologies."[13] The FDA further notes that "[g]ene-based and cellular biologics . . . often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available."[14] For example, one blockbuster biologic, Amgen's EPOGEN®, is a genetically engineered form of the naturally occurring human hormone erythropoietin and is used to combat anemia in patients with chronic kidney disease.[15]

Biologics are distinguishable in several ways from conventional drugs, which are defined statutorily to include products that are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."[16] Whereas biologics "are typically large protein molecules derived from living cells and manufactured through DNA or RNA synthesis," drugs "are typically small molecules derived from chemical synthesis."[17] In addition, drugs "typically have well-defined structures."[18] By contrast, biologics "tend to be a mixture of heterogeneous proteins and impurities, each of which may contribute to the product's biological activity, efficacy, and safety in ways that may be only partly understood, controlled and reproduced."[19] Thus, as ex-

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compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.").

12. Alston & Bird, *supra* note 11, at 1; FDA, Ctr. for Biologics Evaluation and Research, Frequently Asked Questions, http://www.fda.gov/cber/faq.htm [hereinafter FDA FAQs] (last visited June 23, 2008) ("Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.").

13. FDA FAQs, *supra* note 12.

14. *Id.* For a list of the top twenty biologics in 2006, see PipelineReview.com, Top 20 Biologics 2006 (Feb. 12, 2007), http://www.pipelinereview.com/content/view/15649/353.

15. Amgen, Recombinant DNA Technology, http://www.amgen.com/science/about_biotechnology_recombinant_dna_technology.html (last visited June 23, 2008). In fiscal year 2005, the biggest drug expenditure by the Centers for Medicare and Medicaid Services (CMS) on any single drug was $2 billion on EPOGEN®. WAXMAN, *supra* note 4, at 2.

16. 21 U.S.C. § 321(g)(1)(B) (2000).

17. Alston & Bird, *supra* note 11, at 2. Proteins are generally one hundred to one thousand times larger than small molecules. Huub Schellekens, *How Similar Do 'Biosimilars' Need to Be?*, 22 NATURE BIOTECHNOLOGY 1357, 1357 (2004).

18. Alston & Bird, *supra* note 11, at 2.

19. *Id.* In particular, it is the glycosylation of some proteins, which refers to "the variable attachment of small chains of sugars to the protein backbone," that renders glycosylated proteins more complex than nonglycosylated ones. David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for*

plained by one source, "a given biologic is not generally interchangeable with another," and even small changes in the manufacturing process could result in a dramatically different final product.[20] Indeed, "a generic biologic produced by another manufacturer using a distinct manufacturing process could likely produce a product different than intended."[21] Perhaps the most significant difference between biologics and conventional drugs, however, is immunogenicity, meaning that most biologics stimulate an immune response in the body, prompting the formation of antibodies. Some of these antibodies may detrimentally impact patient health.[22]

B. The Importance of Biologics in the Marketplace

The FDA has approved more than 250 biological products,[23] which are serving more than 800 million patients worldwide.[24] In 2005 alone, the FDA approved thirty-nine new biologic products and indications.[25]

Biologics generated revenue of about $32.8 billion in the United States in 2005.[26] While these constituted approximately thirteen percent of the total $251.8 billion in prescription sales to U.S. pharmacies in 2005,[27] biologics are likely to account for an increasing market

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Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies, 60 FOOD & DRUG L.J. 143, 224 (2005).

20. Alston & Bird, *supra* note 11, at 2; Rob Garnick, *Counterpoint: Why Biogenerics Are a Strawman*, 24 NATURE BIOTECHNOLOGY 268, 269 (2006) (stating that "each biopharmaceutical manufacturing process is necessarily unique" and that "small changes to any such process can have profound consequences on the end product").

21. Alston & Bird, *supra* note 11, at 2. See *supra* note 7, regarding the term "generic biologic." For a description of the basic steps in manufacturing a biologic, see BIOTECHNOLOGY INDUS. ORG., THE DIFFERENCE WITH BIOLOGICS: THE SCIENTIFIC, LEGAL, AND REGULATORY CHALLENGES OF ANY FOLLOW-ON BIOLOGICS SCHEME 6-7 (2007) [hereinafter THE DIFFERENCE WITH BIOLOGICS], *available at* http://www.bio.org/healthcare/followonbkg/WhitePaper.pdf. The hundreds of steps typically involved in production, which "involve numerous in-house standards," give rise to the maxim that, for biopharmaceuticals, the "process is the product." Schellekens, *supra* note 17, at 1357. See *infra* notes 295-98 and accompanying text for a discussion of the importance of the production process.

22. *See* Schellekens, *supra* note 17, at 1358 & Box 2 (describing the problem of immunogenicity); *infra* Part VI.B.3. (discussing immunogenicity). Only for one type of protein product, vaccines, does the stimulation of antibodies actually prove beneficial. *Follow-On Biologics: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 110th Cong. 7 (2007) [hereinafter *Hearing on Follow-On Biologics*] (statement of Jay P. Siegel, M.D., Johnson & Johnson), *available at* http://help.senate.gov/Hearings/2007_03_08/2007_03_08.html.

23. *See* Biotechnology Indus. Org., Health Care Overview, http://www.bio.org/healthcare/ (last visited June 23, 2008).

24. *James Greenwood Assumes BIO Presidency as Industry Has Banner Year*, TRACLEER & PPH NEWS, Jan. 5, 2005, http://pph-net.org/news/tracleer-news-0011.htm.

25. Biotechnology Indus. Org., Health Care Overview, *supra* note 23.

26. Rachel Melcer, *Generic Biotech Drugs Are Proposed*, ST. LOUIS POST-DISPATCH, Feb. 15, 2007, at C1.

27. *Id.*

share in the coming years.[28] Of the 2300 pharmaceutical products in clinical development in 2005, twenty-seven percent were biologics.[29] Because biologics are often twenty times more expensive per patient per day than traditional drugs[30] and increasing in cost at a dramatic rate,[31] biologics are expected to drive U.S. health care costs ever higher.[32]

Biologics are rendered even more costly than conventional drugs because they do not face robust generic competition,[33] which is due to the absence in the United States of "a clear regulatory pathway" for approval of follow-on biologics.[34] Generic versions of conventional drugs have served to lower consumers' health care costs considera-

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28. According to Medco Health Solutions, one of the largest pharmacy-benefits managers, spending on biotech and specialty medicines grew 16.9 percent in 2005, as compared to the 5.4 percent average for traditional drugs. Linda Loyd, *Opening a Path For Biotech Generics*, PHILA. INQUIRER, Sept. 19, 2006, at E1. As noted by Rep. Jo Ann Emerson (R-MO), the cost of biologics is of particular concern in terms of the future solvency of the Medicare program. *Access to Life-Saving Medicine Act to Give FDA Biogenerics Framework*, PHARMA MARKETLETTER, Feb. 15, 7007. The Centers for Medicare and Medicaid Services (CMS) estimated that, in 2005, "nearly one-third of top products purchased by Medicare [were] biopharmaceuticals." GENERIC PHARMACEUTICAL ASSOCIATION (GPHA), BIOPHARMACEUTICALS ("FOLLOW-ON" PROTEIN PRODUCTS): SCIENTIFIC CONSIDERATIONS FOR AN ABBREVIATED APPROVAL PATHWAY 4 (2004) [hereinafter GPHA SCIENTIFIC CONSIDERATIONS], *available at* www.gphaonline.org/AM/TemplateRedirect.cfm?template=/CM/ContentDisplay.cfm&ContentID=1670.

29. Press Release, IMS Health, IMS Health Reports Global Pharmaceutical Market Grew 7 Percent in 2005, to $602 Billion (Mar. 21, 2006), *available at* www.imshealth.com/ims/portal/front/article/0,2775,6025_3665_77491316,00.html.

30. *See supra* note 4 and accompanying text (regarding the relative costs of biologics and traditional drugs); William L. Warren et al., *Abbreviated Approval of Generic Biologics,* GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Dec. 1, 2006, *available at* http://www.genengnews.com/articles/chitem.aspx?aid=1936 ("Biologics are typically 20 times more expensive per patient per day than a drug counterpart."). Biologics are relatively expensive when compared to small molecule drugs in large part because biologics require "exquisitely controlled manufacturing with cell culture and protein purification; BIO [Biotechnology Industry Organization] estimates that the cost of materials for biotechnology manufacturing can range from twenty to 100 times that of small molecule drugs." Dudzinski, *supra* note 19, at 179.

31. According to one report, the cost of biologics increased 17.5 percent in 2005, compared to an increase of ten percent for traditional drugs. *See The Generic Drug Maze: Speeding Access to Affordable, Life Saving Drugs: Hearing Before the Special S. Comm. on Aging*, 109th Cong. 11 (2006) (testimony of Mark Merritt, President and Chief Executive Officer, Pharm. Care Mgmt. Ass'n), *available at* http://aging.senate.gov/events/hr161mm.pdf.

32. Alston & Bird, *supra* note 11, at 1 ("Biologics are likely to drive health care costs steadily higher."); *cf.* Warren et al., *supra* note 30 (stating that proposed legislation intended to spur the approval of follow-on biopharmaceuticals "would bring desperately needed competition into the biopharmaceutical marketplace and put an end to indefinite monopolies").

33. See *supra* note 7 regarding the term "generic biologic."

34. *PCMA: Medicare Part B Program Could Save $14 Billion in Prescription Drug Costs Through Biogenerics*, U.S. NEWSWIRE, Jan. 4, 2007 ("Unlike conventional drug products where generic competition is robust, the FDA lacks a clear regulatory pathway to approve follow-on biologics, or 'biogenerics.' ").

bly.[35] Presently, many stakeholders, including the branded pharmaceutical industry, generic pharmaceutical firms, scientific researchers, government officials, employers facing rising health care costs, pharmacy benefits managers, and patient groups, as well as academics, are debating whether Congress should enact legislation to create a regulatory pathway that would enable manufacturers to market follow-on biologics. This issue is growing in importance as some of the blockbuster biologics developed at the inception of the biotech era in the 1980s have lost or will soon lose patent protection.[36] Informed consideration of the implications of enacting an abbreviated approval pathway in order to stimulate the development of follow-on biologics by generic manufacturers first requires a thorough understanding of the separate regulatory pathways for drugs, both branded and generic, and for patented biologics.

III. THE REGULATORY PATHWAYS FOR DRUGS, BOTH BRANDED AND GENERIC, AND FOR BIOLOGICS

In the United States, drugs are regulated exclusively under the Food, Drug and Cosmetics Act (FDCA).[37] Most biologics, however, are approved for marketing under provisions of the Public Health Service Act (PHSA).[38] Because biologics typically meet the definition of "drugs" under the FDCA,[39] they are governed by that statute as

35. *See* Henry Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, 8 GEO. PUB. POL'Y REV. 7, 21 (2003) (stating that congressional legislation, the HWA, "has fostered a vigorous generic industry with substantial benefits to consumers from price reductions"). It should be noted, however, that some commentators believe that, "due to the complexity of the development and testing of biologics, any generic versions would likely result in more modest savings than generic versions of conventional drugs." Alston & Bird, *supra* note 11, at 2. Others contend, however, "that even a price reduction of at least 20 percent could result in significant savings to consumers." *Id.; cf. GPhA Hails Introduction of Legislation to Bring Affordable Generic Biopharmaceutical Medicines to Consumers*, PR NEWSWIRE, Sept. 29, 2006 ("Even a 5% to 10% reduction in biopharmaceutical costs could amount to millions in savings to consumers and the healthcare system."). See *infra* note 215 and accompanying text regarding estimates of cost savings resulting from an abbreviated approval pathway for follow-on biologics.

36. *See* Kirsty Barnes, *Sandoz Approval Could Open the Floodgates for Biosimilars in US*, IN-PHARMA TECHNOLOGIST.COM, June 6, 2006, http://www.in-pharmatechnologist.com/news/ng.asp?id=68163-sandoz-fda-biosimilar-omnitrope-follow-on-protein (citing insulin, human growth factors, epoetin, colony stimulating factors, interferon alpha, and interferon beta as among the biologics that will soon face competition from follow-on biologics).

One source estimates that more than $10 billion worth of biopharmaceutical drugs will come off patent by 2016. ENGEL & NOVITT, *supra* note 5, at 12 tbl.4a.

37. 21 U.S.C. §§ 301-399 (2000).

38. 42 U.S.C. § 262 (2000). According to the FDA, the "majority of protein products are licensed as biological products under the [PHSA], not approved as drugs under the [FDCA]." FDA, Omnitrope Questions and Answers, http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm [hereinafter Omnitrope Q&A] (last visited June 23, 2008).

39. *See supra* note 16 and accompanying text (defining drugs pursuant to the FDCA).

well.[40] Commentators have explained that while "[t]he primary objective of the FDCA is to ensure the safety and effectiveness of the final product, with controlling the manufacturing process a secondary concern," for biologics, "regulation under the PHSA is focused on 'rigid control of the manufacturing process,' which reflects the particular scientific and historical characteristics of biopharmaceuticals."[41]

Both the FDCA and the PHSA fall within the jurisdiction of the FDA.[42] As a result of an October 2003 reorganization of responsibilities within the FDA, the Center for Drug Evaluation and Research (CDER) regulates, under FDCA approval, the marketing of drugs and some biologics, including monoclonal antibodies for in vivo use; proteins intended for therapeutic use; immunomodulators; and growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease, or otherwise alter the production of hematopoietic cells in vivo.[43] The Center for Biologics Evaluation and Research (CBER) of the FDA regulates approval and marketing under the PHSA of a select group of other biologics,[44] including gene cel-

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40. FDA FAQs, *supra* note 12 (stating that "because most biological products also meet the definition of 'drugs' under the Federal Food, Drug, and Cosmetic Act (FD&C Act), they are also subject to regulation under FD&C Act provisions."). Moreover, the PHSA contains a provision stating that nothing in that Act shall affect the FDA's jurisdiction under the FDCA, thereby affirming that the FDA has the authority to regulate all biologics under the FDCA. 42 U.S.C. § 262(g) (2000) ("Nothing contained in this chapter shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the Federal Food, Drug, and Cosmetic Act.").

41. Michael J. Malinowski & Maureen A. O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163, 205-06 (1996). See *supra* notes 16-21 and accompanying text for a discussion of the particular characteristics of biologics that distinguish them from drugs and highlight the importance of their manufacturing process.

42. For a comprehensive discussion of the historical reasons for the separate enactment of the FDCA to regulate drugs and the PHSA to regulate biologics, see Dudzinski, *supra* note 19, at 145-79. For a more succinct description of this subject, see *The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. (2004) (statement of Lester M. Crawford, Acting Commissioner of Food and Drugs, Department of Health & Human Servs.), *available at* http://www.fda.gov/ola/2004/fob0623.html (explaining that "some proteins are licensed under the [PHSA] and some are approved under the [FDCA]").

43. FDA, Ctr. for Biologics Evaluation and Research, Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, http://www.fda.gov/cber/transfer/transfer.htm (last visited June 23, 2008) (explaining the apportionment of regulatory responsibility within the FDA for approval of drugs and biologics); Dawn Willow, *The Regulation of Biologic Medicine: Innovators' Rights and Access to Healthcare*, 6 CHI.-KENT J. INTELL. PROP. 32, 35 (2006) (explaining the apportionment of regulatory responsibility within the FDA for approval of drugs and biologics); *see also* FDA, Ctr. for Drug Evaluation and Research, Frequently Asked Questions to CDER, http://www.fda.gov/cder/about/faq/default.htm#1 (last visited June 23, 2008) (describing the role of CDER generally).

44. Willow, *supra* note 43, at 35 (explaining CBER's role in regulating biologics); FDA, Ctr. for Biologics Evaluation and Research, About CBER, http://www.fda.gov/cber/about.htm (last visited June 23, 2008).

lular products, gene therapy products, vaccines, allergenic extracts for allergy tests, antitoxins, and blood and blood components.[45]

In order to evaluate the viability of an abbreviated approval process for follow-on biopharmaceuticals, it is vital to consider the typical drug development and approval process for drugs, both branded[46] and generic, and also for branded biologic products.

A. The Approval Process for Branded Drugs

Professor Berndt, in a paper coauthored with two others, provides a brief overview of the approval pathway for conventional drugs.[47] This process consists of pre-clinical development, clinical development, approval, and marketing.[48]

The pre-clinical phase of development begins with basic discovery and research, including in vitro and in vivo experiments in "academic, government, and industry laboratories."[49] As explained by Professor Berndt, "a lead or candidate compound is first identified and isolated after screening thousands of chemicals/proteins against a specific biological target," and then, "safety/toxicity animal studies are conducted with this compound."[50] After carrying out extensive testing in various animal models, a process that generally takes one to five years, "the developing company, known as the sponsor, can file an Investigational New Drug ('IND') application."[51] The FDA must evaluate the IND and grant permission before the sponsor can begin clinical studies in humans.[52] Approximately forty percent of INDs transition to the next stage of drug development, clinical testing.[53]

The clinical phase of testing drugs in humans consists of three phases.[54] Phase I clinical trials test for safety and tolerability of the drug in humans; involve about twenty to one hundred healthy, nominally paid volunteers; and generally last between one to three months.[55] Phase II clinical trials continue testing for safety and tol-

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45. Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, *supra* note 43.

46. The terms "brand-name drug," "brand drug," "innovator drug," " 'pioneer' drug," and "reference drug" are synonymous. *See* Willow, *supra* note 43, at 33 & n.14. They will be used interchangeably in this Article.

47. Ernst R. Berndt et al., *Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA* (Nat'l Bureau of Econ. Research, Working Paper No. 11425, 2005), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=745818.

48. *See id.* at 7-10.

49. *Id.* at 7.

50. *Id.*

51. *Id.* at 7-8.

52. *Id.* at 8.

53. *Id.*

54. *Id.*

55. *Id.*

erability and also assess the preliminary efficacy of the drug.[56] Phase II trials often involve several hundred unpaid volunteers diagnosed with a particular condition and generally last about six months to two years.[57] Phase III clinical trials constitute "the most costly stage of drug development."[58] "[D]esigned to evaluate statistically the safety and efficacy of the drug . . . within a larger and typically more diverse population," these trials involve hundreds to several thousand patients and last an average of four years.[59] Approximately sixty-four percent of the drugs that advance to Phase III trials are promising enough to be submitted as New Drug Applications (NDAs) and new Biologic License Applications (BLAs) to the FDA.[60]

An NDA includes, inter alia, the following information: (1) reports of investigations demonstrating the safety and efficacy of the drug; (2) a list of the components of the drug; (3) a statement of the drug's composition; (4) a description of the methods and facilities used for the "manufacture, processing, and packing" of the drug; (5) samples of the drug as required; and (6) samples of the labeling.[61] Currently, the FDA takes, on average, one year to evaluate the NDA or BLA.[62] Approximately ninety percent of the "NDAs/BLAs eventually receive FDA approval and are marketed."[63] Once it approves a new product, the FDA publishes the drug name and related patent information in its *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the *Orange Book*.[64]

Phase IV clinical trials, also called post-marketing studies, are sometimes performed, either "as a condition required by the FDA for initial market approval," "to obtain approval for a new indication," or for "marketing purposes."[65] Phase IV studies often observe the long-term effects of a drug in a larger population and involve thousands of patients over a period of many years.[66]

Ultimately, for small molecule drugs, slightly less than twenty-one percent of the products that enter clinical trials receive market-

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56. *Id.* at 8.
57. *Id.* at 8-9.
58. *Id.* at 9.
59. *Id.*
60. *Id.*
61. 21 U.S.C. § 355(b)(1)(D) (2000).
62. Berndt et al., *supra* note 47, at 9.
63. *Id.*
64. *See* 21 C.F.R. § 314.3(b) (2000) (defining a "listed drug" as one that has received FDA approval and been listed in the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations"). A searchable electronic version of the *Orange Book* is available online at FDA, Electronic *Orange Book*, http://www.fda.gov/cder/ob/ (last visited June 23, 2008).
65. Berndt et al., *supra* note 47, at 9.
66. *Id.* at 9-10.

ing approval;[67] the comparable figure for biologics is less than one-third.[68] While the development of biologics involves a higher likelihood of clinical success, the mean clinical development times are longer for biologics.[69] In terms of research and development costs, biologics and traditional drugs are comparable.[70] Recent estimates suggest that the average cost of bringing a new small molecule medicine to market is between $800 million and $1.7 billion.[71] For a new biologic, the figure is $1.2 billion.[72] Small molecule drugs differ significantly from biologics, however, in that patent-protected small molecule drugs typically have a limited period of market exclusivity before facing generic competition, whereas biologics can potentially enjoy monopoly status indefinitely.[73] In the realm of traditional drugs, however, generic competition thrives due to the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act (HWA),[74] which amended the FDCA.[75]

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67. *Id.* at 8-9. This figure was achieved by multiplying the various probabilities that a drug will proceed through the three phases of clinical trials to NDA status and then on to final FDA approval.

68. THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 4; *see also* Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFFAIRS 1291, 1293 (2006) (citing a recent study finding that "biologics realized higher probabilities of clinical success" and stating that thirty percent of biologics achieve clinical success compared with 21.5 percent of new drugs).

69. Grabowski et al., *supra* note 68, at 1293 (stating that the mean clinical development time is ninety-eight months for biologics as compared to ninety months for traditional drugs).

70. *Id.*

71. PRADEEP SURESH ET AL., IMPACT OF IMPROVING PHARMACEUTICAL PRODUCT DEVELOPMENT AND MANUFACTURING 3 (2006), *available at* http://www.purdue.edu/dp/ptec/aicheV5.pdf. This cost estimate is for new chemical entities, however. According to a May 2002 study by the National Institute for Health Care Management Foundation, "two-thirds of the prescription drugs approved by the FDA between 1989 and 2000 were modified versions of existing medicines or identical to drugs already on the market" and, therefore, were less costly to bring to market. Russell Mokhiber & Robert Weissman, *Stripping Away Big Pharma's Figleaf*, COMMONDREAMS.ORG, June 13, 2002, http://www.commondreams.org/views02/0613-07.htm; *see also* PUBLIC CITIZEN, RX R&D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY'S R&D "SCARE CARD" 7 (2001), *available at* http://www.citizen.org/documents/acfdc.pdf (contending that the cost of developing a new drug is $114 to $150 million).

72. THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 4 (citation omitted).

73. *See* Press Release, U.S. Congress, Waxman, Schumer, and Clinton Unveil Bill to Create Clear Pathway for Generic Biologic Drugs (Feb. 14, 2007) [hereinafter "Access to Life-Saving Medicine Act" Press Release], *available at* http://www.house.gov/waxman/pdfs/biologicspressrelease_2.14.07.pdf ("Currently there is no statutory pathway for generic versions of biotech drugs to enter the market, even after all patents have expired. As a result, the manufacturers of biotech drugs can charge monopoly prices, indefinitely.").

74. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 35, and 42 U.S.C.).

75. 21 U.S.C. §§ 301-399 (2000).

