

Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation

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INTRODUCTION

Advances in biotechnology have created a new class of drugs known as biologics that replace or enhance the proteins the body naturally produces.¹ Biologics are medicinal products that contain complex protein molecules derived from living cells through recombinant DNA technology.² The complexity of both the manufacturing process and the biologics product itself is reflected in

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1. Ingrid Kaldre, *The Future of Generic Biologics: Should the United States “Follow-On” the European Pathway?*, DUKE L. & TECH. REV., Nov. 6, 2008, ¶¶ 1–2, <http://www.law.duke.edu/journals/dltr/articles/2008dltr0009.html>.

2. Huub Schellekens, *Follow-On Biologics: Challenges of the “Next Generation,”* NEPHROLOGY DIALYSIS TRANSPLANTATION, May 2005, at iv31, iv31.

the exorbitant cost of the end product.³ The high price tag for biologics has limited access to treatments by patients who need them and has generated substantial bad press for the brand name biologics manufacturers (commonly referred to as “the innovator industry”).⁴ Some experts believe that exorbitant costs are due to weak competition for biologics from the generics industry because the Food and Drug Administration (FDA) lacks an abbreviated pathway for regulatory approval of generic biologics products, often referred to as “follow-on biologics” (FOBs).⁵ For traditional, small-molecule drugs, the generic manufacturer may rely on the innovator drug manufacturer’s preclinical and clinical data to show that the two products are the same.⁶ Biologics, however, are highly dependent on the environmental conditions of the manufacturing process, and even minor changes may alter the clinical effects of the final product.⁷ Due to the high degree of complexity associated with biologics products, FOB manufacturers must go through the same FDA approval process as the innovators before they can market their product.

FOB manufacturers and consumer advocate groups, which favor an abbreviated FOB approval pathway similar to the one for traditional generics, are lobbying for legislation to