B. The Approval Pathway for Generic Drugs Pursuant to the Hatch-Waxman Act

Prior to the enactment of the HWA in 1984, a generic manufacturer had to conduct the same clinical trials as the firm that was awarded marketing approval for the innovator drug, which greatly delayed the launch of more affordable generic drugs.[76] The HWA affords drug manufacturers two expedited approval pathways that allow certain drugs to avoid the full NDA process.[77]

The first "shortcut" offered by the HWA, known as an abbreviated new drug application (ANDA) or 505(j) application,[78] is the " 'classic' application[] for generic drugs that are identical or almost identical to the pioneer . . . drug."[79] This approval pathway is meant for drugs that are the "same," meaning "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use," to drugs that have already been approved.[80] As noted by one commenta-

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76. *See* George Fox, Note, Integra v. Merck*: Limiting the Scope of the § 271(e)(1) Exception to Patent Infringement*, 19 BERKELEY TECH. L.J. 193, 195 n.16 (2004) ("Prior to the enactment of the Hatch-Waxman Act, generic drug manufacturers seeking approval for a generic drug . . . were required to satisfy the requirements as a new drug applicant. Thus, the cost of approval was a major barrier to the entry of generic drugs into the market."); Stephanie E. Piatt, Note, *Regaining the Balance of Hatch-Waxman in the FDA Generic Approval Process: An Equitable Remedy to the Thirty-Month Stay*, 59 N.Y.U. ANN. SURV. AM. L. 163, 165 (2003) ("Prior to 1984, generic drug companies had to conduct these same new drug clinical trials [as the sponsor], and thus the time to generic availability was . . . protracted.").

77. *See* 21 U.S.C. § 355(j) (2000) (allowing any person to file an abbreviated new drug application (ANDA)); Federal Food, Drug, and Cosmetics Act, Pub. L. No. 75-717, § 505(b)(2), 52 Stat. 1040, 1052 (1938) (codified as amended at 21 U.S.C. § 355(b)(2) (2000) (allowing a sponsor to rely on the FDA's prior approval of the drug); *see also* Dudzinski, *supra* note 19, at 198 ("Hatch-Waxman implemented the ANDA and section 505(b)(2) as complementary routes to approval of a generic drug."). It should be noted that both of these pathways are applicable only when the operative patent and non-patent marketing exclusivity provisions for the innovator drug have expired. *See* FDA, Ctr. for Drug Evaluation and Research, Omnitrope (somatropin [rDNA origin]) Questions and Answers (May 30, 2006), http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm ("A 505(b)(2) application, like an application under 505(j) for approval of a generic drug, can only be approved when the applicable patent and marketing exclusivity protections for the innovator drug have expired."). See *infra* notes 107 & 113 and accompanying text for an explanation of non-patent "marketing exclusivity."

78. 21 U.S.C. § 355(j) (2000).

79. *See* Valerie Junod, *Drug Marketing Exclusivity Under United States and European Union Law*, 59 FOOD & DRUG L.J. 479, 479 n.3 (2004).

80. 21 C.F.R. § 314.92(a) (2007). See *supra* note 64 regarding the use of the term "listed drug" to refer to a drug already approved by the FDA. The HWA provides that an ANDA must state, inter alia, the following information: that the conditions of use proposed in the new drug's labeling have already been accepted by the FDA for the listed drug; that the active ingredient(s) is (are) the same as the listed drug; that the dosage, route of administration, and strength are the same; that bioequivalence exists between the new and listed drug; and the labeling is the same except for changes due to different manufacturing companies. 21 U.S.C. § 355(j)(2)(A)(i)-(v) (2000). Under the HWA, bioequivalence is defined as a situation where "the rate and extent of absorption of the [generic] drug do not show a

tor, "[t]o expedite FDA review and approval, ANDAs require substantially less clinical and scientific information than NDAs" and "need not include any data relating to safety and effectiveness testing."[81] Instead, manufacturers seeking FDA approval via the ANDA pathway can rely in full or in part on the FDA's finding of safety and effectiveness for an already approved drug. The FDA makes such a finding based on data prepared by a third party, usually the sponsor of the pioneer drug who submitted the original NDA and performed the necessary clinical studies,[82] and also based on published scientific literature.[83] There is no need for further safety and efficacy testing for a true copy of a drug that the FDA has already approved.[84] "This reliance on the innovator's safety and effectiveness data allows generic applicants to save" considerable amounts of time and money.[85] Most drugs approved under section 505(j) are considered therapeutically equivalent to the reference drug.[86] As explained by one FDA official, "[i]n many jurisdictions, therapeutically equivalent drugs may be substituted at the pharmacy level, without a physician's intervention."[87]

The second expedited drug approval pathway offered by the HWA, named the 505(b)(2) pathway for the section of the FDCA in which it

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significant difference from the rate and extent of absorption of the listed drug." 21 U.S.C. § 355(j)(8)(B)(i) (2000).

81. James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 269 (2005); *see also* 21 U.S.C. § 355(j)(2)(A) (2000) ("The Secretary may not require that an abbreviated application contain information in addition to [the statutory requirements].").

82. *See* 21 U.S.C. § 355(j) (2000); Elizabeth H. Dickinson, *FDA's Role in Making Exclusivity Determinations*, 54 FOOD & DRUG L.J. 195, 196 (1999) (stating that ANDAs "rely on the [FDA's] previous finding of safety and effectiveness for the referenced innovator drug product."); Junod, *supra* note 79, at 479 n.3 ("Both 505(j) generic ANDAs and 505(b)(2) NDAs imply reliance (in full or in part) on the data prepared by a third party, usually the sponsor of the reference (pioneer) drug.").

83. Dudzinski, *supra* note 19, at 168-69 (explaining that the FDA will "accept published scientific or medical reports (in addition to any unpublished studies conducted by the generic manufacturer) instead of raw data as the main documentation to support evidence of safety and effectiveness of the proposed generic drug").

84. FDA Citizen Petition 2001P-0323/CP1, submitted by Morgan, Lewis & Bockius, LLP, on behalf of Pfizer Inc. and Pharmacia Corp. 7 (July 27, 2001), *available at* http://www.fda.gov/ohrms/dockets/dailys/01/Aug01/081001/cp00001_01.pdf.

85. *See* FEDERAL TRADE COMMISSION, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 5 (2002) [hereinafter FTC STUDY], *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf ("This reliance on the innovator's safety and efficacy data allows generic applicants to save very substantial amounts of money in development costs.").

86. *See Hearing on Biotech Drugs*, *supra* note 6, at 6 (testimony of Dr. Janet Woodcock). Therapeutically equivalent drugs are "approved drug products, often made by different manufacturers" that "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." *Id.* at 4.

87. *Hearing on Biotech Drugs*, *supra* note 6, at 6 (testimony of Dr. Janet Woodcock).

appears,[88] also permits a sponsor to rely on the FDA's prior approval of a drug, which the FDA bases on a third party's clinical data regarding safety and efficacy,[89] and on published scientific literature.[90] Once again, reliance on the innovator's data permits a generic manufacturer to save a great deal of time and money.[91] A 505(b)(2) NDA[92] differs from an ANDA, however, in that, while the latter is used for identical drugs,[93] a 505(b)(2) application is used for drugs that are only similar, not identical, to another drug.[94] For example, the new drug may have the same composition but a different proposed use than the branded drug,[95] or "may have a different dosage or rate of absorption."[96] "Instead of requiring full pre-clinical and clinical testing, an applicant must submit testing only as to the differences," and otherwise may rely on "published scientific literature" and "the FDA's prior finding that the similar branded drug is safe and effective."[97] An approved 505(b)(2) drug may be treated as interchange-

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88. *See* Federal Food, Drug, and Cosmetics Act § 505(b)(2), ch. 675, 52 Stat. 1052 (1938) (codified at 21 U.S.C. § 355(b)(2) (2000)).

89. *See* 21 U.S.C. § 355(b)(2)(A) (2000) (referring to an applicant's reliance on clinical investigations that 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"); 21 C.F.R. § 314.3 (2007) (defining a 505(b)(2) application as one "for which the investigations described in section 505(b)(1)(A) of the act and relied upon by the applicant for approval of the application 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"); Junod, *supra* note 79, at 479 n.3 ("Both 505(j) generic ANDAs and 505(b)(2) NDAs imply reliance (in full or in part) on the data prepared by a third party, usually the sponsor of the reference (pioneer) drug. 505(b)(2) applications can rely on data originating from more than one pioneer application.").

90. *See supra* note 83 and accompanying text.

91. *See supra* note 85 and accompanying text.

92. A 505(b)(2) application is one type of NDA. Dickinson, *supra* note 82, at 195-96 (describing the two types of NDAs, a 505(b)(1) application and a 505(b)(2)).

93. *See supra* notes 78-80 and accompanying text.

94. *See* Letter from Steven K. Galson, Dir., Ctr. for Drug Evaluation and Research, FDA, U.S. Dep't of Health & Human Servs., to Kathleen M. Sanzo, Stephan E. Lawton, and Stephen G. Juelsgaard 13 (May 30, 2006) [hereinafter FDA Response to Citizen Petitions], *available at* http//www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf (stating that "a 505(b)(2) application can be used for approval of those changes [from a listed drug relied upon] that are not so significant that they require a stand alone NDA, but that are significant enough that they may require additional safety or effectiveness data (and, therefore, are not eligible for approval under section 505(j)" (citation omitted)).

95. Junod, *supra* note 79, at 479 n.3 (stating that "505(b)(2) NDAs are used for drugs that are only somewhat similar to another drug (e.g., the same composition but a new indication)"); *see also* Dickinson, *supra* note 82, at 196 (stating that a 505(b)(2) applicant "submits data to support . . . a new indication"). For examples of the types of changes to approved drugs that could be submitted as 505(b)(2) applications, see FDA, GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2) 4-6 (1999) [hereinafter FDA DRAFT GUIDANCE], *available at* http://www.fda.gov/cder/Guidance/2853dft.pdf.

96. Warren et al., *supra* note 30.

97. *Id.*; *see also* Dudzinski, *supra* note 19, at 216 (stating that section 505(b)(2) permits the approval of "generic drugs with slightly less similarity to the pioneer drug than would be possible under ANDAs by allowing these generics to rely primarily on FDA findings, while supplementing these findings with literature-based information and limited

able with a similar branded product if it receives a suitable substitutability rating. If the new version is not considered interchangeable, "doctors must write a prescription specifically for the new version."[98]

Any drugs approved under either the 505(j) or 505(b)(2) pathway are referred to as generic drugs.[99] "While the capitalized cost of developing a new drug to the point of market approval is estimated at over $800 million,"[100] it costs only about $1 to $2 million to obtain approval for a generic version of the drug,[101] with most of the difference due to the fact that generic manufacturers need not conduct lengthy clinical trials.[102] The FDA emphasizes that it does not, however, disclose the underlying data in the pioneer NDA but rather simply permits the ANDA or 505(b)(2) applicant to rely on it rather than performing duplicative clinical studies.[103]

In light of the ease with which generic manufacturers could free ride on the research and development conducted by innovator firms (and later generic entrants could do likewise vis-à-vis the first generic entrant), Congress also included in the HWA several additional provisions relating to intellectual property.[104] Four provisions in particular benefit innovator firms. First, manufacturers of innovator drugs are entitled to apply for patent term restoration for a portion of the time spent obtaining regulatory approval.[105] Second, the Act im-

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clinical data (something prohibited under the ANDA) that describe the dissimilarities from the pioneer drug").

98. Warren et al., *supra* note 30.

99. FDA, Ctr. for Drug Evaluation and Research, http://www.fda.gov/cder/ogd/ (last visited June 23, 2008) ("A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price.").

100. WENDY H. SCHACHT & JOHN R. THOMAS, CONGRESSIONAL RESEARCH SERVICE, CRS REPORT FOR CONGRESS, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 18 (2007); *see also supra* note 71 and accompanying text.

101. SCHACHT & THOMAS, *supra* note 100, at 18.

102. *Id.* at 19.

103. FDA Response to Citizen Petitions, *supra* note 94, at 6 (stating that "[r]eliance on FDA's *finding* or conclusion that an approved drug is safe and effective does not involve disclosure to the ANDA or 505(b)(2) applicant—or to the public—of the data in the listed drug's NDA" and that "permitting appropriate reliance on what is already known about a drug . . . allows the pharmaceutical industry to target investment on innovative drug development and to avoid ethical concerns associated with unnecessary duplicative human testing, saving time and resources in the drug development and approval process").

104. *See* Bruce N. Kuhlik, *The Assault on Pharmaceutical Intellectual Property*, 71 U. CHI. L. REV. 93, 96-97 (2004) (noting that, with the enactment of the HWA, "Congress for the first time linked drug approvals to patents").

105. 35 U.S.C. § 156 (2000) (codifying the patent term extensions of the HWA). Because the patent term runs from the time a patent application is filed, innovators lose some patent time while waiting for the FDA to complete its regulatory review of the patent and grant marketing approval. THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 5. The patent term restoration part of the HWA aims to stimulate innovation by making up for

plemented special provisions for challenging the enforceability, validity, or infringement of approved drug patents.[106] Third, innovator firms may in some cases enjoy non-patent marketing exclusivity, meaning "a period of time during which the FDA affords an approved drug protection from competing applications for marketing approval."[107] The marketing exclusivity provision precludes the FDA from approving any ANDA for a generic drug for five years from the date the FDA approved the corresponding innovator drug, if that innovator drug is a new chemical entity.[108] If the reference drug is not a new chemical entity, then the FDA cannot approve any ANDA for a generic drug for three years after the approval date of the approved drug.[109] Fourth, if a patent owner of an innovator drug brings a patent infringement action against a generic manufacturer within forty-

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some of this lost time. *See id.* ("Importantly, the Hatch-Waxman Act recognizes that there would be no generic market without the products developed by innovators, which is why that system created a system of strong set of economic incentives.").

As explained by one commentator, the patent term restoration part of the Act is comprised of "very long, very complicated provisions." Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 190 (1999). A pioneer receives an extension term equal to the sum of one-half of the time of the investigational new drug (IND) period, commencing from the time during which a pioneer can begin human clinical trials, plus the full NDA review period. 35 U.S.C. § 156(c), (g) (2000). The maximum patent extension time is five years, and the total length of time between FDA approval and the termination of the patent cannot exceed fourteen years. *Id.* § 156(c)(3), (g).

106. *See* WENDY H. SCHACHT & JOHN R. THOMAS, CONGRESSIONAL RESEARCH SERVICE, CRS REPORT FOR CONGRESS, THE HATCH-WAXMAN ACT: LEGISLATIVE CHANGES IN THE 108TH CONGRESS AFFECTING PHARMACEUTICAL PATENTS 3-5 (2004). Commentators have noted that "[t]he core feature of this process is that a request for FDA marketing approval is treated as an 'artificial' act of patent infringement" which thereby allows for "judicial resolution of the validity, enforceability and infringement of patent rights." *Id.* at 3.

107. SCHACHT & THOMAS, *supra* note 100, at 14. Commentators have noted that marketing exclusivity "does not depend on the existence of patent protection and the two rights may actually conflict." WENDY H. SCHACHT & JOHN R. THOMAS, CONGRESSIONAL RESEARCH SERVICE, CRS REPORT FOR CONGRESS, 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") 24 (2005). For more on marketing exclusivity, see *infra* note 113 and accompanying text.

108. 21 U.S.C. § 355(j)(5)(F)(ii) (2000); 21 C.F.R. § 314.108(b)(2) (2007). A new chemical entity "means a drug that contains no active moiety that has been approved by FDA." 21 C.F.R. § 314.108(a). "Active moiety" is defined as "the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance." *Id.*

Some commentators use the term "data exclusivity" to refer to this three- or five-year period when the FDA cannot approve an ANDA for a generic drug. *See, e.g., Safe and Affordable Biotech Drugs—The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 12 (2007) [hereinafter *Hearing on Biotech Drugs*] (statement of Henry G. Grabowski, Ph.D.), *available at* http://oversight.house.gov/documents/20070416132526.pdf.

109. 21 U.S.C. § 355(j)(5)(F)(iii) (2000). This situation could arise where an NDA necessitates additional clinical investigation. SCHACHT & THOMAS, *supra* note 107, at 34.
For example, an applicant might seek approval for "new dosage forms for already approved drugs, a new use for [an existing] drug, or for over-the-counter marketing of a drug." *Id.*

five days of receiving notice of the challenge to its patent,[110] the FDA must suspend final approval of the generic manufacturer's ANDA for thirty months from the date the patent owner received notice of the challenge to its patent.[111]

Under the HWA, generic firms also enjoy enhanced intellectual property rights intended to stimulate the development of generic products. The HWA provides a statutory exemption from claims of patent infringement based on acts reasonably related to seeking FDA approval, thereby enabling a generic competitor to enter the market immediately upon expiration of the innovator patent.[112] The HWA also provides a 180-day period of generic exclusivity for the first generic applicant to successfully challenge the patent for any approved drug, measured from the time of the first commercial marketing of the generic drug.[113] As explained by one commentator, this provision affords the successful generic "a brief amount of time to recoup its litigation costs while it shares duopoly prices with the Brand-name drug."[114]

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110. 21 U.S.C. § 355(c)(3)(C) (2000).

111. *Id.* § 355(j)(5)(B)(iii). This period could be shorter than thirty months if, before thirty months have passed, either (1) a final appellate decision holds that the listed drug's patent is either invalid or not infringed or (2) the listed drug's patent expires. *See* SCHACHT & THOMAS, *supra* note 106, at 4 ("If, prior to the expiration of 30 months, the court holds that the patent is invalid or would not be infringed, then the FDA will approve the ANDA when that decision occurs."); *see also* Beth Understahl, Note, *Authorized Generics: Careful Balance Undone*, 16 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 355, 364 (2005) ("If the patent holder files suit, 'the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice,' unless the district court rules on the infringement claim within the thirty-month period or the patent expires." (footnotes omitted)). Of course, if a "court holds that the patent is not invalid and would be infringed by the product proposed in the ANDA," then "the FDA will not approve the ANDA until the patent expires." SCHACHT & THOMAS, *supra* note 106, at 4.

112. 35 U.S.C. § 271(e)(1) (2000). This provision, "which permits generic companies to manufacture and test their products before patent expiration for the purpose of seeking FDA approval," expressly overruled *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984) and is commonly referred to as the "*Bolar* exception" or the "safe harbor." Kuhlik, *supra* note 104, at 97 n.19; SCHACHT & THOMAS, *supra* note 100, at 13 (referring to the "safe harbor" provision).

113. 21 U.S.C. § 355(j)(5)(B) (2000); SCHACHT & THOMAS, *supra note* 106, at 9. This 180-day period is another form of non-patent marketing exclusivity. *See supra* note 107 and accompanying text (discussing the term "non-patent marketing exclusivity"); *see also* Erika Lietzan & David E. Korn, *Issues in the Interpretation of 180-day Exclusivity*, 62 FOOD & DRUG L.J. 49, 50 (2007) (referring to "180 days of marketing exclusivity"). Some commentators refer to this 180-day period as "generic exclusivity." *E.g.*, Ashlee B. Mehl, Note, *The Hatch-Waxman Act and Market Exclusivity for Generic Drug Manufacturer: An Entitlement or an Incentive?*, 81 CHI.-KENT. L. REV. 649 (2006). For a discussion of which events trigger the commencement of the 180-day period, see Stephanie Greene, *A Prescription for Change: How the Medicare Act Revises Hatch-Waxman to Speed Market Entry of Generic Drugs*, 30 J. CORP. L. 309, 349-50 (2005).

114. Steven W. Day, Note, *Leaving Room for Innovation: Rejecting the FTC's Stance Against Reverse Payments in* Schering-Plough v. FTC, 57 CASE W. RES. L. REV. 223, 229-30 (2006).

C. The Approval Framework for Branded Biologics

As noted above, the FDA regulates biologics under both the FDCA and the PHSA.[115] Congress did, however, assure manufacturers of biologics that filing an application for a biologic license (BLA) obviates the need to file an NDA.[116]

Pursuant to PHSA, a BLA must demonstrate that: (1) the biological product is "safe, pure, and potent;" (2) the facility in which the product is "manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent;" and (3) the applicant "consents to inspection of [its] facility."[117] Once the applicant receives a BLA, it need only comply with a labeling requirement in order to market the biologic in interstate commerce.[118]

As noted by Professor Mandel, "[t]he NDA and BLA review processes now are nearly identical—in either case the applicant must establish, through clinical studies and other information, that their product is safe and effective."[119] During "the past decade[,] both the FDA and Congress have moved to harmonize the two approval processes" for biologics and conventional drugs.[120] Indeed, congressional legislation enacted in 1997 expressly instructed the FDA to " 'minimize differences in the review and approval of products' under BLAs and NDAs," while at the same time confirming that biologics were indeed "subject to the FDCA."[121] Professor Mandel explains that "[t]he primary differences between the two approval processes are that BLAs must meet additional requirements concerning manufacturing plant inspection and must demonstrate product stability," while only NDA applicants must "submit patent information and a statement of the full composition of the drug."[122]

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115. *See supra* note 40 and accompanying text.

116. *See* Dudzinski, *supra* note 19, at 152 (stating that Congress enacted a statutory provision, 42 U.S.C. § 262(g) (2000), that was intended "to confirm joint applicability of the PHSA and the FDCA to biologics, but also to allay concerns of the biologics producers that they would be required to file new drug applications in addition to biologics licenses").

117. 42 U.S.C. § 262(a)(2)(B); *see also* 21 C.F.R. § 601.2(d) (2007) ("Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products.").

118. 42 U.S.C. § 262(a)(1).

119. Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission that Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 8, ¶ 38 (2006).

120. *Id.* (citing a 1996 FDA proposed rule, Well-Characterized Biotechnology Products; Elimination of Establishment License Application, 61 Fed. Reg. 2733-02, 2733-36 (proposed Jan. 29, 1996) (codified at 21 C.F.R. pts. 600 & 601), that made the BLA approval process more similar to the NDA process).

121. *Id.* (citing the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 123(a), (f), (g), 111 Stat. 2296, 2323-24 (codified at 42 U.S.C. § 262(a) (2000)).

122. *Id.* at ¶ 39.

D. The Lack of an Approval Pathway for Off-Patent Biologics

While the approval processes for drugs and biologics are quite similar, the FDCA and PHSA differ significantly in that there is no official regulatory pathway for approval of follow-on biologics. The HWA does not expressly provide for abbreviated approval of biologics and protein-based therapeutics,[123] most likely because, at the time of its enactment, the potential of biotechnology was not fully realized.[124] Furthermore, according to some commentators, "[p]erhaps Congress also appreciated the difficulty in verifying bioequivalence in biologically derived drugs given the extant technology."[125]

Legal analysis of the abbreviated approval pathways for generic drugs demonstrates clearly that the ANDA pathway is not applicable to follow-on biologics.[126] First, it seems that the FDA's own interpretation of the HWA precludes the approval of follow-on biologics via the ANDA pathway.[127] Second, a Senate report on the Food and Drug Administration Modernization Act (FDAMA)[128] stated that the FDAMA's "requirement for harmonization between [the FDCA and the PHSA] does not apply in the case of generic products, however, since the authority for abbreviated new drug applications under section 505(j) is not applicable to biological products."[129] Finally, it would prove exceedingly difficult, in scientific terms, to satisfy the requirement under the HWA that, for an ANDA to be applicable, the generic therapeutic must be the "same"[130] as the pioneer drug. The legislative history of the HWA indicates that for the ANDA pathway to apply, the original drug and the generic should be chemically identical

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123. It is notable that the HWA amended the Patent Act in a couple of ways that do pertain to protein products. *See infra* text accompanying notes 367-69.

124. Dudzinski, *supra* note 19, at 167 (noting that, at the time of the enactment of the HWA, "the ultimate influence of biotechnology was not at that time fully appreciated," and therefore "biologics and protein-based therapeutics seemingly would be excluded" from the legislation); *see also* David Schmickel, *The Biotechnology Industry Organization's View on Hatch-Waxman Reform*, 54 FOOD & DRUG L.J. 241, 241 (1999) (stating that "biologics currently are not part of the Hatch-Waxman scheme" because the modern biotechnology industry and the Biotechnology Industry Organization did not exist in 1984).

125. Arman H. Nadershahi & Joseph M. Reisman, *Generic Biotech Products: Provisions in Patent and Drug Development Law*, BIOPROCESS INT'L, Oct. 2003, at 26.

126. Dudzinski, *supra* note 19, at 196-97.

127. *See* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,951 (Apr. 28, 1992) (codified at 21 C.F.R. pts. 2, 5, 10, 310, 314, 320, & 433) ("Title I amended section 505 of the [FDCA] by establishing a statutory ANDA procedure for duplicate and related versions of human drugs approved under section 505(b) of the act. These procedures are inapplicable to antibiotics (which are approved under section 507 of the act) and biological drug products licensed under 42 U.S.C. 262.").

128. Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, 1111 Stat. 2296 (codified in scattered sections of 21 U.S.C. and 42 U.S.C.). FDAMA aimed to improve the FDA's operations and effectuated several important changes in biologics regulation. Dudzinski, *supra* note 19, at 177.

129. S. REP. NO. 105-43, at 40 (1997).

130. See *supra* note 80 and accompanying text for the HWA's concept of sameness.

molecules.[131] One of the most important requirements in this statute is a showing of bioequivalence between the generic and brand name product.[132] Demonstrating bioequivalence between biologics is particularly difficult,[133] as compared to the relatively straightforward process for proving bioequivalence between chemically synthesized drugs.[134] Because additional clinical studies may be necessary to prove bioequivalence for biologics,[135] the ANDA route is inapplicable in light of the fact that the FDA cannot request supplementary preclinical or clinical testing under an ANDA.[136]

While it appears clear that the FDA will not approve follow-on biologics under existing ANDA provisions, it seems that section 505(b)(2) of the HWA offers an abbreviated approval pathway for follow-on versions of certain biologics. This view is supported both by a draft guidance document issued in October 1999 by the FDA[137] as well as by the FDA's use of section 505(b)(2) to approve Omnitrope, a biologic product.[138] In approving Omnitrope, however, the FDA emphasized that the 505(b)(2) pathway is applicable only to those follow-on biologics that were originally approved under an NDA and governed by the FDCA, not for those approved under a BLA and subject to the PHSA.[139] Indeed, the lack of any clear statutory approval pathway for most biologics led the FDA's reluctance to address the Omnitrope application submitted by Sandoz Inc., a German generic pharmaceutical firm.[140] The FDA ruled on the application only after

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131. Dudzinski, *supra* note 19, at 197 (stating that, pursuant to the legislative history of the HWA, "the ANDA only would apply to special cases wherein a generic protein therapeutic could be proved to be literally identical to the listed pioneer protein therapeutic"); *see also* H.R. REP. NO. 98-857, pt. 1, at 21-23 (1984).

132. *See* 21 U.S.C. § 355(j)(2)(A)(iv) (2000).

133. *See* Lincoln Tsang & Donald Beers, *Follow-On Biological Products: The Regulatory Minefield,* GLOBAL COUNSEL LIFE SCIENCES HANDBOOK 105, 109 (2004/2005), *available at* http://www.arnoldporter.com/pubs/files/Article-Follow-on_biological_products.pdf (explaining that it is difficult to demonstrate "sameness" for biologics given the challenges of characterizing these products through chemical analysis).

134. Biotechnology Indus. Org., Follow on Biologics (FOBs): How Do Drugs and Biologics Differ?, http://www.bio.org/healthcare/followonbkg/DrugsVBiologics.asp (last visited June 23, 2008) ("The bioequivalence of the generic drug is demonstrated through relatively simple analyses such as blood level testing, without the need for human clinical trials.").

135. Tsang & Beers, *supra* note 133, at 110.

136. *See* 21 U.S.C. § 355(j)(2)(A) (2000) ("The Secretary may not require that an abbreviated application contain information in addition to [the statutory requirements]."); *see also supra* note 81 and accompanying text.

137. *See generally* FDA DRAFT GUIDANCE, *supra* note 95.

138. *See generally* Omnitrope Q&A, *supra* note 38.

139. *See id.* ("For products approved under section 505 of the Food, Drug, and Cosmetic Act, we believe there is existing authority to allow applications for follow-on protein products to be approved under section 505(b)(2) of the Act through a process that relies on the earlier approval of the innovator product. In contrast, there is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) of the Act for protein products licensed under section 351 of the Public Health Service Act.").

140. *See* Sandoz, Facts & Figures, http://www.sandoz.com/site/en/about_sandoz/

Sandoz brought legal action against the FDA compelling it to act.[141] The resulting judicial decision in *Sandoz, Inc. v. Leavitt*[142] and the FDA's response to it is discussed in Part IV.

IV. *SANDOZ* REQUIRES THE FDA TO TAKE ACTION ON A FOLLOW-ON BIOLOGIC APPLICATION

In July 2003, Sandoz submitted to the FDA an abbreviated NDA under 505(b)(2) for Omnitrope, a recombinant growth hormone for treatment of pediatric patients who suffer growth failure and adults with growth hormone deficiency.[143] Some commentators refer to Omnitrope as a biogeneric because its active ingredient, somatropin, is the same as in Pfizer Inc.'s Genotropin, another recombinant human growth hormone, which has been marketed since 1998.[144] Indeed, "Sandoz's abbreviated NDA was based, in part, on the FDA's previous approval of Genotropin."[145] Sandoz contended that " 'Omnitrope is indistinguishable from Genotropin and . . . [is] safe and effective.' "[146]

In May 2004 Pfizer urged the FDA to reject the Omnitrope NDA.[147] In August 2004, the FDA informed Sandoz that "it had completed its review of Omnitrope but that because of the application's 'nature and complexity . . . [the] FDA is deferring a decision on whether the data submitted in [the NDA] are adequate to support a conclusion that Omnitrope is safe and effective for the proposed indications.' "[148] The FDA sought additional time in order to conduct a public process to consider the scientific and legal issues raised in citizen petitions filed regarding Omnitrope approval.[149]

Sandoz then filed suit in September 2005, seeking equitable relief in light of the FDA's alleged failure to comply with its statutory obli-

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company_overview/index.shtml (last visited June 23, 2008).

141. *See supra* Part III.

142. 427 F. Supp. 2d 29 (D.D.C. 2006).

143. *Sandoz*, 427 F. Supp. 2d at 31-32.

144. Aaron J. Bouchie, *Controversial New Biologic Approved in U.S.*, THE SCIENTIST, June 14, 2006, http://www.the-scientist.com/news/display/23516/; *see also supra* note 12 and accompanying text (describing recombinant protein products as biologics). The FDA, however, took care to call Omnitrope a "follow-on protein product" rather than a biogeneric. *See infra* note 161 and accompanying text.

145. *Sandoz*, 427 F. Supp. 2d at 32. Sandoz needed to perform only four additional phase III clinical trials to complement its reliance on the FDA's approval of Pfizer's Genotropin. FDA Response to Citizen Petitions, *supra* note 94, at 10 & n.26. *But cf.* THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 15 (describing Sandoz's performance of four phase III clinical trials as the submission of "extensive original clinical data").

146. *Sandoz*, 427 F. Supp. 2d at 32 (citation omitted).

147. *Id.*

148. *Id.* (citation omitted).

149. Omnitrope Q&A, *supra* note 38 (referring to the FDA's consideration of citizen petitions, the discussions in public meetings, and docket submissions in deciding whether to approve Omnitrope).

gation to act on Sandoz's NDA within 180 days of its submission.[150] In April 2006, the U.S. District Court for the District of Columbia granted Sandoz's motion for summary judgment, holding that the FDA was required to proceed in its consideration of the 505(b)(2) NDA.[151] The following month, the FDA approved Sandoz's application for Omnitrope,[152] while simultaneously cautioning that its approval did not indicate its intent to permit follow-on versions of all protein products approved under section 505 of the FDCA.[153]

The FDA based its approval of Omnitrope on its finding that Omnitrope is "sufficiently similar" to Pfizer's Genotropin.[154] Thus, the FDA relied on its prior finding of safety and effectiveness for Genotropin, which was supported by clinical data provided by Pfizer.[155] According to the FDA, Omnitrope presented a special case because "human growth hormone (hGH) has several characteristics that enable one rhGH product to be adequately compared to another for purposes of approval under section 505(b)(2) of the [FDCA]."[156] These include hGH's relative lack of complexity; existing knowledge of its structure; its "long and well documented history of clinical use;"[157] and the existing information about its mechanism of drug action and human toxicity profile.[158] Thus, the FDA was able to establish that Omnitrope is "highly similar" to Genotropin without relying on proprietary CMC (chemistry, manufacturing, and control) data[159] in

150. *Sandoz*, 427 F. Supp. 2d at 32; *see also* 21 U.S.C. § 355(c) (2000) (citing the 180-day statutory period for acting on a 505(b) application).

151. *Sandoz*, 427 F. Supp. 2d at 41.

152. Approval Letter from Dr. Robert J. Meyer, Director, Office of Drug Evaluation II, Center for Drug Evaluation & Research, FDA, to Beth Brannan, Sandoz, Inc. (May 30, 2006), *available at* http://www.fda.gov/cder/foi/appletter/2006/021426s000LTR.pdf.

153. FDA Response to Citizen Petitions, *supra* note 94, at 52 ("The approval of Omnitrope does not signal that the Agency has concluded that—regardless of the nature and complexity of the active ingredient and the indications for use—every protein product approved under section 505 of the [FDCA] is an appropriate candidate for reference by an applicant seeking approval of a follow-on protein product through an abbreviated pathway.").

154. *Id.* at 8.

155. *Id.*

156. Omnitrope Q&A, *supra* note 38.

157. *Id.* Somatropin was first used as a treatment in 1958 and, at the time the FDA approved Omnitrope in 2006, it had already approved seven other recombinant human growth hormone products since 1985. *See* FDA Response to Citizen Petitions, *supra* note 94, at 7; Bouchie, *supra* note 144. Although these recombinant human growth hormone products differ from one another in some respects, they are all considered somatropin and share certain identifying characteristics. FDA Response to Citizen Petitions, *supra* note 94, at 15 n.35.

158. Omnitrope Q&A, *supra* note 38; *see also* Alston & Bird, *supra* note 11, at 3 (noting that the FDA "emphasized that the relative lack of complexity of the hormone, the availability of current analytical technology, and available compendial standards greatly simplified agency review").

159. CMC data include, among other information, "product specifications, analytical testing procedures, recipes, equipment, [and] purification and fermentation processes." THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 25.

Pfizer's Genotropin NDA because technological advances permit "relatively simple" proteins such as somatropin "to be adequately identified and characterized irrespective of the product's manufacturing process."[160] Furthermore, the FDA emphasized that "Omnitrope is not rated as therapeutically equivalent to (and therefore substitutable for) any of the other approved human growth hormone products" and is therefore more properly called a "follow-on protein product" as opposed to a generic biologic.[161] Nonetheless, with its approval of Omnitrope, the FDA clearly asserted its authority to approve applications for follow-on protein products under section 505(b)(2) of the FDCA via reliance on the earlier approval of an innovator product as well as published scientific data, so long as that innovator protein product was approved under the FDCA.[162] Indeed, the FDA noted that 505(b)(2) "expressly permits" an applicant to support its application with clinical studies that "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."[163]

Even while asserting its authority, the FDA seemed to downplay somewhat its approval of Omnitrope by pointing out that it had approved a handful of other follow-on protein products under section 505 of the FDCA.[164] Sandoz, however, emphasized that Omnitrope was "the first recombinant product that refer[red] in its application to the prior FDA approval of an existing recombinant product," whereas the other FDA approvals of biologics under 505(b)(2) related to " 'previously approved naturally-sourced or synthetic products.' "[165] According to the FDA, however, its approval of Omnitrope pursuant to 505(b)(2) did not indicate that "more complex and/or less well un-

160. FDA Response to Citizen Petitions, *supra* note 94, at 15, 46 ("Recombinant hGH (somatropin) products are not necessarily defined by their manufacturing processes []. Rather, through improved analytical techniques and other testing, we have been able to determine that two rhGH products, Omnitrope and Genotropin, are highly similar even though they may be produced through different processes.").

161. Omnitrope Q&A, *supra* note 38; *see also* FDA Response to Citizen Petitions, *supra* note 94, at 2 n.7 (defining "follow-on protein products" as "protein[] and peptide[] [products] that are intended to be sufficiently similar to a product already approved . . . or licensed . . . to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product."); *see also supra* note 7 (defining follow-on protein products).

162. *See* Omnitrope Q&A, *supra* note 38 ("For products approved under section 505 of the Food, Drug, and Cosmetic Act, we believe there is existing authority to allow applications for follow-on protein products to be approved under section 505(b)(2) of the [FDCA] through a process that relies on the earlier approval of the innovator product.").

163. FDA Response to Citizen Petitions, *supra* note 94, at 42 (citing 21 U.S.C. § 355(b)(2)).

164. *See* Omnitrope Q&A, *supra* note 38 (listing other follow-on protein products approved under section 505 of the FDCA).

165. Barnes, *supra* note 36 (quoting Sandoz spokesperson Kurt Leidner) (emphasis omitted).

derstood proteins approved as drugs under the [FDCA]" could gain approval as follow-on products.[166] What is more, the FDA explicitly stated that the 505(b)(2) approval pathway does not apply to biologic products originally licensed under the PHSA,[167] which accounts for most biologics.[168] In the FDA's view, Congress would need to enact new legislation amending the PHSA in order for the FDA to have authority to approve generic or biosimilar biologics.[169] Congressional legislation establishing a proper regulatory pathway would provide the industry with clear guidelines.

In the absence of an approval pathway for follow-on biologics, pioneer biologics enjoy de facto patent exclusivity even after their patent protection expires, since the FDA does not have legal authority to approve any competing follow-on products.[170] Would-be follow-on

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166. Omnitrope Q&A, *supra* note 38.

Commentators have explained that the FDA's approval of Omnitrope provides "some informal guidance regarding the likelihood of approval of future generic biologic applications under 505(b)(2)." Alston & Bird, *supra* note 11, at 3. According to these commentators:

> [A] generic biologic most likely will be approved under the 505(b)(2) pathway when: (1) it is a product that has traditionally been regulated under the FDCA as an NDA and not under the PHSA as a BLA; (2) it shares other key characteristics with reference biologics, in particular, their proposed strengths, indications, route of administration, and conditions of use; (3) FDA's prior finding of safety and effectiveness for the reference product provides some, but not necessarily all or sufficient, support for the proposed generic's approval; and (4) data demonstrate that the proposed product, to the extent that it differs from the listed product referenced in the application, is safe and effective. For example, any impurities found in the proposed product that were not present in the reference product should be adequately characterized by non-clinical and clinical studies and should be found not to have a negative impact on safety or effectiveness.

Id.

167. Omnitrope Q&A, *supra* note 38; FDA Response to Citizen Petitions, *supra* note 94, at 2 n.7 ("We note that there is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) of the [FDCA] for protein products licensed under section 351 of the PHSA."). The FDA took care to distinguish recombinant human growth hormone, which had "long been regulated under section 505 of the [FDCA]" from protein products that are regulated under the PHSA. *Id.* at 44 "Human growth hormone (somatropin) falls within the definition of a drug and hGH products have been regulated as drugs under section 505 of the Act since before the enactment of the Hatch-Waxman Amendments" *Id.* Other proteins approved under section 505 before the enactment of the Hatch-Waxman Amendments include "insulin, hyaluronidase, mentropins, and glucagon" and also meet the statutory definition of drugs. *Id.* at 44 n.82. In addition, "Genotropin and other innovator rhGH products were submitted for approval under section [505]" of the FDCA "and have been regulated as drug products under the Act since 1985." *Id.* at 45-46 n.89. The regulation of these protein products under the FDCA as opposed to the PHSA is the result of historical practice rather than scientific rationale. *See* Dudzinski, *supra* note 19, at 161-65.

168. As noted above, the majority of biologics are licensed under the PHSA. Omnitrope Q&A, *supra* note 38.

169. *See* Omnitrope Q&A, *supra* note 38 (stating that an abbreviated approval pathway for "the approval or licensure of follow-on protein products under the Public Health Service Act would require new legislation").

170. "Access to Life-Saving Medicine Act" Press Release, *supra* note 73. ("Currently there is no statutory pathway for generic versions of biotech drugs to enter the market,

manufacturers cannot simply imitate the original manufacturing process, because pharmaceutical manufacturers, in addition to their patent protection, retain the right under FDA rules to maintain indefinitely certain confidential business information within their drug applications, including information deemed a trade secret. Thus, for each follow-on version of a biologic, an applicant must currently submit a new BLA, which necessitates costly preclinical and clinical testing.[171] As noted by Professor Mandel, the resultant approval process for follow-on biologics is "much more expensive, lengthy, and uncertain than for conventional generics, and substantially forecloses biologic generics from the market."[172] Seeking to rectify this problem, several congressional representatives introduced legislation in 2007 that would create an abbreviated approval pathway for follow-on biologics.

V. PENDING LEGISLATION PROPOSES AN APPROVAL PATHWAY FOR FOLLOW-ON BIOLOGICS

On February 14, 2007, a bipartisan group of congressional representatives, including Representatives Henry Waxman (D-CA),[173] Jo Ann Emerson (R-MO), and Frank Pallone (D-NJ), as well as Senators Charles E. Schumer (D-NY) and Hillary Rodham Clinton (D-NY), introduced House Bill 1038, the Access to Life-Saving Medicine Act, [174]

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even after all patents have expired. As a result, the manufacturers of biotech drugs can charge monopoly prices, indefinitely.").

171. *See* Warren et al., *supra* note 30.

172. Mandel, *supra* note 119, at ¶ 44.

173. Rep. Waxman (D-CA) also sponsored, with Sen. Orrin Hatch (R-UT), the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. *See* Statement of Henry A. Waxman, U.S. Congress, House of Reps., Introduction of the Access to Life-Saving Medicine Act (Feb. 14, 2007), *available at* http://www.house.gov/waxman/pdfs/biologicsstatement_2.14.07.pdf. See *supra* Part III.B. for a discussion of the Hatch-Waxman Act.

174. Rep. Henry Waxman, Issues and Legislation, Access to Life-Saving Medicine Act, http://www.house.gov/waxman/issues/health/generic_biologics.htm (last visited June 23, 2008). Other original cosponsors of this legislation are Representatives Rahm Emanuel (D-IL) and Mazie Hirono (D-HI) and Senators David Vitter (R-LA), Susan M. Collins (R-ME), Patrick J. Leahy (D-VT), and Debbie Stabenow (D-MI). *Id.* The text of the House bill, The Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007), is available at http://www.house.gov/waxman/pdfs/biologicsbilltext_2.14.07.pdf. The Senate companion bill is S. 623, 110th Cong. (2007), and is available at http://thomas.loc.gov/ (click "Bill Number," then search "Bill Text" for "S 623").

See Update: "Comparable" Biologics Bill Reintroduced, CLIENT ADVISORY (Arnold & Porter LLP), Feb. 2007, at 1 [hereinafter Arnold & Porter], *available at* http://www.arnoldporter.com/resources/documents/A&PCAdvisory-Update-ComparableBiologicsBillReintroduced_0207.pdf.

House Bill 1038 was first introduced in September 2006, *see* Alston & Bird, *supra* note 11, at 5, but because it had not passed by the end of the session, its sponsors reintroduced it the following session. Maribel Rios, *Congressional Bill Establishes Biogenerics Approval Path*, EPT: THE ELECTRONIC NEWSLETTER OF PHARMACEUTICAL TECHNOLOGY, Feb. 15, 2007, http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=405501. House Bill 1038 is similar, but not identical, to the previous version. *See* Arnold & Porter, *supra*

which would give the FDA express legal authority to approve abbreviated applications for biological products that are "comparable" to previously approved brand name biological products.[175] In light of the variability of biologic products, the bill proposes a product-by-product process for approving biologics, granting the FDA the discretion to require any additional clinical studies that it deems necessary in order to determine whether a new product is comparable to a brand name product.[176]

More specifically, House Bill 1038 proposes to amend the PHSA, and would therefore apply to biologics licensed under that Act.[177] It would authorize the Secretary of Health and Human Services (the Secretary) to approve abbreviated applications for biological products that are "comparable"[178] to and "interchangeable"[179] with previously approved brand name biological products.[180]

The bill requires an abbreviated application for a comparable biological product to contain information showing that, among other things, the new product is comparable to the reference product; the two products have "highly similar principal molecular structural features"; the two products have the same mechanism of action, to the extent such mechanism is known; the proposed product label carries one or more of the approved indications for the reference product; and the route of administration, dosage form, and strength of the two products are the same.[181] House Bill 1038 allows the FDA to require

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(explaining that the bill is similar to legislation introduced in September 2006 by some of the same sponsors).

As of June 2008, House Bill 1038 was in the first stage of the legislative process, where it was considered in committees that deliberate, investigate, and revise bills before they go to general debate. GovTrack.us, H.R. 1038, 110th Congress, http://www.govtrack.us/congress/bill.xpd?bill=h110-1038 (last visited June 23, 2008). The bill was referred to the House Energy and Commerce Committee and the House Judiciary Committee. *Id.* The House Energy and Commerce Committee referred the bill to the Subcommittee on Health. *Id.* As noted by one bill-tracking Web site, the majority of bills never advance past the committee stage. *Id.*

175. *See* "Access to Life-Saving Medicine Act" Press Release, *supra* note 73.

176. *See* The Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3(k)(1)(B) (2007), *available at* http://www.house.gov/waxman/pdfs/biologicsbilltext_2.14.07.pdf ("Two biological products . . . may be demonstrated to contain highly similar principal molecular structural features based upon such data and other information characterizing the two products as the Secretary [of HHS] determines to be necessary.").

177. *Id.* at Preamble (describing the bill's purpose "[t]o amend the Public Health Service Act to provide for the licensing of comparable and interchangeable biological products").

178. *See id.* § 2(a)(4) (defining "comparability" as "the absence of clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.").

179. *See id.* § 2(a)(5) (defining "interchangeability" as comparability coupled with the ability to "produce the same clinical result as the reference product in any given patient").

180. *See id.* § 3(k).

181. *See id.* § 3(k)(1). The FDA would even have discretion to approve a comparable biologic that does not meet these criteria so long as the application establishes the safety,

any necessary clinical studies in order "to confirm safety, purity, and potency."[182] Tracking the HWA, House Bill 1038 also seems to permit a manufacturer of a follow-on protein to rely upon, as part of its application, the FDA's approval of a brand name biologic.[183]

The Secretary is required to approve a comparable biological application unless there is insufficient information to establish that the above conditions have been met; the product is in some way unsafe, impure, or ineffective; or the application contains an untrue statement of material fact.[184] A comparable biologic may even be given the same name as the innovator product, if the Secretary determines that this is "necessary or desirable in the interests of usefulness or simplicity."[185]

An applicant for a comparable biological product may also choose, but is not required, to establish interchangeability,[186] meaning that the "new product can be substituted for the brand name product at the pharmacy level."[187] The Secretary is granted discretion to deter-

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purity, and potency of the follow-on product relative to the branded product for its proposed use. *See id.* § 3(k)(2).

182. *Id.* § 2(a)(4)(B).

183. *See id.* § 3(k)(1)(G) (providing that an abbreviated biological product application may include, "[a]t the applicant's option, publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent."); *supra* notes 82 & 84, and accompanying text (explaining that both 505(j) and 505(b)(2) applications may rely on the FDA's approval of another drug even if the applicant has not conducted the clinical studies itself and has no right of reference to the proprietary information). As commentators have noted, it is not clear whether the language in House Bill 1038, permitting reliance upon "publicly-available information," is "the same as the 'finding' of safety and effectiveness that FDA says supports approvals of 505(b)(2) applications, but this provision would potentially allow the agency to cite its publicly articulated findings with respect to the innovator biologic to greatly reduce the product-specific data required for approval of a 'generic' biologic." Arnold & Porter, *supra* note 174, at 2 (citations omitted).

184. *See* H.R. 1038, § 3(k)(4)(A).

185. *Id.* § 3(k)(6).

186. *Id.* § 3(k)(8) ("In an original application or a supplement to an application under this subsection, an applicant may submit information to the Secretary to demonstrate the interchangeability of a comparable biological product and the reference product. An applicant may withdraw an interchangeability submission at any time.").

187. REP. HENRY WAXMAN, QUICK SUMMARY, THE ACCESS TO LIFE-SAVING MEDICINE ACT 2, *available at* http://www.house.gov/waxman/pdfs/biologicsquicksummary_2.14.07.pdf (last visited June 23, 2008). As explained in literature disseminated by Representative Waxman, interchangeable products would "generate the greatest cost savings," but it is costly and difficult to determine if two biologics are truly interchangeable. REP. HENRY WAXMAN, DETAILED OUTLINE, THE ACCESS TO LIFE-SAVING MEDICINE ACT 3 [hereinafter DETAILED OUTLINE], *available at* http://www.house.gov/waxman/pdfs/biologicsbillsummary_2.14.07.pdf (last visited June 23, 2008). In contrast, a determination of " 'bioequivalence' " is fairly easy to achieve for traditional drugs. *See id.* Thus, House Bill 1038 provides incentives for the development of interchangeable products, but does not mandate that each comparable product achieve interchangeability. *Id.*

mine what studies are required to establish interchangeability.[188] If a biologic is found interchangeable and the applicant requests, the bill permits the label of the new product to state that it is interchangeable with the reference product.[189] In order to stimulate the development of interchangeable products, the bill grants the first applicant to obtain approval of an interchangeable product a 180-day period of market exclusivity during which time no other interchangeable version of the product may be approved.[190] In addition, the bill prohibits the reference drug company from rebranding authorized generics[191] for sale during the 180-day exclusivity period.[192] House Bill 1038 seeks in this way to heighten the incentive for a generic firm to undertake a patent challenge and also to increase the likelihood that the generic firm will be able to recoup the costs of doing so.[193]

House Bill 1038 also provides a process for early resolution of patent disputes which could otherwise delay competition.[194] If an applicant of a comparable biologic elects to ask the patent holder of the reference product for a list of all patents related to the product, the patent holder must disclose this information within sixty days.[195] There are also provisions for keeping this list updated.[196] A patent

188. H.R. 1038, § 3(k)(8)(B) (charging the Secretary of the U.S. Department of Health and Human Services, within one year after the legislation's enactment, with issuing "guidance regarding standards and requirements for interchangeability").

189. *Id.* § 3(k)(9). Interchangeability may be demonstrated "for one or more specified conditions of use prescribed, recommended, or suggested in the labeling of the biological product." Arnold & Porter, *supra* note 174, at 1. Commentators have noted that, where the innovator product had multiple conditions of use, this language would offer the follow-on manufacturer great "flexibility in achieving an interchangeability" designation. *Id.*

190. H.R. 1038, § 3(k)(10)(A). This provision mirrors a similar one in the HWA. *See supra* note 113 and accompanying text.

191. Authorized generics are the brand firm's own reference products that are repackaged and marketed either through the brand's subsidiary or a third-party generic distributor. *GPhA Calls PhRMA's Authorized Generics Study 'Disingenuous'*, LAB BUSINESS WEEK, May 6, 2007, at 799 [hereinafter LAB BUSINESS WEEK]; *Generic Pharmaceutical Association; Recent Activities Involving Generic Pharmaceutical Association Announced*, AGING & ELDER HEALTH WEEK, Jan. 14, 2007, at 429 [hereinafter AGING & ELDER HEALTH WEEK].

192. *See* H.R. 1038, § 3(k)(10)(B).

193. *See* LAB BUSINESS WEEK, *supra* note 191 (noting that the purpose of the 180-day generic exclusivity period is "to permit the generic company alone to compete with the brand company, allowing the generic to recoup costs incurred for undertaking a patent challenge"). Under the HWA, the FDA treats authorized generics as branded products for the purposes of product approval and therefore allows them to compete with generic products awarded 180-day exclusivity. AGING & ELDER HEALTH WEEK, *supra* note 191. See *supra* notes 113-14 and accompanying text regarding the generic exclusivity provision under the HWA. See *infra* Part VI.C.4. for a policy discussion of the generic exclusivity period pursuant to House Bill 1038.

194. The HWA has been criticized for failing to ensure early resolution of patent disputes. *See* DETAILED OUTLINE, *supra* note 187, at 3.

195. Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3(k)(17)(A)(i).

196. *Id.* §§ 3(k)(17)(A)(iii) (2007); *see also* 3(b) (Additional Amendments). This provision was included in order to provide follow-on manufacturers of biologics with information about patents held by innovator firms analogous to the information available to manufacturers of generic drugs. Generic drug manufacturers can access such patent information in

holder must also commence a patent infringement suit within forty-five days of notice of a challenge or else forfeit the opportunity to seek any remedy other than a reasonable royalty.[197]

Several organizations have expressed their support of House Bill 1038, including the Generic Pharmaceutical Association (GPhA)[198] and its members, as well as numerous insurance companies; patient and consumer groups; and unions.[199] Among those opposed to the bill are the Biotechnology Industry Organization (BIO)[200] and its members.[201] Part VI will analyze the arguments for and against follow-on biologics in general, as well as this legislation in particular.

VI. POLICY ANALYSIS OF FOLLOW-ON BIOLOGICS AND HOUSE BILL 1038

The creation of an abbreviated approval pathway for follow-on biologics involves consideration of several policy issues.[202] First, because

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the *Orange Book*, *see supra* note 64 and accompanying text, but manufacturers of biologics do not publish their patent information in the *Orange Book*. *See* Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 111 (2007) (stating that "a biologic approved under a BLA is not listed in the *Orange Book*").

197. H.R. 1038, §§ 3(k)(17)(C), 3(b) (Additional Amendments). Similarly, the HWA provides that an innovator firm has forty-five days in which to bring an action for patent infringement against a follow-on manufacturer. *See* 21 U.S.C. § 355(c)(3)(C) (2000).

198. "The Generic Pharmaceutical Association (GPhA) represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry." Generic Pharmaceutical Association, About Us, http://www.gphaonline.org/AM/Template.cfm?Section=about_us (last visited June 23, 2008).

199. *See* Rep. Henry Waxman, Issues and Legislation, Access to Life-Saving Medicine Act, Letters of Support, http://www.house.gov/waxman/issues/health/generic_biologics_letters_support.htm (last visited June 23, 2008) (providing links to letters of support).

200. BIO is a nonprofit trade group that describes itself as representing "more than 1,000 biotechnology companies, academic institutions, biotechnology centers and related organizations in all 50 U.S. states and 33 other nations." Biotechnology Indus. Org., Join BIO, http://bio.org/join/ (last visited June 23, 2008).

201. *BIO Restates Opposition to H.R. 1038*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Mar. 26, 2007, http://www.genengnews.com/news/bnitem.aspx?name=14818497. Some commentators maintain that House Bill 1038 strongly favors the generic industry and awaits further negotiation with the branded industry. Arnold & Porter, *supra* note 174, at 2 (stating that the legislation, "despite bi-partisan sponsorship, is unlikely to be enacted as written" and instead "appears to be the opening negotiating position of the generic industry"); Xenia P. Kobylarz, *The Patent Killer*, IP LAW & BUSINESS, May 2007, (citing legal counsel to several biotech companies as stating that House Bill 1038 is biased against innovators and is in an early stage of drafting).

202. The constitutional takings issue surrounding the FDA's reliance upon an innovator's safety and effectiveness data is beyond the scope of this Article. This Article assumes, for the sake of the analysis herein, that the FDA is permitted, under the U.S. Constitution, to rely indirectly on proprietary data submitted by a manufacturer of a branded drug when the FDA considers a follow-on drug. Several authors have examined this constitutional issue. *See* John C. Yoo, *Takings Issues in the Approval of Generic Biologics*, 60 FOOD & DRUG L.J. 33, 39-42 (2005) (concluding that FDA reliance on its approval of earlier biologics to approve follow-on biologics would not present a takings problem because the FDA need not

the HWA created an abbreviated approval pathway for generic drugs, it is important to evaluate whether the HWA has had a salutary effect on the market for traditional drugs, paying close attention to any differences that might arise in the case of biologics. Second, one must assess whether the FDA has the scientific capability to assess follow-on protein products for safety and efficacy in the absence of a full complement of clinical trials for these products. Third, one must consider how best to preserve incentives for innovation by branded firms. Analysis of these issues will help to determine whether an abbreviated approval pathway for follow-on biologics, and whether House Bill 1038 in particular, is likely to encourage the development of a robust market for safe and effective follow-on biologics, and simultaneously preserve incentives for innovation by branded firms.

A. An Abbreviated Approval Pathway for Follow-On Biologics Modeled on the HWA Ultimately Will Stimulate the Development of More Affordable Biologics

Government agencies, academics, and industry participants generally consider the HWA a success overall, both in terms of stimulating generic competition and in providing incentives for innovation.[203]

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rely on the pioneer manufacturer's underlying data, but rather simply on the public fact that the FDA had already approved the innovator drug based on the drug's satisfaction of the safety and efficacy requirements, just as is done under the HWA for conventional drugs); Wasson, *supra* note 7, at ¶ 30 (stating that "it is unlikely that the approval of off-patent biologics originally approved under the FDCA would be a taking" because "brand name manufacturers had notice, under the Hatch-Waxman amendments, that the FDA would consider follow-on products in light of previous safety and effectiveness findings").

203. *See* CONGRESS OF THE UNITED STATES, CONGRESSIONAL BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 50 (1998), *available at* http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf (stating that "many purchasers are better off since the act, as most top-selling off-patent brand-name drugs now have generic versions available" and "[o]verall, it appears that the incentives for drug companies to innovate have remained intact since the Hatch-Waxman Act; even as sales revenues from innovator drugs have more than tripled, the percentage of those revenues that manufacturers reinvest in R&D has risen from 14.7 percent to 19.4 percent between 1983 and 1995"); Presentation, Gary J. Buehler, Director, Center for Drug Evaluation & Research, FDA, The FDA Process for Approving Generic Drugs 4 (Oct. 29, 2002), *available at* http://www.fda.gov/cder/ogd/02-10_BCBS_gjb/sld001.htm (stating that the HWA is "[c]onsidered one of the most successful pieces of legislation ever passed."); Grabowski, *supra* note 35, at 21 ("Overall, Hatch-Waxman has provided a relatively balanced approach to the trade-offs between pharmaceutical R&D and generic competition. Improvements on the margin could be considered by policy makers . . . . Nevertheless, the law has provided a reasonably well structured system of incentives for both innovative and generic firms. Both R&D investments and generic utilization have increased dramatically in the period since the passage, consistent with the objectives of the act."); *Hatch-Waxman Reform Shifts Into High Gear in Debate*, THE FOOD & DRUG LETTER, June 26, 2002, (quoting the Executive Vice President of the Pharmaceutical Research and Manufacturers of America (PhRMA),

Since the enactment of the HWA, generic drugs are indeed widely available.[204] According to the GPhA, relying on data from other sources, four of the top five U.S. pharmaceutical companies, based on the number of prescriptions dispensed, are generic companies—Novartis (Sandoz), Teva, Mylan, and Watson.[205] In addition, 8730 of the 11,487 drugs listed in the FDA's *Orange Book* have generic counterparts.[206] Generic drugs are also considerably cheaper than their branded counterparts.[207] According to the GPhA, generics represented sixty-five percent of the total prescriptions dispensed in the United States, but only 20.5 percent of all dollars spent on prescription drugs.[208] In that same year, the average retail price of a generic prescription drug was $32.23, while the average retail price of a brand name prescription drug was $111.02.[209] At the same time, the pharmaceutical industry has enjoyed significant profits and was recently ranked the second most profitable industry in the United States in terms of return on revenue.[210]

Based on the success of the HWA, it would seem that an abbreviated approval pathway for biologics would likewise stimulate the development of follow-on products and that incentives for innovation would not weaken. One study of the market potential of follow-on biologics, coauthored by Professor Grabowski, predicted that "limited competition of either the nonbranded or the branded variety is most likely in the short run because of regulatory conservatism, relatively high barriers to entry, and initial caution on follow-on product acceptance."[211] According to this study, "for the typical drug, generic prices begin to approach their long-run marginal cost when there are at least ten competitors in the market."[212] For commercially successful drug products, this occurs quickly, typically less than a year after

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which represents the branded pharmaceutical industry, as describing the HWA as "a balanced success for patients, generics and innovators").

204. FTC STUDY, *supra* note 85, at i (stating that "Hatch-Waxman has increased generic drug entry" and noting that prior to the enactment of the HWA, nineteen percent of prescriptions were for generics, compared to more than forty-seven percent in 2000); Grabowski, *supra* note 35, at 21 ("The Hatch-Waxman Act has fostered a vigorous generic industry with substantial benefits to consumers from price reductions."); Mossinghoff, *supra* note 105, at 194 *("*"The robust generic drug industry owes its very existence to the Act . . . .").

205. Generic Pharmaceutical Association, About Generics, Statistics, http://www.gphaonline.org/Content/NavigationMenu/AboutGenerics/Statistics/default.htm (last visited June 23, 2008).

206. *Id.*

207. *See id.*

208. *Id.*

209. *Id.*

210. CNNMoney.com, FORTUNE 500, *Most Profitable Industries: Return on Revenue* (Apr. 30, 2007), http://money.cnn.com/magazines/fortune/fortune500/2007/performers/industries/return_on_revenues/index.html.

211. Grabowski et al., *supra* note 68, at 1296.

212. *Id.*

patent expiration, and, more recently, even within a few months.[213] For follow-on biologics, the authors expect that more time will be needed in order to drive prices down to their marginal cost because in the short run fewer competitors will enter and average prices will drop less than was the case after the enactment of the HWA.[214] Thus, Professor Grabowski and his coauthors urge those who attempt to calculate the budgetary savings from follow-on biologics to make conservative assumptions.[215] Nevertheless, Professor Grabowski and his coauthors conclude that, over time, a "robust follow-on market is likely to emerge as regulatory standards evolve and demand develops."[216]

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213. *Id.*

214. *Id.* at 1291, 1296; *see also* John Ansell, *Biogenerics Part I: Set to Make Real Inroads or Not?*, PHARMA WEEK, Oct. 17, 2007, http://www.pharmaweek.com/Exclusive_Content/1_26.asp (stating that "it will still take several more years than expected, in many cases, for competition with original biotech products to emerge" and that "[t]his potential lag in competition is an important factor that should be taken into account when forecasting biotech product sales").

215. Grabowski et al., *supra* note 68, at 1299; *see also Hearing on Biotech Drugs*, *supra* note 108, at 7 (testimony of Dr. Henry G. Grabowski) (projecting, for markets with one to three entrants, that follow-on biologics would cost ten to twenty-five percent less than branded versions, which accords with results achieved in Europe); *Access to Life-Saving Medicine Act to Give FDA Biogenerics Framework*, PHARMA MARKETLETTER, Feb. 15, 7007 (citing a 2007 study sponsored by the Pharmaceutical Care Management Association (PCMA) estimating that follow-on biologics would cost ten to twenty-five percent less than the branded versions).

According to this 2007 study by the PCMA, the national association representing pharmacy benefits managers, *see* PCMA, About PCMA, http://pcmanet.org/about/ (last visited June 23, 2008), the estimated cost savings to Medicare Part B, if the FDA were to develop a framework for evaluation and approval of follow-on protein products, is roughly $14.9 billion for the period from 2007-2016. Engel & Novitt, *supra* note 5, at 2. Another study published in 2007 by Express Scripts, one of the nation's leading pharmacy benefit management companies, *see* Express Scripts, Investor Information, Corporate Profile, http://phx.corporate-ir.net/phoenix.zhtml?c=69641&p=irol-homeprofile (last visited June 23, 2008), estimated that an abbreviated approval pathway for follow-on protein products could potentially save the U.S. healthcare system $71 billion over a ten-year period. STEVE MILLER & JONAH HOUTS, EXPRESS SCRIPTS, POTENTIAL SAVINGS OF BIOGENERICS IN THE UNITED STATES 7 (2007), *available at* http://www.express-scripts.com/ourcompany/news/outcomesresearch/onlinepublications/study/potentialSavingsBiogenericsUS.pdf.

For its part, BIO, *see supra* note 200 and accompanying text, has disputed the conclusions set forth in these two studies and maintains that they significantly overestimate the potential savings from follow-on biologics. Ted Buckley, *Recent Studies of Follow-On Biologics Are Based on Seriously Flawed Assumptions*, BIOTECHNOLOGY INDUS. ORG., Feb. 22, 2007, http://www.bio.org/healthcare/followon/20070222.pdf. BIO contends that these two studies are based on several flawed premises, including erroneously high estimations of market penetration rates for follow-on products and inaccurate predictions as to the likelihood that all biologics will have follow-ons in the near future. *See id.* ¶¶ 4 & 7. As noted by Professor Grabowski and his coauthors, purchasers of biologics might not readily accept follow-on products. Grabowski et al., *supra* note 68, at 1298; *see also infra* notes 227-30 and accompanying text. What is more, given the complexity of biologics, it is certainly possible that it will not be scientifically feasible to create a follow-on version of each one. See *infra* Part VI.B. regarding the scientific challenges surrounding follow-on biologics.

216. Grabowski et al., *supra* note 68, at 1299.

In their study, Professor Grabowski and his coauthors cite three reasons why they believe that the market for follow-on biologics will develop more slowly than the market for generic drugs.[217] First, they point out that there is no clear regulatory pathway for follow-on biologics.[218] Given the variability and complexity of biologics, it is likely that any abbreviated pathway would require follow-on manufacturers to conduct at least some clinical testing.[219] Naturally, enactment of House Bill 1038 would greatly decrease this barrier to market competition.

Second, Professor Grabowski and his coauthors believe that the market for follow-on biologics will develop slowly as compared to the market for generic drugs due to technology and manufacturing barriers to entry and barriers that impede the decline of manufacturing costs over time.[220] They posit that a recent wave of biologics approvals and investments in biologic manufacturing suggests that firms will not be easily able to increase their production in the near future.[221] As noted by Professor Grabowski and his coauthors, only the largest or most firmly established generic manufacturers would be able to face the major financial hurdles and risks engendered by expanding operations.[222]

Capital investment in property, plants, and equipment and the costs of manufacturing are higher for biologics than for generic drugs.[223] For example, cell culture facilities take three to five years to construct and cost $250-$450 million, and materials cost twenty to one hundred times more than those used for traditional drugs.[224] Professor Grabowski and his coauthors do point out, however, that, over longer time frames, expansion in manufacturing capacity and techno-

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217. *Id.* at 1296-98.

218. *Id.* at 1296.

219. *Id.* at 1296-97. Extrapolating from figures in Europe, where follow-on biologics have been approved, *see supra* Part VI, the cost of clinical trials for biologics is estimated to be ten to forty million dollars, compared to roughly one to two million dollars to demonstrate bioequivalence for generic drugs. Grabowski et al., *supra* note 68, at 1293.

220. Grabowski et al., *supra* note 68, at 1297.

221. *Id.*

222. *Id.*; *see also* Ansell, *supra* note 214 (stating that only established biopharmaceutical firms have the resources to pursue development of biopharmaceuticals, but noting that, given that the regulatory demands will prove exacting, such firms are "probably better off developing entirely novel biotech products instead"); Lisa Roner, *Is the Biogenerics Battle About to Heat Up?*, EYE FOR PHARMA, Feb. 22, 2006, http://www.eyeforpharma.com/index.asp?news=49866 (stating that only a few biogeneric firms, namely Sandoz, Teva, BioPartners, ratiopharm, and Stada, have the strong financial backing and regulatory expertise necessary to support a follow-on protein product through the necessary clinical trials). As noted by Professor Grabowski and his coauthors, very few biotech companies are mature firms. Grabowski et al., *supra* note 68, at 1294. Most are in the early stages of development and not profitable. *Id.*

223. Grabowski et al., *supra* note 68, at 1294.

224. *Id.*; *see also supra* note 30 (describing the high cost of materials for manufacturing protein products).

logical advances in process engineering could facilitate lower costs for follow-on biologics, especially as certain firms choose to specialize in generic biologics and others begin to outsource some of their manufacturing.[225]

Third, Professor Grabowski and his coauthors expect that purchasers of biologics might not readily accept follow-on products.[226] Even if a biologic has been subject to adequate clinical testing to ascertain that it is therapeutically equivalent to an existing product, some users will be particularly cautious about using follow-on products in the short term.[227] Moreover, there has traditionally been less substitution of biologics than of drugs. Because many biologic therapies are designed to treat life-threatening diseases and do not have close substitutes, managed care organizations have been reluctant in the past to restrict access or require the use of generics.[228] In addition, biologics have often been treated as medical benefits under insurance plans, rather than as pharmacy benefits, and, therefore, have been less subject to centralized formulary controls.[229] Nonetheless, Professor Grabowski and his coauthors indicate that this situation is changing and that, once concerns about the safety of follow-on biologics are allayed, these products ultimately will be substituted for branded ones; the speed at which this change will occur, however, is not known.[230] Significant debate currently surrounds the question whether technology is sufficiently advanced to ensure that follow-on protein products are indeed as safe and effective as their branded analogues.

B. Current Scientific Knowledge Permits an Abbreviated Approval Pathway for Certain Follow-On Protein Products

While opponents of an abbreviated approval pathway for biologics, including many brand firms, assert that current scientific knowledge does not permit an abbreviated approval pathway for biologics, proponents of such legislation, with generic manufacturers foremost among them, contend that present day scientific techniques do "support the approval of most biopharmaceutical products under an abbreviated approval pathway."[231] These two groups differ on several points, including the ability of scientists, using current technology, to

225. Grabowski et al., *supra* note 68, at 1297-98. The authors further note, however, that lower costs might not actually be passed on to the consumer, but rather captured by new market entrants. *Id.* at 1298.

226. Grabowski et al., *supra* note 68, at 1298.

227. *Id.*

228. *Id.* at 1295.

229. *Id.*

230. *Id.*

231. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 5.

assess innovator and follow-on protein products for comparability, whether two biologics produced using different manufacturing processes can be truly comparable, and whether the immunogenicity profile of most biologics renders them ineligible for an abbreviated approval pathway.

1. It Is Possible, Using Current Scientific Techniques, to Assess Follow-On Protein Products for Comparability with Innovator Products

It is generally acknowledged that, because biologics exhibit a great deal of complexity and structural heterogeneity, scientists cannot fully characterize them at the present time.[232] Nevertheless, the GPhA maintains that current scientific techniques permit manufacturers of follow-on protein products to assess their products for comparability with brand products without the need for some or any of the preclinical and clinical studies.[233] According to the GPhA, a manufacturer of a brand biopharmaceutical could "execute a comprehensive side-by-side comparative analytical characterization on the biopharmaceutical product and the reference product" and if the follow-on protein achieved the requisite standard of comparability, then "the need to conduct further studies, such as preclinical, pharmacokinetic, pharmacodynamic, or clinical studies could be reduced or even eliminated."[234] This scientific capability would allow manufacturers of follow-on protein products to benefit from an abbreviated approval pathway for follow-on protein products if Congress were to implement one.

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232. Schellekens, *supra* note 17, at 1357 (stating that biologics cannot "be fully characterized physicochemically by current analytical methods" and that they "show a high degree of heterogeneity (e.g., in glycosylation or in folding)"); Biotechnology Indus. Org., BIO Principles on Follow-On Biologics (Mar. 26, 2007), http://www.bio.org/healthcare/followonbkg/Principles.asp [hereinafter BIO Principles] (stating that biologics are "different and far more complex than most small molecule chemical drugs" and that "[d]ue to their size and complexity, biologics generally cannot be scientifically characterized to the same degree as small molecule chemical drugs"); GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 7-14 (acknowledging that "no 'one' analytical method is currently capable" of comprehensive characterization of biopharmaceuticals).

233. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 7-14; *see also The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. (2004) [hereinafter *Hearing on the Law of Biologic Medicine*] (statement of William Schultz, Partner, Zuckerman Spaeder L.L.P., on Behalf of the Generic Pharmaceutical Association), *available at* http://judiciary.senate.gov/testimony.cfm?id=1239&wit_id=3627 (stating that "analytical scientific techniques and methods have rapidly advanced over the past decade" such that "[c]omparative studies between the brand biopharmaceutical product and the generic biopharmaceutical have shown similarity in the primary, secondary, and tertiary structures of these products").

234. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 8.

GPhA further explains that there are two possible characterization methods for biologics: absolute and comparative.[235] Absolute characterization involves comprehensive analysis of the product at the atomic level; for example, characterization could include "determination of the complete three-dimensional structure of a protein at the atomic level."[236] As explained by the GPhA, "absolute characterization is the norm for the vast majority of small molecular pharmaceutical products, but is much less common for biopharmaceuticals."[237]

According to the GPhA, however, absolute characterization of biologics is not essential in developing follow-on biologics, because comparative characterization is more relevant in assessing comparability.[238] An analysis of a biologic as *compared* to a reference product would aim to determine the degree of similarity of the two products "in all meaningful ways," without fully characterizing either the reference or the follow-on biologics in absolute terms.[239] The GPhA cites as an example that a comparative characterization would not reveal the complete three-dimensional structure of both proteins at the atomic level, but rather compare their degree of similarity or dissimilarity by using various analytical methods that would "detect any differences in the three-dimensional structures of the two proteins."[240] According to the GPhA, since the goal of such characterization is "to assess comparability between the two products," methods that permit detection of a biochemical "fingerprint" are useful even if these "methods do not enable complete description of [either] product in absolute terms."[241]

The GPhA asserts that comparative analysis is presently technologically possible for "most, if not all" biologics.[242] Indeed, the GPhA asserts that each time brand firms alter their manufacturing processes, they are already able to assess the comparability of their products prior and subsequent to such change,[243] even with respect to

235. *Id.* at 9.
236. *Id.*
237. *Id.*
238. *Id.* at 10 ("The distinction between absolute and comparative characterization is critical, because only comparative characterization is relevant to the determination of similar [sic] of two biopharmaceuticals.").
239. *Id.* at 9-10.
240. *Id.* at 10.
241. *Id.*
242. *Id.* at 10-11. For a brief mention of the current analytical technology supporting absolute and comparative characterization, see *id.* at 11.
243. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 7 ("A within-manufacturer comparison could arise when a pioneer seeks to change its process, formulation, manufacturing site, etc."); *Hearing on the Law of Biologic Medicine*, *supra* note 233 (testimony of William Shultz) ("Changes to the manufacturing process for generic biopharmaceuticals are addressed in the same manner as brand manufacturers in that comparability between the product prior and subsequent to such change is established.").

highly complex products, in order to detect changes that may affect the safety and efficacy of their biologics.[244] Further, GPhA contends that an appropriate combination of analyses "can provide comprehensive comparative characterization of all clinically meaningful properties of a biopharmaceutical" and that such results "are often more sensitive to product changes than are clinical studies."[245]

The GPhA asserts that, once the differences between the reference and follow-on product have been determined, the next step is to develop criteria to determine when products will be considered sufficiently similar analytically so that their clinical effect will be expected to be comparable.[246] The GPhA maintains that "[t]he greater the extent of characterization" of the reference and test biologics, "and the closer the match between [them], the greater the assurance of comparable clinical effect," which, therefore, reduces the need for pre-clinical and clinical testing.[247] The GPhA suggests that, when assessing the degree of comparability of the reference and test products, one must take into account the fact that biological products are inherently variable, some more so than others, and therefore, a rather wide range of values for each analytical parameter should be accepted.[248]

For its part, BIO strongly disagrees with the GPhA that analytical tests, unaccompanied by pre-clinical and clinical tests, would "pro-

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244. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 10 ("Indeed, it is precisely this type of comparative characterization that brand firms employ routinely in comparability studies, even on highly complex, heterogeneous products, to detect changes relevant to safety and efficacy."). See *infra* Part VI.B.2. and accompanying text, regarding the question whether two biologics produced using different manufacturing processes can be truly comparable.

245. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 11; *see also Safe and Affordable Biotech Drugs—The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 3-5 (2007) [hereinafter *Hearing on Biotech Drugs*] (testimony of Theresa L. Gerrard, TLG Consulting Inc.), *available at* http://oversight.house.gov/documents/20070326121929-50046.pdf (stating that the "critically important point" is that the "FDA recognized that analytical testing was far more sensitive in the ability to detect product changes than a typical clinical trial" and explaining that this is due to the fact that "variation among people in their response to a biopharmaceutical does not allow one to detect subtle product differences").

246. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 14.

247. *Id*. The GPhA proposes that, since the complexity of biologic products varies along a continuum, the FDA should take into account the particular characteristics of the product in question when determining when to require submission of pre-clinical and clinical studies. *Id.* at 3-4. For example, some proteins, such as inteferons, are relatively simple, whereas others, such as erythropoetin, are more complex because they are glycosylated. *See id.* at 4 (noting the "continuum of product complexity" for protein products and stating that the FDA should take this into account when devising an abbreviated approval pathway); *Hearing on the Law of Biologic Medicine*, *supra* note 233 (testimony of William Shultz) (stating that "a simple protein, such as interferon, should have a reduced preclinical and clinical program when compared to a glycosylated protein (proteins with sugar molecules), such as erythropoetin").

248. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 14-15.

vide sufficient evidence to justify approval of a follow-on protein," citing two reasons for its view.[249] First, BIO contends that such tests are specific to the particular manufacturing process used and therefore "completely irrelevant to a similar product developed through a different manufacturing process by another company."[250] Second, BIO maintains that "although testing technology is rapidly evolving, current analytical tests remain limited in their ability to detect product variations that may affect clinical safety and effectiveness."[251]

With respect to its first claim, that analytical testing is process-specific, BIO explains that

> Throughout the manufacturing process, the protein mixture is subject to various tests to ensure characteristics such as structure, and potency, as well as the absence of impurities and contaminants. However, analytical tests performed by the innovator may rely on testing limits and criteria that have been shown to be valid only with respect to a particular process, and/or may involve proprietary reagents and equipment. . . . For this reason, it can be difficult to establish a "standard" or "uniform" array of analytical tests for use with particular types or classes of products.[252]

In terms of its second contention, that analytical tests cannot detect all clinically significant product variations, BIO asserts that "it can be difficult for a manufacturer to identify appropriate analytical technologies to detect/explain changes when the biochemical basis for the changes is unknown."[253] What is more, "a high degree of analytical correlation between an innovator and follow-on product might not translate into the same degree of clinical quality, safety, or effectiveness, while analytically dissimilar products may have similar safety and effectiveness profiles."[254]

In sum, while acknowledging improvements in analytical technology and allowing that it may be possible for follow-on manufacturers "to conduct certain analytical correlation assessments," BIO asserts that "laboratory assays . . . cannot currently be used as surrogates for establishing high quality, safety, and effectiveness of a follow-on pro-

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249. Letter from Sara Radcliffe, Managing Dir., Sci. and Regulatory Affairs, Biotechnology Indus. Org., to FDA 30 (Dec. 13, 2004), *available at* www.bio.org/reg/20041213.pdf [hereinafter Dec. 13, 2004 BIO Letter to FDA].

250. *Id.* Indeed, BIO rejects the use of the term "comparability" in describing the relationship between reference and follow-on products, maintaining that this term should be "restricted to 'intra-manufacturer' situations; *e.g.,* to describe the relationship between a manufacturer's product before and after manufacturing changes." *Id.* at 10-11. According to BIO, any true assessment of comparability requires historical data about the manufacturing process and the product, proprietary information to which a follow-on manufacturer would not be privy. *Id.* at 10-13.

251. Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 30.

252. *Id.*

253. *Id.* at 31.

254. *Id.*

tein," because "differences (and the absence of differences) detected using a combination of biochemical and bioassay assessments cannot fully predict clinical safety or efficacy consequences."[255]

The FDA, the body responsible for assessing the safety and effectiveness of drugs and biologics, takes a view somewhere between the GPhA and BIO. The FDA has indicated that it is possible, using current characterization techniques, to accurately assess relatively simple follow-on protein products for comparability with reference products without requiring clinical trials, but that it is not possible to do so for more complex protein products. Testifying before the House Committee on Oversight and Government Reform in March 2007, Dr. Janet Woodcock, Deputy Commissioner for Operations at the FDA, stated that "the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product."[256] She added that while such a comparison "may be currently possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products."[257] With respect to these more complex protein products, Dr. Woodcock stated that the FDA may require clinical trials on a case-by-case basis and that future scientific advances may enable the agency to approve follow-on protein products based solely on characterization.[258] Nonetheless, Dr. Woodcock urges Congress to " 'leave room for the evolving science,' " predicting that " 'within this decade we will be able to characterize some of the very simple proteins well enough that we will probably be able to decide that they're similar enough to an innovator product.' "[259]

House Bill 1038 contains specific statutory language addressing the issue of similarity of biological products.[260] The bill would require an abbreviated biological product application to include data demon-

255. *Id.* at 31-32.

256. *Hearing on Biotech Drugs*, *supra* note 6, at 9 (testimony of Dr. Janet Woodcock).

257. *Id.*

258. *Id.* at 8-10.

259. RUCKER, *supra* note 2, at 3 (quoting Dr. Janet Woodcock) (citation omitted). FDA officials do, however, acknowledge the current difficulty of assessing the similarity of a reference biologic and a follow-on product; *see also* E-mail from Dr. Emily Shacter, Chief, Lab. of Biochemistry, Div. of Therapeutic Proteins, Office of Biotechnology Prods., Ctr. for Drug Evaluation & Research, FDA, to Donna M. Gitter, Assistant Professor of Legal and Ethical Studies, Fordham Univ. Schs. of Bus. (Apr. 23, 2007, 12:44 PM) (on file with author) [hereinafter April 23rd E-mail from Dr. Emily Shacter] (stating that "we don't necessarily know what to do if and when differences are seen (and they WILL be seen; it's just the nature of the beast)" and adding that "the term 'similarity' is a poor choice and is a bit misleading. How similar? How do you define 'similar[?]' ").

260. Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3(k)(1)(B) (2007).

strating, inter alia, that "the biological product and reference product contain highly similar principal molecular structural features."[261] House Bill 1038 then describes various scenarios where two protein products that differ in certain ways would still be deemed "highly similar."[262] Some commentators have expressed concerns about the bill's provisions for assessing similarity.

Testifying in March 2007 before the Senate Committee on Health, Education, Labor, and Pensions regarding Senate Bill 623, the companion bill to House Bill 1038,[263] Dr. Jay P. Siegel of Johnson & Johnson critiqued, on scientific grounds, the statutory language in Senate Bill 623 setting forth when two protein products will be considered "highly similar" and therefore eligible for a demonstration of comparability pursuant to that statute.[264] First, the legislation would consider protein products with "minor differences in amino acid sequence" to be considered "highly similar."[265] According to Dr. Siegel, differences in even just one amino acid "often have adverse effects on the molecule, with the potential to pose great danger to patients."[266] What is more, Senate Bill 623 would also consider two protein products to be "highly similar" and eligible for a demonstration of comparability under the statute where the products' differences are "solely due to post-translational events."[267] Dr. Siegel asserts that " '[p]ost-translational modification' refers to the important processes that occur after the backbone of a protein has been synthesized" and "can result in major chemical modifications of the protein" that may significantly impact its "activity, half-life in circulation, and immunogenicity."[268] He contends that many post-translational modifications are "so profound, they should simply be considered to make the biologic a different biologic, requiring a full application."[269] Senate Bill

261. *Id.*

262. *Id.*

263. *See supra* note 174 and accompanying text. The text of the two bills is identical.

264. *See Hearing on Follow-On Biologics*, *supra* note 22, at 10-13 (testimony of Dr. Jay P. Siegel).

265. H.R. 1038, § 3(k)(1)(B)(i) (providing that two protein biological products will be deemed "to contain highly similar principal molecular structural features" where they have "minor differences in amino acid sequence"); *id.* § 3(k)(1)(B)(iii) (providing that two glycosylated protein biological products will be deemed "to contain highly similar principal molecular structural features" where they have "minor differences in amino acid sequence").

266. *Hearing on Follow-On Biologics*, *supra* note 22, at 11 (testimony of Dr. Jay P. Siegel).

267. *See* H.R. 1038, § 3(k)(1)(B)(i) (providing that two protein biological products will be deemed "to contain highly similar principal molecular structural features" where the differences in structure between them are "solely due to post-translational events"); *id.* § 3(k)(1)(B)(iii) (providing that two glycosylated protein biological products will be deemed "to contain highly similar principal molecular structural features" where the differences in structure between them are "solely due to post-translational events").

268. *Hearing on Follow-On Biologics*, *supra* note 22, at 11-12 (testimony of Dr. Jay P. Siegel).

269. *Id.* at 12.

623 also deems "highly similar" any "[c]losely related, complex partly definable biological products with similar therapeutic intent, such as two live viral products for the same indication."[270] Dr. Siegel maintains that this provision "allows abbreviated applications for living cells and organisms and other biologic products far more complex and difficult to define than proteins" and asserts that since these products are only partly definable, there is "no scientifically valid basis for determination that they are comparable."[271] In his view, in most cases, all of the aforementioned differences give rise to a need for full clinical testing of the follow-on products comparable to that initially required of the innovator products.[272]

Dr. Siegel also opposes House Bill 1038's provisions concerning interchangeability, stating that "[n]o follow-on biologic product should be considered interchangeable with its reference product."[273] Senate Bill 623 provides that a biological product shall be deemed "interchangeable" and therefore substitutable for the reference product[274] where the follow-on product is comparable to the reference product and "can be expected to produce the same clinical result as the reference product in any given patient."[275] Dr. Sigel maintains that "[n]o amount of non-clinical testing of a biologic product can ensure or predict it will have identical effects to another product" and that the very concept of interchangeability is dangerous considering the risk of clinically important differences between the products.[276] Indeed, the FDA acknowledged in a submission to the World Health Organization, in the context of a discussion of international nonpro-

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270. H.R. 1038, § 3(k)(1)(B)(v).

271. *Hearing on Follow-On Biologics*, *supra* note 22, at 12 (testimony of Dr. Jay P. Siegel).

272. *See id.* at 11-12 (advocating for full, not abbreviated, applications for protein products that present minor differences in amino acid sequence, differences "due solely to post-translational events," and " 'closely related, complex partly definable biological products with similar therapeutic intent' (for example, two live viral products for the same indication)" (quoting S. 623, 110th Cong. § 3(k)(1)(B)(v) (2007)).

273. *Id.* at 13.

274. See *supra* notes 186-87 and accompanying text regarding the significance of a designation of interchangeability.

275. H.R. 1038, § 2(a)(5)(B).

276. *Hearing on Follow-On Biologics*, *supra* note 22, at 14 (testimony of Dr. Jay P. Siegel). Dr. Siegel also expresses concern that the designation of interchangeability, which would lead patients to switch between therapies, would render it more difficult to attribute emergent adverse events to a specific therapy. *Id.* He posits that this situation "could severely impair the ability of pharmacovigilance systems to deal with emerging safety problems." *Id.* at 15; *see also Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Comm. on Energy and Commerce, Subcomm. on Health*, 110th Cong. 18 (2007) [hereinafter *Hearing on Biosimilar Policy*] (statement of Dr. David Schenkein, Vice President, Clinical Hematology/Oncology, Genentech, on behalf of the Biotechnology Indus. Org.), *available at* http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Schenkein-testimony.pdf (stating that "[t]he ability to detect that a new follow-on biologic has a significantly higher risk would be highly impaired and . . . could go unnoticed").

prietary names for biologics, that as of September 2006, "[w]ith protein products, . . . the FDA has not determined how interchangeability can be established for complex proteins."[277]

Other industry professionals disagree with Dr. Siegel's conclusions, however. In terms of comparability, Dr. Ajaz Hussain, Vice President and Global Head of Biopharmaceutical Development at Sandoz, a generic division of Novartis,[278] stresses that the biologics industry and the FDA already "accept that batch-to-batch variation is inevitable for biologics."[279] Under accepted comparability principles for already-approved reference products, so long as subsequent batches meet certain parameters, they are made available to the public. Dr. Hussain therefore rejects any "sameness" requirements for follow-on products that are not the current regulatory standards and instead calls for "consistent and appropriate regulatory standards applied to all biologics independent of their sponsor."[280]

With respect to interchangeability, Dr. Schwieterman, formerly an FDA official and most recently an independent consultant to the brand biopharmaceutical industry as well as to firms interested in biogenerics,[281] declares "without hesitation, that adequate scientific tools currently exist to assess and deem certain products as interchangeable."[282] Dr. Ganesh Venkataraman, cofounder and Senior Vice President of Research at Momenta Pharmaceuticals, Inc.[283] claims that "[w]hile interchangeability may not be possible for most

277. FDA, U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars (Sept. 1, 2006), http://www.fda.gov/cder/news/biosimilars.htm.

278. Dr. Hussain emphasizes that, as a representative of Novartis, which he describes as "unique among pharmaceutical companies because it has made large investments in both branded and generic drugs," he represents a "balanced" position with respect to follow-on biologics rather than a position biased by commercial interests on one side of the question. *Follow-On Biologics: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 110th Cong. 1 (2007) (statement of Ajaz Hussain, Ph.D., Vice President & Global Head of Biopharmaceutical Development, Sandoz, on behalf of the Novartis Group of Companies), *available at* http://help.senate.gov/Hearings/2007_03_08/Hussain.pdf.

279. *Id.* at 5.

280. *Id.* Dr. Hussain warns that one unintended consequence of a sameness standard is that even brand firms might not meet this requirement from one batch to the next, resulting in a situation where patients cannot get access to sorely needed biologic products. *Id.*

281. *See Safe and Affordable Biotech Drugs—The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 2 (2007) [hereinafter *Hearing on Biotech Drugs*] (statement of Dr. William Schwieterman), *available at* http://oversight.house.gov/documents/20070326121827-46231.pdf.

282. *Id.* at 8.

283. *Safe and Affordable Biotech Drugs—The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 2 (2007) [hereinafter *Hearing on Biotech Drugs*] (statement of Dr. Ganesh Venkataraman, Momenta Pharmaceuticals, Inc.), *available at* http://oversight.house.gov/documents/20070326121658-50108.pdf. Momenta's research and development focuses on both generic as well as novel drug candidates. *Id.* at 3.

biologics today, it is well within reach in the near term for a number of products."[284] As noted by Dr. Schwieterman, given the current state of scientific understanding and the importance to patients of access to safe, effective, and affordable biologics, the FDA should be given "legislative authority to use scientific data and make critical judgments to determine, when appropriate, that two products are interchangeable."[285]

2. Two Biologics Produced Using Different Manufacturing Processes Can Be Truly Comparable

In addressing whether two biologics can be comparable even if they are manufactured using different processes, the GPhA asserts that the focus in evaluating follow-on protein products for safety and efficacy should be on the end product, rather than the process, which is not an end in itself.[286] According to the GPhA, the essential elements of the manufacturing process include robustness, reproducibility, validation, controls, and testing, and if the appropriate standards are maintained for these features, the follow-on protein product is likely to meet the requisite standards for identity, potency, purity, quality, and safety.[287] The GPhA emphasizes that an analytical comparability exercise can demonstrate comparability of the reference and follow-on products, notwithstanding their different means of manufacture.[288]

The GPhA position is buttressed by the May 2007 congressional testimony of independent consultant Dr. Schwieterman.[289] He explains that, in the last fifteen years, scientific advances have permitted the FDA to apply comparability principles to allow postapproval changes in brand biopharmaceuticals, even for very significant

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284. *Hearing on Biotech Drugs*, *supra* note 283, at 4 (testimony of Dr. Ganesh Venkataraman).

285. *Hearing on Biotech Drugs*, *supra* note 281, at 9 (testimony of Dr. William Schwieterman). It should be noted that another proposed legislative bill, the Patient Protection and Innovative Biologic Medicines Act of 2007, introduced in the House of Representatives by Representative Jay Inslee (D-WA) in April 2007, would amend the PHSA to authorize the FDA to approve "similar" biological products but would preclude any determination of interchangeability. H.R. 1956, 110th Cong. (2007), *available at* http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h1956ih.txt.pdf.

286. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 17 ("The process is, therefore, not the end in and of itself, but rather a means to achieve the end. The objective is really a final product (composition) that is approvable. Any reproducible process that yields a final product that matches the desired composition (based on comparability to the reference product) should, therefore, be equally acceptable.").

287. *Id.* at 18.

288. *Id.* "Specific aspects of the manufacturing process do not determine the characteristics of a protein product. . . . An analytical comparability exercise should be conducted to demonstrate comparability of the biopharmaceutical product[s] to the reference product." *Id.*

289. *See supra* note 281 and accompanying text.

manufacturing changes, such as cell line replacements and relocations of the manufacturing facility site.[290] According to Dr. Schwieterman, "[c]ontrary to what others may say, the scientific evidence has not required the vast majority of post-approval brand product changes to be supported by large clinical outcome studies."[291] Instead, the FDA relies on analytic tests to assess molecular structure along with, when needed, "short-term assessments of the pharmacokinetics (assessing blood levels in various tissues) and pharmacodynamics (assessing the short-term impact of the agent on laboratory parameters)," studies that typically involve fewer than one hundred patients and last just weeks.[292] Dr. Schwieterman notes that:

> Large clinical outcome studies are indispensable for determining the safety and efficacy of a new and untested agent. However, they are often poor tools for use in comparing differences between two different agents unless the studies are made to include 1000s of patients—which may or may not reveal the difference in the product, [sic] In fact, I can think of only one example where the FDA required a large clinical outcome study for a product—yet the FDA first deemed the product not comparable due to analytic and pharmacokinetic and pharmacodynamic measures.[293]

Thus, Dr. Schwieterman states his belief

> that based on the wealth of experience with brand post-approval manufacturing changes in the biopharmaceutical industry, the evidence clearly demonstrates that comparability processes

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290. *Hearing on Biotech Drugs*, *supra* note 281, at 4 (testimony of Dr. William Schwieterman). Another former FDA official and independent consultant to the biotech industry, Dr. Theresa L. Gerrard, concurs in this view. *See Hearing on Biotech Drugs*, *supra* note 245, at 2 (testimony of Theresa L. Gerrard). She notes that the FDA developed scientific policies on comparability in the 1990s at the behest of the innovator biotech manufacturers who "pressed FDA for this change" so as to avoid the need for clinical trials after each manufacturing process change, "rightly claim[ing] that their biopharmaceuticals were so well characterized." *Id.* Dr. Gerrard cites two complex biologic products, Biogen's Avonex and IsnMed's Iplex, as ones for which the manufacturers changed the cell line, the purification scheme, and additionally for Avonex, the manufacturing site. *Id.* at 4. Dr. Gerrard further notes that since 1996, CBER no longer requires a separate license for each manufacturing facility during the biologic approval process, thereby indicating the "FDA's growing confidence in its ability to determine comparability, and thus, safety and efficacy, based on results from analytical testing of the finished product, independent of the manufacturing process" and the agency's recognition "that in most cases analytical testing could support these changes without [the] need for retesting the product in clinical trials." *Id.* at 3.

291. *Hearing on Biotech Drugs*, *supra* note 281, at 4 (testimony of Dr. William Schwieterman). *But see Hearing on Biosimilar Policy*, *supra* note 276, at 8 (testimony of Dr. David Schenkein) (stating that "[w]hen a biologics manufacturer makes a substantial change to its process (e.g., new cell line), given the incomplete ability of laboratory testing to identify or predict differences, FDA requires substantial testing in humans (clinical testing) to validate the comparability of the product").

292. *Hearing on Biotech Drugs*, *supra* note 281, at 6 (testimony of Dr. William Schwieterman).

293. *Id.* at 6-7.

> soundly support the approval of biogenerics without the need for large and questionable clinical trials which for most products, would needlessly delay access to affordable life-saving medicines.[294]

In contrast, BIO asserts that the adage "the 'product is the process' " exemplifies the potentially critical impact that even minor manufacturing changes can have on a protein product.[295] The manufacture of protein products involves "numerous highly variable and specialized steps,"[296] and even a slight change in any one of these could have a negative clinical impact.[297] BIO cites several examples of cases where innovator companies intentionally effectuated changes in their manufacturing processes that resulted in unanticipated alterations in the final product.[298]

BIO also denies the GPhA's assertion that the manufacture of a follow-on product is analogous to an innovator's change in its manufacturing process.[299] BIO contends that "[w]hile the scope and scale for intra-manufacturer manufacturing process changes are almost always limited, the scope and scale of differences for a follow-on product necessarily would be extensive."[300] For example, BIO points out that there would be numerous differences between the manufacturing processes of an innovator protein product and a follow-on, including "cell line, raw materials, manufacturing process and process controls, test methods, reference materials, specifications, container/closure system, and manufacturing and testing facilities."[301] Moreover, follow-on manufacturers lack "the particular extensive knowledge of a specific product's manufacturing history and critical product quality attributes to guide them through product development," which are typically protected as trade secrets.[302]

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294. *Id.* at 7.

295. Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 18.

296. *Id.* at 19; *see also supra* note 21 and accompanying text.

297. *See* Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 29.

298. *Id.* at 21-28 (citing examples of manufacturing changes with respect to several protein products and the resultant impact on the products in terms of immunogenicity, potency, pharmacokinetics, bioavailability, and purity).

299. Letter from Sara Radcliffe, Managing Dir., Sci. and Regulatory Affairs, Biotechnology Indus. Org., to FDA 4 (Mar. 16, 2005) [hereinafter March 16, 2005 BIO Letter to FDA], *available at* http://www.bio.org/reg/20050316.pdf ("[T]he manufacture of a follow-on product is not analogous to innovators making manufacturing changes."). See *supra* notes 286-88 and accompanying text for the GPhA's view.

300. Mar. 16, 2005 BIO Letter to FDA, *supra* note 299, at 3.

301. *Id.* at 3-4.

302. *Id.* at 4; *see also* Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 19 ("Much of the knowledge and data about the manufacturing process are proprietary to the innovator and therefore would be unavailable to follow-on manufacturers."); *id.* at 29 ("A manufacturer attempting to make a follow-on product may certainly be as technically capable as the innovator manufacturer, but often will lack critical product-specific information to evaluate the impact of using a process that is different from that of the innovator.").

In his March 2007 congressional testimony, Johnson & Johnson's Dr. Siegel explains the types of critical manufacturing information that follow-on manufacturers would lack, thereby limiting their ability to identify clinically important differences short of clinical testing.[303] First, "[w]hen a manufacturer makes [a] substantial change[] in its manufacturing process, that manufacturer is able to compare not only final product but also various components and intermediates that are produced during various stages of the new and old manufacturing process."[304] "Such comparisons may detect important differences that remain in the final product, but at [low] levels" that might not otherwise be detected.[305] In contrast, follow-on manufacturers will not have access to these intermediate products, and will conduct their comparisons using only the final, marketed reference product.[306]

Second, unlike follow-on manufacturers, brand firms possess years of experience comparing their products before and after manufacturing changes.[307] This experience affords them an understanding of which parameters are essential for ensuring safety and efficacy of the molecule, the best approaches for assessing this information, and which differences are clinically important.[308] Thus, in light of the importance of the manufacturing process, BIO and its members believe that follow-on manufacturers must perform clinical studies in all cases to assure safety and effectiveness of their products.[309]

Some FDA officials have expressed their concordance with the GPhA position that two biologics can achieve comparability even if they are manufactured using different processes, at least with respect to recombinant products created through genetic engineering, as opposed to naturally-derived ones such as blood- and tissue-derived products and vaccines.[310] This view was presented at a De-

303. *Hearing on Follow-On Biologics*, *supra* note 22, at 4 (testimony of Dr. Jay P. Siegel).

304. *Id.*

305. *Id.*

306. *Id.*

307. *Id.* at 4-5.

308. *Id.*

309. Mar. 16, 2005 BIO Letter to FDA, *supra* note 299, at 4 ("We believe that, in all cases, follow-on manufacturers would need to perform adequate clinical studies to assure safety and effectiveness of their protein products."); *see also Hearing on Follow-On Biologics*, *supra* note 22, at 5 (testimony of Dr. Jay P. Siegel) (stating his belief that "there will always be a need (in the foreseeable future) for some amount of clinical testing of a follow-on biologic," though the "amount and type of testing will depend on the specifics of the products and assessment of potential risks").

310. *See* E-mail from Dr. Emily Shacter, Chief, Lab. of Biochemistry, Div. of Therapeutic Proteins, Office of Biotechnology Prods., Ctr. for Drug Evaluation and Research, FDA, to Donna M. Gitter, Assistant Professor of Legal and Ethical Studies, Fordham Univ. Schs. of Bus. (Apr. 20, 2007, 10:11 AM) (on file with author) [hereinafter April 20th E-Mail from Dr. Emily Shacter] (expressing the opinion of some FDA officials that, at least for certain biologics, comparability with a reference product could be achieved even using a different manufacturing process).

cember 2005 public workshop titled *Scientific Issues in Assessing the Similarity of Follow-on Protein Products*, cosponsored by the FDA, along with the National Institute for Standards and Technology (NIST)[311] and the New York Academy of Sciences (NYAS).[312] In her presentation entitled *Follow-On Biologics Workshop Meeting Goals and Outcomes*, the FDA's Dr. Emily Shacter explained that, at least for recombinant proteins (though not for naturally-derived products), the manufacturing process "impacts but does not necessarily define the product," and therefore "[i]f you can define the desired endpoint (product), [you] can probably design the process to achieve that product ('reverse engineering')."[313] Dr. Shacter explains why the manufacturing process is less important for recombinant proteins as follows:

> One of the main differences between a recombinant protein and one that is naturally-derived is in the complexity and multiple biological activities found in the source material. Blood has hundreds of proteins, all of which have biological activities in humans. Most are in low abundance and require complex purification processes that may or may not be able to remove all impurities, and these can be difficult to identify and quantify. Even very low levels of some blood proteins can pose significant safety issues. So you want the intended protein product and impurities to be highly consistent and reflective of the "mixture" tested in clinical safety and efficacy trials. In contrast, recombinant proteins are over-expressed in cell lines (like E. coli and Chinese Hamster Ovary (CHO) cells), so the protein of interest is the most abundant protein in the gemische, and the residual host cell proteins generally have been extensively

311. NIST is a nonregulatory federal agency within the U.S. Department of Commerce and is charged with promoting "U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve . . . quality of life." National Institute of Standards and Technology, General Information, http://www.nist.gov/public_affairs/general2.htm (last visited June 23, 2008).

312. The New York Academy of Sciences (NYAS) is an "independent, nonprofit, membership-based organization" that describes itself as "one of the world's foremost organizers of scientific conferences and symposia." N.Y. Acad. of Scis., About the Academy, http://www.nyas.org/about/index.asp (last visited June 23, 2008). On its Web site, the NYAS emphasizes the scientifically objective information presented at the December 2005 public workshops, declaring that "[t]o obtain the most objective, state-of-the-art input, speakers primarily from academia and government were invited to speak, including scientists from the USA and Europe" and that "[t]here were no speakers from the regulated industry or from potential FOB [follow-on biologic] manufacturers." Angelo DePalma, The New York Academy of Sciences, Follow-On Biologics Workshop, Overview, (May 3, 2006), http://www.nyas.org/ebriefreps/main.asp?intEBriefID=477.

313. Presentation, Dr. Emily Shacter, Chief, Lab. of Biochemistry, Div. of Therapeutic Proteins, Office of Biotechnology Prods., Ctr. for Drug Evaluation & Research, FDA (Dec. 14, 2005), http://www.fda.gov/cder/regulatory/follow_on/200512/200512_shacter_wrapup.pdf. Dr. Shacter notes that these statements represent the consensus view of the FDA and NIST officials who arranged the December 2005 public workshops on follow-on protein products. *Id.* However, she has explained that "like with other huge and complex organizations, the formulation of controversial FDA policies also involves higher management, political appointees, and lawyers, and there is sometimes a disconnect between the major policies that we might recommend." April 20th E-Mail from Dr. Emily Shacter, *supra* note 310.

> studied and have a well known safety profile. The process used to manufacture recombinant proteins is still important, but becomes less so as our ability to analyze highly-purified products increases.[314]

As noted by Dr. Shacter, reverse engineering would be possible for recombinant protein products, though not for naturally-derived products at the present time.[315] Moreover, "as analytical and purification processes advance, so will our ability [to] reverse engineer a naturally-derived protein product."[316]

3. The Immunogenicity Profile of Most Biologics Renders Them Eligible for an Abbreviated Approval Pathway

"Immunogenicity" refers to "an allergic response that can originate in the manufacturing process and from intrinsic properties of the biologic."[317] The GPhA emphasizes that this issue pertains to all biologics, not just follow-on products, and in any event is not always a harmful phenomenon, as "many therapeutic proteins generate antibodies with no clinical consequence."[318] For those cases where immunogenicity is a concern (for example, where hypersensitivity reactions have occurred after administration of a brand protein product), the GPhA notes that because these incidences are rare, "it is unlikely that clinical trials would be useful in addressing whether a biopharmaceutical product was different from the reference product in the induction of hypersensitivity."[319] The GPhA therefore proposes a risk management approach, advocating the use of advanced technological tools in order to assess those products that pose the greatest danger of immunogenicity.[320] As noted by Dr. Schwieterman, the FDA currently uses an arsenal of scientific techniques, including assessments of aggregation, analytic studies, and, in some cases, clinical data, and postmarketing safety studies, in order to evaluate the immunogenicity of brand products that undergo postapproval manufacturing

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314. April 20th E-Mail from Dr. Emily Shacter, *supra* note 310.

315. *Id.*

316. *Id.*

317. Alston & Bird, *supra* note 11, at 4.

318. GPHA SCIENTIFIC CONSIDERATIONS, *supra* note 28, at 23. The GPhA also emphasizes that conventional drug products have been known to induce hypersensitivity reactions, but that the FDA has not required immunogenicity testing in this context. *See id*.

319. *See id*. As explained by the GPhA, in order to assess immunogenicity accurately, a clinical trial would need to be huge and would therefore prove impractical. *See id.* at 24.

320. *See id.* at 23-24 (explaining that aggregation is "the primary product factor associated with immunogenicity" and describing the advanced techniques available for performing analytical testing of biologics for aggregation so as to minimize the potential for immunogenicity). As explained by one scientist, "[t]o a far greater extent than small molecules, biologics frequently can bind to themselves to form pairs or aggregates." *Hearing on Follow-On Biologics*, *supra* note 22, at 3 (testimony of Dr. Jay P. Siegel).

changes on a case-by-case basis.[321] An abbreviated approval pathway for follow-on biologics would allow the agency to do the same for follow-on protein products. Thus, Dr. Schwieterman concludes that "[w]hile immunogenicity is an important consideration for both brands and biogenerics, it is not an obstacle to their development."[322]

BIO agrees with the GPhA that immunogenicity is of great concern only in rare cases,[323] but nevertheless cautions that "when clinically relevant immunogenic responses do occur they can have serious consequences including hypersensitivity, severe allergic or anaphylactic responses, or autoimmunity to endogenous proteins."[324] BIO emphasizes that the causes of immunogenicity are unclear and offers examples of cases where analytical studies of the molecular structure of protein products failed to accurately predict immunogenic events.[325] In particular, BIO cites the case of Eprex®, a biologic product made by Johnson & Johnson to treat anemia and sold in Europe.[326] In 1998, Johnson & Johnson changed the stabilizer in its Eprex® formulation at the request of European authorities due to concern in Europe that the original stabilizer could transmit Mad

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321. *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Comm. on Energy and Commerce, Subcomm. on Health*, 110th Cong. 8 (2007) [hereinafter *Hearing on Biosimilar Policy*] (testimony of Dr. William Schwieterman), *available at* http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Schwieterman-testimony.pdf. What is more, another industry expert has pointed out that whereas "[m]any brand biopharmaceutical products were approved in an era when the importance of testing for aggregates was not recognized" and testing procedures for these products may not have changed since the original FDA approval, new biologics approved by the FDA today, including follow-on protein products, would be tested for aggregation. *Hearing on Biotech Drugs*, *supra* note 245, at 6 (testimony of Theresa L. Gerrard).

322. *Hearing on Biosimilar Policy*, *supra* note 321, at 8 (testimony of Dr. William Schwieterman); *see also Hearing on Biotech Drugs*, *supra* note 245, at 6 (testimony of Theresa L. Gerrard) ("While immunogenicity is an important consideration for biogenerics, it is certainly not a hurdle to their development.").

323. Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 33 (stating that "for the vast majority of protein products immunogenic responses are not a concern, and differences in immunogenicity are not always clinically relevant"). The branded industry disagrees, however, with the GPhA's contention that if an immunogenic event for an innovator product is too rare to be detected in a clinical program then clinical testing for its follow-on should be minimal. The Pharmaceutical Research and Manufacturers of America (PhRMA) argues that "[a] rare or unusual immunogenic event triggered by one factor related to one biologic, does not guarantee that such an event will be just as rare when triggered by another factor related to the follow-on product." Letter from Dr. Caroline J. Loew, Vice President, Scientific and Regulatory Affairs, Pharm. Research and Mfrs. of America (PhRMA), to FDA, Attachment A, at 12 (Nov, 12, 2004) [hereinafter PhRMA Letter to FDA], *available at* http://www.fda.gov/ohrms/dockets/dockets/03p0176/03p-0176-c000003-Tab-A-vol3.pdf.

324. Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 33; *see also* BIO Petition, *supra* note 7, at 45 (stating that immunogenicity causes a patient "to produce antibodies that may inactivate a therapeutic protein resulting in *loss of efficacy and disease progression*, or may inactivate one of the body's naturally occurring proteins resulting in *side effects that can be severe*").

325. Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 23, 34-35.

326. *Id.* at 28.

Cow Disease.[327] Subsequently, there was an increase of a serious disorder called pure red cell aplasia among patients taking Eprex®.[328] Patients suffering from this disorder suffer a severe form of anemia[329] and require weekly blood transfusions for the remainder of their lives.[330] According to one expert, "[i]t took four years of extensive investigations involving more than 100 experts from clinical, preclinical, manufacturing, process sciences, logistics, quality, analytical, and regulatory fields and in excess of one hundred million dollars" to determine that the uncoated rubber stoppers of the vials containing Eprex®, when exposed to the new stabilizer, released substances into the Eprex® solution that most likely caused the increase in the product's immunogenicity and led to the increased occurrence of pure red cell aplasia.[331] In light of situations such as this, BIO advocates clinical studies in the form of "process-specific immunogenicity and safety testing" for each new protein product, warning that "anything less could be detrimental to patient health."[332]

An additional concern of the branded pharmaceutical industry with respect to immunogenicity that arises from Senate Bill 623 is the bill's language providing that "the Secretary shall issue a comparable biological product license for all conditions of use of the reference product sharing the same mechanism or mechanisms of action for which the applicant has demonstrated comparability for a single condition of use."[333] According to Dr. Siegel of Johnson & Johnson, this provision presumes that "if the drug has the same mechanism in two conditions, evidence of safety in one condition can be used to establish comparable safety in the other."[334] Dr. Siegel charges that this presumption "is not scientifically correct" because some biologics are "immunogenic when used in some diseases and not in others."[335] Citing examples of such immunogenic events, Dr. Siegel questions "the wisdom of approval for all indications with the same mechanism of action after demonstration of comparability in just one indication."[336] He maintains that it risks patient safety to study a particular biologic product's immunogenicity in patients less susceptible to an ad-

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327. *Hearings on Biosimilar Policy*, *supra* note 276, at 13 (testimony of Dr. David Schenkein).

328. *Id.*

329. Kobylarz, *supra* note 201.

330. *Hearing on Biosimilar Policy*, *supra* note 276, at 14 (testimony of Dr. David Schenkein).

331. *Id.* at 13-14; Kobylarz, *supra* note 201.

332. Dec. 13, 2004 BIO Letter to FDA, *supra* note 249, at 35.

333. Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3(k)(4)(A) (2007).

334. *Hearing on Follow-On Biologics*, *supra* note 22, at 9 (testimony of Dr. Jay P. Siegel).

335. *Id.*

336. *Id.*

verse immune response and then apply this information to a patient population prone to a heightened adverse immune response.[337]

For the reasons described above, the branded pharmaceutical industry suggests that immunogenicity should be monitored through pre-market clinical trials as well as post-market surveillance.[338] The industry insists that, for reasons of patient safety, the latter cannot substitute for the former.[339]

The branded industry criticizes Senate Bill 623 with respect to its provisions relating to post-marketing safety surveillance and post-marketing clinical studies. First, as noted by Dr. Siegel, the legislation is "silent on the matter of post-marketing safety surveillance."[340] Moreover, Senate Bill 623 limits the FDA's ability to require post-market clinical studies from a follow-on manufacturer.[341] Dr. Siegel asserts that post-marketing surveillance and clinical studies are imperative in order to address safety concerns such as immunogenicity profile or unexpected toxicities that may arise only after marketing the product.[342] In his view, in the absence of such studies, careful regulators might feel obliged to require even more pre-marketing testing, which would simultaneously undermine the purpose of the abbreviated approval pathway and fail to protect patient safety nonetheless.[343]

The FDA seems to have identified immunogenicity as the most serious obstacle to follow-on biologics. Dr. Janet Woodcock, Deputy Commissioner of the FDA, states that "some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed."[344] The FDA's Dr. Shacter has similarly expressed the view that because immunogenicity is nearly impossible to predict, clinical

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337. *See id.* at 6-10.

338. PhRMA Letter to FDA, *supra* note 323, at 2.

339. *Id.* at 12.

340. *Hearing on Follow-On Biologics*, *supra* note 22, at 16 (testimony of Dr. Jay P. Siegel).

341. *See* Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3(k)(5) (2007) (providing that, upon agreement of the Secretary and the follow-on manufacturer seeking abbreviated approval, the follow-on manufacturer shall conduct one or more postmarketing safety studies "upon a reasonable showing that such study or studies would provide relevant information not available from the studies on the reference product," but precluding the Secretary from conditioning approval on any additional postmarketing studies).

342. *See Hearing on Follow-On Biologics*, *supra* note 22, at 16-17 (testimony of Dr. Jay P. Siegel) (stating that follow-on biologics raise safety concerns that "will require studies beyond the scope that pre-marketing studies can reasonably address" and that "[s]ome safety concerns can be identified only after broad, large-scale or prolonged exposure such as can best be studied in the post-marketing period").

343. *Id.* at 17.

344. *Hearing on Biotech Drugs*, *supra* note 6, at 11 (testimony of Dr. Janet Woodcock) (stating that "[t]he extent of independent testing [of immunogenicity] needed will . . . depend on a variety of scientific factors such as the indication, . . . the overall assessment of the product's immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule").

studies are therefore "necessary to rule out adverse immunogenic events."[345]

When analyzing the various scientific issues relating to an abbreviated approval pathway for biologics, including the difficulties of analytical characterization, changes in the manufacturing process, and immunogenicity, it is critical to recall that House Bill 1038 does not require the FDA to approve any abbreviated applications for follow-on protein products.[346] Rather, the Bill simply grants the agency the flexibility to do so under certain circumstances. If Congress were to enact this legislation, the FDA would retain the right to assess each follow-on product on a case-by-case basis depending upon its degree of complexity and tailor its requests for clinical studies accordingly. As explained by one scientist, "[a]doption of this comparability approach to biogenerics is scientifically sound, and [the] FDA should use a case-by-case approach for determining the appropriate approval criteria for biogenerics—just as it said in a recent White Paper that it has been doing with brand biopharmaceuticals."[347] With respect to brand manufacturers, the current case-by-case approach employed by the FDA includes not only analytical testing, which constitutes "the first tier for comparability determination," but also pharmacokinetic and pharmacodynamic testing.[348] In addition, as noted by one industry expert, when a brand firm changes the manufacturing process for a biologic product, the FDA currently has the discretion to request "data from clinical studies or decide that products are not comparable" and deny approval to the product made via the new process.[349] The FDA would possess this same authority under House Bill 1038.[350]

Indeed, if House Bill 1038 were enacted, the details of implementation would be left to the FDA, which would need to develop a process for scientifically evaluating follow-on biologics.[351] At the Seventh Annual Generic Drugs Summit, hosted by the Institute of International Research in 2006, Senator Waxman predicted that companies will advocate to the FDA in support of the tests they use to demonstrate that their products are comparable to the reference product.[352]

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345. April 23rd E-mail from Dr. Emily Shacter, *supra* note 259.

346. Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007).

347. *Hearing on Biosimilar Policy*, *supra* note 321, at 3 (testimony of Dr. William Schwieterman).

348. *Hearing on Biotech Drugs*, *supra* note 245, at 4 (testimony of Theresa L. Gerrard).

349. *Id.*

350. *See supra* note 176 and accompanying text.

351. *See* Grabowski et al., *supra* note 68, at 1297 (stating that "we expect that the scientific criteria for what constitutes a biosimilar product will be left to the discretion of the FDA").

352. *Lawmakers Introduce Bill to Create Biogenerics Approval Path*, THE FOOD & DRUG LETTER, Oct. 13, 2006.

Commentators expect the FDA to develop different generic approval processes for different classes of drugs, likely beginning with the less complex products first, so that approval of more complex products does not delay the approval of the simpler ones.[353] While Congress can delegate the details of the scientific issues surrounding follow-on biologics to the FDA, it is entirely within Congress's province to fashion itself an intellectual property scheme that preserves incentives for innovation.

C. An Abbreviated Approval Pathway for Follow-On Biologics Modeled on the Hatch-Waxman Act Must Preserve Incentives for Investment in Innovator Products

Any legislation providing an abbreviated approval pathway for follow-on protein products must also preserve incentives for innovation. As noted by Professor Grabowski, intellectual property is especially important to biotech firms seeking to attract venture capital and create "partnerships with larger firms."[354] Indeed, "[m]ost of these firms have few, if any, profitable products" and therefore rely heavily on their intellectual property portfolios.[355] House Bill 1038 provides intellectual property protection for biologics, including both patent protection as well as some measure of non-patent marketing exclusivity, including data exclusivity and generic exclusivity.[356] House Bill 1038 seems to provide adequately for prompt resolution of patent challenges,[357] and it ameliorates some of the problems engendered by the HWA by banning authorized generics during the 180-day period of generic exclusivity.[358] The bill would be strengthened, however, by the addition of a provision ensuring a significant period of data exclusivity[359] as well as the inclusion of a thirty-month stay of generic entry where a follow-on manufacturer challenges an innovator's patent.[360]

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353. *Id.* (citing comments of Representative Henry Waxman); *see also* Ansell, *supra* note 214 ("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.").

354. *See Hearing on Biotech Drugs*, *supra* note 108, at 11 (testimony of Dr. Henry G. Grabowski).

355. *Id.*

356. *See supra* notes 107 & 113 (discussing non-patenting marketing exclusivity).

357. *See infra* Part VI.C.1.

358. *See infra* Part VI.C.4.

359. *See infra* Part VI.C.2.

360. *See infra* Part VI.C.3.

1. House Bill 1038 Establishes an Efficient System for Patent Dispute Resolution

The primary form of intellectual property protection available for biological products is patent protection.[361] Biological products may receive patent protection in two different ways. First, although patent law does not permit patenting of a naturally occurring substance,[362] an inventor who isolates a biological entity from its natural source may obtain patent protection.[363] For example, Amgen's EPOGEN®, a genetically engineered form of erythropoietin that stimulates the production of red blood cells and is used to treat anemia, enjoys patent protection.[364] Second, process patents are available for new processes used to manufacture known biologics; such patents would not cover the biological product itself.[365] Patents run for twenty years from the date the patent application is filed.[366]

Two particular patent provisions of the HWA, the patent term restoration[367] and the Bolar exception,[368] already apply to biological products, without regard to whether such biologics achieved approval under the FDCA or the PHSA.[369] Congress enacted the remaining intellectual property provisions of the HWA, including those establishing specialized dispute resolution procedures and marketing exclu-

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361. A patent grant by the U.S. Patent and Trademark Office (USPTO) and an award of marketing approval by the FDA are separate events conditioned upon different criteria. FDA review determines whether a given product is sufficiently safe and effective to be marketed, while the USPTO grants patents for inventions that satisfy the statutory criteria of novelty, utility, and nonobviousness. SCHACHT & THOMAS, *supra* note 107, at 19; *see also* 35 U.S.C. §§ 101-103 (2000) (setting forth the patent law criteria). Marketing a drug requires a firm both to obtain FDA approval and to consider whether such marketing would infringe any patents on the drug. *See* SCHACHT & THOMAS, *supra* note 107, at 19.

362. Diamond v. Diehr, 450 U.S. 175, 185 (1981) ("Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas.").

363. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) (holding that even though DNA sequences exist naturally in the human chromosome, they constitute patentable subject matter if they are "purified and isolated" from the original organism in nature).

364. *See* U.S. Patent No. 5,955,422 (filed Aug. 2, 1993) (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").

365. SCHACHT & THOMAS, *supra* note 100, at 13.

366. 35 U.S.C. § 154(a)(2) (2000). Commentators have noted, however, that "effective patent life for pharmaceuticals—the time remaining following FDA approval—is approximately eleven to twelve years in practice," which is substantially shorter than the 18.5 year average in other industries. Kuhlik, *supra* note 104, at 96-97.

367. *See supra* note 105 and accompanying text.

368. *See supra* note 112 and accompanying text.

369. *See* SCHACHT & THOMAS, *supra* note 100, at 14 (citation omitted) (explaining that the patent term restoration and "safe harbor" provisions in Title II of the HWA "were enacted as general amendments to the Patent Act;" that the patent term restoration provision expressly includes " 'human biological product[s]' " approved under the PHSA; and that "[t]he 'safe harbor' provision . . . has been construed to apply to biologics as well").

sivity, as specific amendments to the FDCA rather than as amendments to the patent code. Thus, these provisions apply only to those biologics approved under the FDCA, not to those governed by the PHSA.[370]

House Bill 1038 proposes to amend the PHSA so as to create special patent dispute resolution proceedings for biologics analogous to those available to generic drug manufacturers under the HWA. The proposed legislation provides that if an applicant of a comparable biologic elects to ask the patent holder of the reference product for a list of all patents related to the product, the patent holder must disclose this information within sixty days.[371] The reference product patent holder is also obliged to update the list within thirty days from obtaining a new patent.[372] Brand-name firms can demand payment of up to $1000 for the patent list.[373]

A follow-on applicant can then challenge any patent by furnishing the patent holder with the basis for the challenge.[374] The patent holder wishing to bring an infringement action must commence it within forty-five days of notice of a challenge or else forfeit the opportunity to seek any remedy other than a reasonable royalty.[375]

Dr. Grabowski notes that, while legislators might view legislation such as House Bill 1038, which encourages patent challenges as a "good short-term mechanism for exposing more biologics to follow-on price competition," pharmaceutical firms take a long view when mak-

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370. *See id.*

371. Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. § 3(k)(17)(A)(i) (2007).

372. *Id.* These provisions were included in order to provide follow-on manufacturers of biologics with information about patents held by innovator firms analogous to the information available to manufacturers of generic drugs. Generic drug manufacturers can access such patent information in the *Orange Book*, *see supra* note 64 and accompanying text, because the HWA requires each holder of an approved NDA to list in the *Orange Book* any product patents it believes would be infringed if a generic drug were marketed before the expiration of these patents. SCHACHT & THOMAS, *supra* note 106, at 3. Commentators have noted that these listings "offer generic firms easy access to information required for filing an [ANDA]," and that, absent this listing, "generic manufacturers would be forced to independently generate the data at considerable expense in terms of time and money." *Id.* at 10.

Manufacturers of biologics do not, however, publish their patent information in the *Orange Book*. *See* Dinh, *supra* note 196, at 111 (stating that "a biologic approved under a BLA is not listed in the *Orange Book*"). House Bill 1038 therefore requires the patent holder of the reference product to furnish this information to the follow-on manufacturer.

373. H.R. 1038, § 3(k)(17)(A)(ii).

374. H.R. 1038, §§ 3(k)(17)(B), 3(b) (Additional Amendments). Currently, manufacturers of follow-on protein products must wait to be sued by a patent holder for patent infringement before they can mount a legal challenge to a patent. Kobylarz, *supra* note 201.

375. H.R. 1038, § 3(k)(17)(C). Similarly, the HWA provides that an innovator firm has forty-five days in which to bring an action for patent infringement against a follow-on manufacturer. *See* 21 U.S.C. § 355(c)(3)(C) (2000).

ing R&D decisions.[376] Thus, he warns that "increased uncertainty and IP litigation in biotech . . . would have significant negative incentive effects on capital market decisions for developing private and public biotech firms with promising pipelines."[377] For this reason, Dr. Grabowski strongly supports data exclusivity[378] for innovator firms and has criticized House Bill 1038 for the absence of such protection, a view shared by the brand industry as well.[379]

Moreover, the brand industry points out that patent protection is often of limited use with respect to biological products, thereby rendering data exclusivity all the more essential. BIO has expressed concern that, under a statutory scheme permitting abbreviated approval of follow-on protein products, manufacturers of follow-on products will be able to secure abbreviated regulatory approval based, in part, on the innovator's prior approval, while at the same time avoiding infringing patents that protect the innovator's product.[380]

According to BIO, this likelihood arises from two particular characteristics of biologic products. First, in light of the fact that biologics are highly variable molecules, a manufacturer of follow-on products will be required only to demonstrate that the product is "similar" or "highly similar" to the corresponding innovator product, not that it is identical.[381] As a result, a follow-on biologic might be sufficiently similar to the innovator biologic to rely on the FDA's finding of safety and effectiveness for the innovator product, but at the same time prove different enough from the innovator product to avoid a patent infringement claim. The follow-on product could thus achieve market entry before the innovator's patent expires, which discourages investment in innovation.[382] Second, because of characteristics specific to biologic products, which are "large molecules produced by living cells and organisms[,] patent protection is often narrower and easier to 'design around' than . . . [for] small molecule drugs."[383] Thus, the

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376. *Hearing on Biotech Drugs*, *supra* note 108, at 11 (testimony of Dr. Henry G. Grabowski).

377. *Id.*

378. *See generally supra* note 108 and accompanying text (defining data exclusivity).

379. See *infra* Part VI.C.2 for a discussion of House Bill 1038's lack of data exclusivity for biologics.

380. *See infra* notes 381-83 and accompanying text.

381. *See* BIOTECHNOLOGY INDUS. ORG., A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY WILL STIFLE THE DEVELOPMENT OF NEW MEDICINES 1 [hereinafter BIO DATA EXCLUSIVITY], *available at* http://www.europa.bio.org/healthcare/followonbkg/FOBMarketExclusivity_050307.pdf.

382. *Id.* at 2.

383. *Id.* at 1. BIO explains that the trend in patent law has been toward narrower patent claims. *See id.* at 3; *see also* Bruce S. Manheim, Jr. et al., *'Follow-On Biologics': Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFFAIRS 394, 399-400 (2006) (explaining the reasons for the general trend in patent law toward the issuance of narrower patents for all products). What is more, biologic products in particular are sus-

issue of data exclusivity is one of the most contested aspects of House Bill 1038.

2. An Abbreviated Approval Pathway for Follow-On Biologics Should Furnish a Significant Period of Data Exclusivity for Innovator Firms

The HWA includes a data exclusivity provision that prevents the FDA from approving any ANDA for five years from the date on which the FDA approved the corresponding new chemical entity.[384] This provision, which furnishes a market incentive to engage in innovation by providing a limited monopoly period to the pioneer, "applies even if there is no patent on the [innovator] drug."[385] In contrast, House Bill 1038 does not presently contain any provisions for data exclusivity for biological innovators.[386] Thus, if this legislation were enacted, manufacturers of innovative protein products would face follow-on entry as soon as a new biological entity receives FDA approval.[387]

BIO emphasizes that a substantial period of data exclusivity is particularly important in order to preserve incentives to research, develop, and manufacture new biologic products.[388] BIO also claims

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ceptible to narrow construction of their patents for three reasons. BIO DATA EXCLUSIVITY, *supra* note 381, at 2-3. First, because of patent law limitations on patenting naturally occurring substances, many biologics qualify only for process patent protection, which is easier to " 'design around' " than product patent protection. *Id.* Second, the patent law specific to biotechnology requires that patent claims be rather "narrowly drawn" (for example, to the particular protein), whereas patents on small molecule drugs often claim a whole class of related molecular structures. *Id.* at 3. Third, the large size of biologic products renders it possible to alter the product slightly so that it would still qualify as a follow-on product but yet prove "different enough to be outside the scope of the patents on the original product." *Id.*

384. 21 U.S.C. § 355(j)(5)(F)(ii) (2000); 21 C.F.R. § 314.108(b)(2) (2007); *see also supra* note 108 and accompanying text (discussing data exclusivity); BIO DATA EXCLUSIVITY, *supra* note 381, at 1 n.1 (defining data exclusivity as "the time period after approval of the innovator's product during which the FDA may not approve a follow-on biologic product relying to any degree on the safety and effectiveness of the innovator product"). As noted by one commentator, "[a] competitor willing to develop its own full package of safety and effectiveness data need not wait for the exclusivity period to expire before challenging a patent." Kuhlik, *supra* note 104, at 99 n.30. In light of the time and expense necessary to conduct clinical trials relating to safety and effectiveness, however, the ability to rely on the innovator's data is particularly attractive to generic manufacturers.

385. SCHACHT & THOMAS, *supra* note 107, at 34.

386. *Hearing on Biotech Drugs*, *supra* note 108, at 12 (testimony of Dr. Henry G. Grabowski) (stating that that House Bill 1038 lacks any data exclusivity provision); Letter from James C. Greenwood, President and CEO, Biotechnology Ind. Org., to Rep. Henry A. Waxman and Rep. Thomas M. Davis, III, Comm. on Oversight and Gov't Reform, U.S. House of Representatives (Mar. 26, 2007), *available at* http://bio.org/healthcare/followonbkg/20070326Waxman-Davis.pdf.

387. *Hearing on Biotech Drugs*, *supra* note 108, at 12 (testimony of Dr. Henry G. Grabowski).

388. BIO Principles, *supra* note 232, at 2-3 (stating that, because patent protection is of limited use with respect to biological products, "non-patent exclusivity is necessary to

that the particular characteristics of follow-on protein products render it more difficult for innovator biologic products, as compared to innovator small molecule drugs, to qualify for data exclusivity even if it is available.[389] As noted above, an innovator product qualifies for data exclusivity only against a generic product that contains "the same active moiety," or active ingredient, as the reference product.[390] "To determine whether a follow-on product contains the same active moiety as the innovator product, [the] FDA analyzes such characteristics as the molecule's amino acid sequence and covalently bonded structure."[391] As noted above, however, it is not always possible to characterize a biologic product,[392] particularly the more complex ones, and, as a result, it might not be possible for the FDA to determine whether a follow-on product contains a previously approved active moiety.[393] BIO warns that a follow-on manufacturer might provide the FDA enough information about its active moiety to earn the right to rely upon the innovator's safety and effectiveness data in conferring an expedited approval on the follow-on product pursuant to the proposed House Bill 1038, but still not enough information for the innovator to take advantage of the five-year exclusivity.[394] BIO explains that this precise circumstance arose with two biologic products which, as members of the class of hyaluronidase products,[395] are regulated as drugs and therefore subject to the HWA.[396] As noted by BIO, because the "FDA considered each product to be a member of the same general class of hyaluronidase products, which allowed the products to rely on [the] FDA's previous safety and effectiveness determinations regarding hyaluronidase."[397] Nevertheless, "for exclusivity purposes, [the] FDA treated each product as a new chemical entity. As such, each product received its own exclusivity and was not blocked by the other product."[398]

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maintain effective market protection" and that "the fledgling nature of the biologics industry, its heavy dependence on access to significant amounts of high-cost public and private investment capital, and the high risks and costs involved in the development of new biologic medicines all warrant a substantial period of exclusivity").

389. *Id.*

390. 21 C.F.R. § 314.108(b)(2) (2007); *see also supra* note 108 and accompanying text.

391. THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 18.

392. *See supra* note 232 and accompanying text.

393. THE DIFFERENCE WITH BIOLOGICS , *supra* note 21, at 18-19 (citing the example of hyaluronidase, a biologic traditionally regulated by the FDA as a drug product).

394. *See id.* at 22 ("[T]he follow-on may provide enough information about its active moiety to rely on the innovator's data, but not enough to be blocked by the innovator's exclusivity.").

395. The hyaluronidases are enzymes used, among other things, "to increase the absorption and dispersion of other injected drugs." *Hearing on Biotech Drugs*, *supra* note 6, at 14 (testimony of Dr. Janet Woodcock).

396. THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 19.

397. *Id.* at 22.

398. *Id.*

BIO contends that any such system that allows a follow-on manufacturer to rely on the innovator's data, but does not furnish concomitant data exclusivity, "disrupt[s] the balance achieved by the [HWA]" in terms of facilitating generic competition while simultaneously protecting the pioneer's investment.[399] BIO advocates that innovators should enjoy the benefit of data exclusivity provisions for "any follow-on product that relies to any degree on the clinical data provided to the FDA in support of approval of the pioneer biologic."[400]

In terms of the optimal length of such data exclusivity, Professor Grabowski maintains that even the five-year period of data exclusivity furnished by the HWA is inadequate, and advocates for the inclusion in House Bill 1038 of a ten-year data exclusivity period modeled on that of the European Union.[401] According to Professor Grabowski, "R&D costs have increased substantially since Hatch-Waxman was enacted over 20 years ago," and, consequently, "[b]reakeven returns on R&D for the average new drug products typically take more than a decade."[402] He also notes that a significant data exclusivity period encourages investment in new indications for approved biologics, which has resulted in important advances in treating many serious diseases, including cancer.[403] Without such protection, "innovat[or] firms will have much less economic incentive to invest in the costly and risky process to gain approval for these new indications."[404]

BIO advocates for an even longer period of data exclusivity for biologics, suggesting a minimum of fourteen years "if biologics are to receive the same length of effective market protection as drugs, and thus avoid skewing investment away from higher risk biologics research and development."[405] BIO arrived at this figure by referencing the HWA, which allows for the extension of patent on innovator

399. *Id.* at 28.

400. *Id.* at 21.

401. *See Hearing on Biotech Drugs*, *supra* note 108, at 12 (testimony of Dr. Henry G. Grabowski) ("A ten year exclusivity period, like that currently exists in Europe, would help balance innovation incentives and price competition when instituting a new regulatory pathway for biologicals.").

402. *Id.*

403. *Id.* See *infra* note 405 regarding the importance of new indications for existing pharmaceutical products.

404. *Hearing on Biotech Drugs*, *supra* note 108, at 12-13 (testimony of Dr. Henry G. Grabowski).

405. BIO DATA EXCLUSIVITY, *supra* note 381, at 1. BIO also advocates an additional period of exclusivity, not less than two years beyond the fourteen-year period, for new indications for already approved products, in light of the importance of new indications for serious conditions such as cancer. *Id.* at 4 ("Data exclusivity for new indications is critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies most often occur much later in time.").

products for up to fourteen years following product approval.[406] As further support for its view, BIO emphasizes that the biotechnology industry is made up of small start-up companies that are particularly vulnerable to changes in investment incentives.[407]

BIO emphasizes that a fourteen-year period of data exclusivity would run concurrently with the patent term for the product, which itself may run for at least fourteen years, and thus would not actually extend the effective period of market exclusivity.[408] Instead, in cases where patent protection proved insufficient because a follow-on manufacturer was able to work around the innovator's patents but still gain approval for the follow-on product, a fourteen-year period of data exclusivity would furnish some measure of effective protection.[409] As explained by BIO, "a 14-year period of data exclusivity serves essentially as an insurance policy that provides the innovator with some certainty of protection, given that a FOB [follow-on biologic] can be approved on the basis of a less stringent standard of similarity."[410]

In light of the importance of intellectual property in the biologics industry and the European example which provides ten years of data protection, it is clear that an abbreviated approval pathway for follow-on biologics ought to provide some period of data exclusivity. In the United States, "the effective patent life for pharmaceuticals—the time remaining following FDA approval—is approximately eleven to twelve years."[411] Thus, a data protection period of ten to twelve years, which would run concurrently with the patent term for the product, would provide pioneer firms with the assurance that they would earn a reasonable monopoly period in return for the time, money, and effort they expended in developing an innovator biologic product.

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406. *Id.* at 3-4 ("Given that Congress has previously concluded that 14 years of patent protection is appropriate for drugs and biological products, any statutory formula that allows for FOBs should at least guarantee that same degree of effective market protection . . . ."); *see also supra* note 105 and accompanying text (describing the provision in the HWA providing for up to fourteen years of market exclusivity in total).

407. *See* BIO DATA EXCLUSIVITY, *supra* note 381, at 1-2, 6-8 (noting that most biotechnology companies are small start-ups that have not yet turned a profit and therefore are highly reliant upon venture capital). Relative to the traditional pharmaceutical industry, the biotech industry faces high costs of capital and production and significant manufacturing uncertainties. *See id.* at 5-6 (describing the challenges facing manufacturers of biologics); *see also supra* notes 354-55 (regarding the importance of the preservation of investment incentives as particularly important in the biopharmaceutical industry).

408. BIO DATA EXCLUSIVITY, *supra* note 381, at 4.

409. *Id.*

410. *Id.*

411. Kuhlik, *supra* note 104, at 96-97.

3. An Abbreviated Approval Pathway for Follow-On Biologics Should Provide a Thirty-Month Stay for the Innovator Firm While Infringement Litigation Is Pending

Another way in which House Bill 1038 differs from the HWA is that the proposed legislation does not offer innovator firms a thirty-month stay or any other delay in approval based on an infringement action brought by an innovator firm.[412] As noted above,[413] the HWA provides that during a patent holder's infringement action against a generic manufacturer,[414] the FDA must suspend final approval of the generic manufacturer's ANDA for thirty months from the date the patent owner received notice of the challenge to its patent.[415] The thirty-month stay aims to foster the resolution of the patent infringement litigation before the marketing of a generic product, thereby avoiding a loss of profits by the innovator.[416] The HWA also provides that the patent holder may bring an action for damages if, after the thirty-month stay ends, the patent in question is found valid and infringed.[417]

Concerned about innovator firms' use of multiple thirty-month stays to achieve de facto patent extensions,[418] in 2003, Congress

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412. Arnold & Porter, *supra* note 174, at 4.

413. See *supra* note 111 and accompanying text regarding the functioning of the thirty-month stay pursuant to the HWA.

414. *See supra* notes 374-75 and accompanying text.

415. *See* 21 U.S.C. § 355(j)(5)(B)(iii) (2000).

416. Day, *supra* note 114, at 229. When it enacted the HWA, Congress did recognize that the thirty-month stay might expire before the disposition of the infringement lawsuit. Catherine E. Creely, Comment, *Prognosis Negative: Why the Language of the Hatch-Waxman Act Spells Trouble for Reverse Payment Agreements*, 56 CATH. U. L. REV. 155, 184 (2006). In this circumstance, the FDA can approve the generic product for marketing. *Id.* at 166 ("If the thirty-month period expires without an unappealable resolution to the patent infringement suit, the FDA may approve the generic product for marketing."). At the time Congress enacted the HWA, however, thirty months was the approximate time required for FDA review and approval of generic applicants' ANDAs, as well as roughly the amount of time required for judicial resolution of the infringement lawsuit. FTC STUDY, *supra* note 85, at iii.

417. *See* 21 U.S.C. § 355(j)(5)(B)(iii) (2000). The patent owner's remedies for infringement under the HWA include recovery of lost profits and, possibly, "treble damages if the infringement was willful." SCHACHT & THOMAS, *supra* note 106, at 6. The patent owner may also have the infringing product removed from the market. *Id.* Commentators have noted that these remedies might be difficult to enforce, however, because in practice it is hard to achieve removal of the infringing product from store shelves and "individual medicine cabinets." *Id.* What is more, it may be impossible for a generic firm, given their often small capitalization, to compensate the plaintiff for significant financial harm, especially where blockbuster drugs are concerned. *Id.* It should be noted that, as a protection for generic firms under the HWA, the patent holder is required to post a bond covering its competitor's market losses should the patent be found invalid or not infringed. *Id.*

418. *See* FTC STUDY, *supra* note 85, at iv-v (describing this problem and stating that "[t]he history thus far of multiple 30-month stays caused by the filing of later-issued patents appears problematic"); Anne-Marie C. Yvon, Note, *Settlements Between Brand and Generic Pharmaceutical Companies: A Reasonable Antritrust Analysis of Reverse Payments*, 75 FORDHAM L. REV. 1883, 1895 (2006) (explaining that some brand companies de-

amended the original HWA, and the FDA promulgated a rule in order to limit brand name companies to only one thirty-month stay per ANDA application.[419] Innovator firms could request a stay only with respect to those patents listed in the *Orange Book* at the time of a follow-on firm's challenge.[420] One commentator, speaking at the time of this amendment, noted that a single thirty-month stay "would not be likely to cause a significant delay in the generic's introduction to the marketplace, because the stay would run concurrent to the FDA's consideration of the application, which usually takes 18-25 months" for generic small molecule drugs.[421]

BIO strongly critiques the absence of a thirty-month stay provision in House Bill 1038, advocating that "[a]ny follow-on biologics regulatory pathway should ensure that any patent challenge involving the follow-on biologic product will be litigated prior to marketing approval of the follow-on product, in order to protect the innovator's intellectual property rights and avoid confusion in the medical, patient, and payer communities."[422] If a generic product is launched before the resolution of any patent challenges and then is later found to be infringing on the innovator's patent, the ensuing loss of the innovator's profits is not the only harm to result. Because the offending product must be withdrawn from the market, there is the potential for confusion on the part of doctors and consumers, which may lead

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veloped strategies for obtaining multiple thirty-month stays, thereby delaying generic drug entry for several years).

419. *See* Medicare Prescription Drug and Modernization Act of 2003, Pub. L. No. 108-173, § 1101, 1102, 117 Stat. 2066, 2448-60 (codified as amended at 21 U.S.C. §§ 355(j)(2) and (5) (2000)); Applications for FDA Approval to Market a New Drug, 68 Fed. Reg. 36676, 36677 (June 18, 2003) (codified at 21 C.F.R. pt. 314).

420. SCHACHT & THOMAS, *supra* note 106, at 10 (discussing changes to the Hatch-Waxman Act in P.L. 108-173, limiting brand name companies to only one 30-month stay on those patents listed in the *Orange Book* at the time of a challenge to the innovator's patent); *see also* Medicare Prescription Drug and Modernization Act of 2003, Pub. L. No. 108-173, § 1101, 1102 117 Stat. 2066, 2448-60 (codified as amended at 21 U.S.C. §§ 355(j)(2) and (5) (2004)); Applications for FDA Approval to Market a New Drug; 68 Fed. Reg. 36676, 36677 (June 18, 2003) (codified at 21 C.F.R. pt. 314); 21 C.F.R. § 314.53(b) (2007) (setting forth the type of patent information that patent holders may include in their *Orange Book* listings).

421. Sarah E. Eurek, Note, *Hatch-Waxman Reform and Accelerated Market Entry of Generic Drugs: Is Faster Necessarily Better?,* 2003 DUKE L. & TECH. REV. 0018, ¶13, http://www.law.duke.edu/journals/dltr/articles/pdf/2003DLTR0018.pdf; *see also* FDA, White Paper, New FDA Initiative on "Improving Access to Generic Drugs" (June 12, 2003), http://www.fda.gov/oc/initiatives/generics/whitepaper.html ("On average, it takes more than 20 months for a new generic drug to be approved by the FDA."). *But see The Generic Drug Maze: Speeding Access to Affordable, Life Saving Drugs: Hearing Before the Special S. Comm. on Aging*, 109th Cong. 5 (2006) (testimony of Gary Buehler, Dir. of the Office of Generic Drugs, Ctr. for Drug Evaluation and Research, FDA), *available at* http://aging.senate.gov/events/hr161gb.pdf (stating that the median approval times for the FDA's office of generic drugs "have decreased from 18.4 months in FY 2001 to 16.3 months in FY 2005").

422. BIO Principles, *supra* note 232, at 3.

to adverse implications for human health.[423] What is more, BIO asserts that "[a]ddressing patent issues as part of the approval process allows the FDA to prioritize its resources" by focusing first on those generic products that are not facing patent challenges and can, therefore, be brought to market more quickly.[424]

Congress should include in House Bill 1038 a provision allowing one thirty-month stay of FDA approval of a follow-on biologic pending resolution of infringement litigation, modeled on the HWA.[425] In amending the HWA to resolve the problems engendered by multiple thirty-month stays, Congress nonetheless chose to retain a single thirty-month stay.[426] This thirty-month period essentially runs concurrently with the FDA approval process, somewhat less than thirty months.[427] In light of the fact that approval of follow-on biologics takes the FDA an even longer time on average, roughly 34.7 months in 2003,[428] the inclusion of a single thirty-month stay in legislation creating an abbreviated approval pathway for follow-on biologics would not appreciably delay the market entry of such products. The benefit offered by such a provision would be to allow for resolution of some patent challenge before launch of a follow-on product, thereby preserving incentives for innovation by pioneer firms.

4. An Abbreviated Approval Pathway for Follow-On Biologics Should Retain House Bill 1038's Ban on Authorized Generics During 180-Day Period of Generic Exclusivity

House Bill 1038 proposes a ban on authorized generics during the 180-day period of generic exclusivity enjoyed by brand firms.[429] This provision reflects a debate currently surrounding the 180-day generic exclusivity period for traditional drugs regulated under the HWA.[430]

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423. *See* THE DIFFERENCE WITH BIOLOGICS, *supra* note 21, at 11, 23.

424. *Id.* at 23.

425. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, 1594 (codified as amended in scattered sections of 15, 21, 35, and 42 U.S.C.).

426. Medicare Prescription Drug and Modernization Act of 2003, Pub. L. No. 108-173, § 1101, 1102, 117 Stat. 2066, 2448-60 (codified as amended at 21 U.S.C. §§ 355(j)(2) and (5) (2000)).

427. *See supra* note 421 and accompanying text.

428. *See* Robert Rogoyski, Note, *The Orphan Drug Act and the Myth of the Exclusivity Incentive*, 7 COLUM. SCI. & TECH. L. REV. 4, ¶ 4 (2006), http://www.stlr.org/html/volume7/rogoyski.pdf.

429. *See supra* notes 113-14 and accompanying text (discussing generic exclusivity under the HWA); *supra* notes 190-93 and accompanying text (discussing House Bill 1038's proposed treatment of authorized generics).

430. In January 2007, Sen. John Rockefeller (D-WV) reintroduced a bill that would amend the HWA so as to preclude the marketing of authorized generic drugs during the 180-day exclusivity period. *See* Fair Prescription Drug Competition Act, S. 438, 110th Cong. § 2 (2007). This bill was referred to the Senate Committee on Health, Education, Labor, and Pensions. *See* The Library of Congress, Thomas, http://www.thomas.gov/cgi-bin/bdquery/z?d110:s.00438: (last visited June 23, 2008). In addition, in March 2006, the

Many commentators contend that a ban on authorized generic versions of traditional drugs will encourage generic firms to undertake a patent challenge, since the first generic firm to bring a successful patent challenge will earn a 180-day period of market exclusivity.[431]

As noted above, the FDA currently treats authorized generics as branded products for the purposes of product approval and therefore allows them to compete with generic products awarded 180-day exclusivity.[432] As a result, branded firms have taken advantage of this loophole, either by creating subsidiaries to market authorized generics or by licensing generic manufacturers to sell them.[433]

The generic pharmaceutical industry contends that permitting authorized generics to take advantage of the 180-day generic exclusivity period "devalue[es]" the 180-day exclusivity that generic firms could otherwise enjoy, and thus dissuades generic firms from entering the market, resulting in higher drug prices for consumers.[434] The generic pharmaceutical industry especially decries authorized generics in light of the fact that brand firms, in marketing their generics, are not required to submit to the rigorous abbreviated approval process necessary for "true" generics.[435] One industry analyst estimates that authorized generics cause generic firms to lose "potentially half of the windfall that comes from an exclusive generic launch, an amount that could easily reach a billion dollars" for certain blockbuster drugs.[436] According to the generic industry, this circumstance decreases the incentives for generic manufacturers to challenge patents. If generic firms stop challenging patents, this would "remove the incentive that caused brand-name companies to create authorized generics in the first place."[437] Ultimately, consumers would suffer from the lack of low-cost alternatives to branded products.[438]

In response, the branded industry cites two recent studies in support of its contention that the entry of authorized generics during the

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U.S. Federal Trade Commission announced its intention to study the short- and long-term competitive effects of authorized generics and to publish its finding in 2007. Press Release, Fed. Trade Comm'n, FTC Proposes Study of Competitive Impacts of Authorized Generic Drugs (Mar. 29, 2006), *available at* http://www.ftc.gov/opa/2006/03/authgenerics.shtm. Research did not reveal any such publication as of May 2008.

431. *See supra* notes 113-14 and accompanying text.

432. *See supra* note 193.

433. *Knock It Off*, THE ECONOMIST, Feb. 24, 2007, at 77.

434. *See* AGING & ELDER HEALTH WEEK, *supra* note 191, at 429.

435. *See* LAB BUSINESS WEEK, *supra* note 191, at 799.

436. *Knock It Off*, *supra* note 433, at 77.

437. Olga Pierce, *Analysis: Authorized Generic Bad Medicine?*, UNITED PRESS INT'L, July 31, 2006, http://www.upi.com/HealthBusiness/view.php?StoryID=20060731-051519-9696r (quoting Aidan Hollis, Academic Dir. of the Ctr. for Regulatory Affairs at the Van Horne Institute, Canada and author of the study referenced *infra* notes 441-43).

438. *See id.* (citing Hollis's concerns about "indefinitely high drug prices" in the absence of competition by generic firms).

180-day period of generic exclusivity does not harm consumers. The first study, published by IMS Health in 2006 and funded by PhRMA, claims that the entry of an authorized generics competitor actually leads to greater generic price discounts relative to the branded drug's price, both during and after the 180-day exclusivity period.[439] The second study, conducted by a team consisting of an academic and consultants and also funded by PhRMA, concludes that increased authorized generic entry has not delayed the entry of generic competitors and has in fact benefited consumers through lower drug prices.[440]

In contrast, another study, funded by the GPhA and conducted by two academics, reviewed the IMS study and revealed several flaws in terms of its methodology and analysis.[441] In particular, this critique of the IMS study notes that brand firms inflate drug prices in markets with authorized generics in order to differentiate their products, thereby falsely increasing the apparent discount generated by authorized generics.[442] Ultimately, the study's authors conclude that authorized generics "undermine the generic exclusivity period that Congress created to encourage the generic companies to challenge the patents that block competition" and "in the process, negatively impact consumers."[443]

Certainly, it undermines the purpose of the 180-day generic exclusivity period to allow authorized generics to compete with "genuine" generics, thereby upsetting the carefully crafted balance of the HWA. This effect is magnified by the fact, documented in several sources, that authorized generics do not offer genuine savings to consumers because brand firms inflate the prices of branded products in markets where they offer authorized generics.[444] Consequently, House Bill 1038 should maintain its ban on authorized generics.

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439. IMS CONSULTING, ASSESSMENT OF AUTHORIZED GENERICS IN THE U.S. 1-2 (2006), *available at* http://www.phrma.org/files/IMS%20Authorized%20Generics%20Report_6-22-06.pdf.

440. Ernst R. Berndt et al., *Do Authorized Generic Drugs Deter Paragraph IV Certifications? Recent Evidence* 13 (April 7, 2007) (PhRMA Working Paper), *available at* http://www.analysisgroup.com/analysisgroup/uploadedFiles/Publishing/Articles/PhRMA_Authorized_Generic_Entry.pdf.

441. Aidan Hollis & Bryan A. Liang, *An Assessment of the Effect of Authorized Generics on Consumer Prices* 5-8 (July 31, 2006), *available at* http://www.gphaonline.org/AM/Template.cfm?Section=Issues&Template=/CM/ContentDisplay.cfm&ContentID=2647.

442. *See* Hollis & Liang, *supra* note 441, at 16-18 (noting the trend toward higher brand prices in markets with authorized generics); SCHACHT & THOMAS, *supra* note 107, at 33 ("Brand name firms have reacted to the opportunities for establishing a generic market provided in the 1984 Act by 'maintaining and even raising the price of the brand-name product on the theory that the demand for it was more inelastic than the demand for the price-sensitive segment; they have embarked on a new aggressive strategy designed to serve the brand-loyal segment and capture a substantial share of the generic market.' "(citation omitted)).

443. Hollis & Liang, *supra* note 441, at 1.

444. *See supra* note 442.

5. An Abbreviated Approval Pathway for Follow-On Biologics Would Promote Innovation by Stimulating Further Improvements to Existing Biologics

In crafting an abbreviated approval pathway for follow-on biologics, it is crucial to preserve incentives for innovation by pioneer firms. It is also important, however, to consider how implementation of an abbreviated approval framework will itself stimulate competition. According to industry expert Dr. Scott Gottlieb, a resident fellow at the American Enterprise Institute and the former Director of Medical Policy Development and Deputy Commissioner for Medical and Scientific Affairs at the FDA, one major benefit flowing from an abbreviated approval pathway that has been overlooked by most commentators is the likelihood that increased competition will stimulate further improvements to existing biologics.[445] Dr. Gottlieb predicts that:

> [l]egislation to expose today's biologics to easier competition, after legitimate patents have expired, is going to accelerate development of improved products, not just lower-cost, copycat versions of outdated proteins. Those making static assumptions against today's standards of care about how much savings this legislation is likely to bring are losing sight of the competition and progress they will have unleashed.[446]

Dr. Gottlieb's assertion that an abbreviated approval pathway for follow-on biologics will stimulate innovation undercuts the biotech industry's concern that the FDA's consideration of abbreviated applications for follow-on protein products will undermine the development of new drugs and biologics. According to Dr. Schenkein of Genentech, follow-on biologics "raise novel and complex questions of science and law," and FDA consideration of these issues threatens to drain agency resources from the important task of reviewing new drugs and biologics.[447] This view overlooks, however, the potential for innovation that arises from an environment that fosters and supports the development of follow-on and second- and third-generation biologics.

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445. Scott Gottlieb, *Biologics Legislation Will Speed Progress*, FORBES, Apr. 16, 2007, http://www.forbes.com/personalfinance/2007/04/16/biologics-genentec-amgen-pf-guru-in_sg_0416soapbox_inl.html (stating that "the most enduring effect of the legislation may be to accelerate the development of much-improved second- and third-generation versions of today's medicines").

446. Gottlieb, *supra* note 445*; see also* ENGEL & NOVITT, *supra* note 5, at 16 ("Increased competition for follow-on products to first-generation biologics would be anticipated to create a pressure to reduce the cost of these products, thereby producing a positive cost disparity between the first and subsequent generations of biologic products that does not presently occur, thereby potentially enabling increased savings as well as producing incentives for further innovation.").

447. *Hearing on Biosimilar Policy*, *supra* note 276, at 23 (testimony of Dr. David Schenkein).

Keeping in mind these dual goals of lowering health care costs for consumers as well as stimulating the development of products that promote human health, the European Union recently became the first western market to implement an abbreviated approval pathway for follow-on biologics.[448] The E.U. model can offer important guidance to U.S. legislators and policy makers considering this issue.

VII. THE EUROPEAN UNION FRAMEWORK FOR ABBREVIATED APPROVAL OF BIOSIMILARS

In 2004, the E.U. adopted legislation establishing a regulatory framework for the evaluation, approval, and monitoring of follow-on protein products, which are referred to as similar biological medicinal products or biosimilars.[449] As noted by one E.U. Commission[450] official testifying before a congressional committee considering House Bill 1038, which proposes a case-by-case approach to follow-on protein products, the E.U. has indeed embraced a case-by-case evaluation of biosimilars.[451] He explains that

> [t]he type and amount of pre-clinical and clinical data are not predefined in legislation but are determined on a case by case basis, on the basis of the relevant scientific guidelines. This approach reflects the wide spectrum of molecular complexity among the various products concerned, ranging from relatively simple molecules such as insulin to far more complex ones. Thus, the requirements to demonstrate safety and efficacy of a biosimilar are essentially product class-specific. In theory, a biosimilar application could therefore range from being almost 'as abridged' as a generic appli-

448. Katja Feick, *Patent Expiries and the Prospect of Cost Savings to Underline the Popularity of Generics and Biogenerics in Europe*, BUSINESS BRIEFING: PHARMAGENERICS 2004, 16, 16 (2004). Commentators have noted that cost containment is particularly important for European national health care systems. *Id.* at 998 ("Lower-priced biogenerics . . . hold great appeal for cash-strapped governments and are set to experience wider usage."). Moreover, the concept of follow-on protein products is familiar in this region because follow-on protein products are already produced in eastern Europe. *See id.* at 998 ("At present, biogenerics are being produced without such regulatory constraints in eastern Europe.").

449. Council Directive 2004/27, 2004 O.J. (L314) 34 (EC); *Follow-On Biologics: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 110th Cong. 1 (2007) [hereinafter *Hearing on Follow-On Biologics*] (statement of Nicolas Rossignol, Admin., European Comm'n Pharms. Unit), *available at* http://help.senate.gov/Hearings/2007_03_08/Rossignol.pdf.

450. The European Commission's role with respect to pharmaceuticals is threefold: to propose new legislation; to implement existing legislation; and to authorize for market entry and monitor certain types of medicines, including all biotech products created via recombinant DNA technology. *Hearing on Follow-On Biologics*, *supra* note 449, at 1 (testimony of Nicolas Rossignol). The Commission bases its decisions regarding market authorization on scientific standards developed by the European Medicines Agency (EMEA). *Id.* at 3; *see also infra* note 453 and accompanying text.

451. *Hearing on Follow-On Biologics*, *supra* note 449, at 3 (testimony of Nicolas Rossignol).

> cation (with very limited non-clinical/clinical studies), to being nearly as complete as a full, stand-alone application.[452]

E.U. legislators have charged the European Medicines Agency (EMEA)[453] with developing scientific guidelines setting forth the required nonclinical and clinical data to be furnished by manufacturers submitting applications for approval of biosimilars.[454] It should be noted that the EMEA does not require that a follow-on protein product demonstrate bioequivalence; instead, it imposes a "comparability" standard.[455] However, existing EMEA guidelines do not at this time address the issue of interchangeability.[456]

To date, the E.U. Commission has given market authorization to two biosimilars, both in April 2006.[457] Both products, Sandoz's Omnitrope[458] and Biopartners' Valtropin, are growth hormones.[459] Several other relatively simple biosimilars, including erythropoietins, interferons, insulins, and granulocyte-colony stimulating factors, are also the subject of applications presently in the EMEA pipelines.[460] Because the E.U. regulatory framework is so new, it is quite difficult to assess the impact that the introduction of biosimilars will have on prices of biologics in Europe.[461] In terms of safety and efficacy, the E.U. framework provides for post-market monitoring, which is required for all pharmaceutical products in that region.[462] In moving forward on its biosimilar framework, the E.U. exerts pressure on the U.S. to do the same, both in order to lower health care costs and to

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452. *Id.*

453. The EMEA is an E.U. agency responsible for "protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use." European Medicines Agency, About EMEA, http://www.emea.europa.eu/htms/aboutus/emeaoverview.htm (last visited June 23, 2008).

454. *Hearing on Follow-On Biologics*, *supra* note 449, at 3 (testimony of Nicolas Rossignol).

455. Alston & Bird, *supra* note 11, at 4.

456. *Hearing on Follow-On Biologics*, *supra* note 449, at 7 (testimony of Nicolas Rossignol).

457. *Id.* at 6; Grabowski et al., *supra* note 68, at 1297.

458. The E.U.'s approval of Omnitrope undoubtedly influenced the FDA's decision to do the same the following month. See *supra* Part IV for a discussion of the U.S. FDA's approval of Omnitrope.

459. *Hearing on Follow-On Biologics*, *supra* note 449, at 6 (testimony of Nicolas Rossignol).

460. *Id.*

461. *Id.* It should be noted that E.U. authorities impose price controls on pharmaceutical products. Thus far, Omnitrope has been priced at twenty to thirty percent below the innovator product. Press Release, European Generic Meds. Ass'n., IAPO Paper Ignores the Science of Biosimilars (Dec. 5, 2006), http://www.egagenerics.com/pr-2006-12-05.htm. The European Generic Medicines Association estimates a two to three million euro reduction in health care costs annually resulting from the use of just five biosimilar medicines. *Id.*

462. European Generic Medicines Ass'n, FAQ on Biosimilars, http://www.egagenerics.com/FAQ-biosimilars.htm (last visited June 23, 2008) ("Guidance on risk management systems has also been developed which assures safe market entry and post-marketing monitoring of these medicines.").

attract investment in research and development relating to follow-on protein products.

VIII. CONCLUSION

In light of the high cost of biopharmaceuticals and their importance for human health, Congress is currently considering House Bill 1038, a bill that proposes an abbreviated approval pathway for follow-on biologics. Consideration of the legal and policy implications of an abbreviated approval pathway demonstrates that, in the main, enactment of House Bill 1038 will achieve the stated goals of the legislation. First, legislative enactment of an abbreviated approval pathway for follow-on protein products will indeed, over time, stimulate a robust market in such products, analogous to the market for small molecule drugs effectuated by the Hatch-Waxman Act. Second, the FDA, the agency responsible for drug approval in the United States, indicates that the current state of scientific knowledge supports an abbreviated approval pathway, at least for simpler protein products. Moreover, House Bill 1038 allows for consideration of follow-on protein products on a case-by-case basis, permitting the FDA to require the safety and efficacy data it needs in support of the approval process. Finally, with some small adjustments, House Bill 1038 can preserve incentives for innovation by pioneer firms while simultaneously encouraging competition from follow-on firms. This Article proposes two adjustments to House Bill 1038, the inclusion of a substantial period of data exclusivity for innovators and a thirty-month stay of approval for a follow-on product pending resolution of patent infringement litigation, in order to help this legislation attain in the realm of biologics the success that the Hatch-Waxman Act has achieved with respect to conventional drugs.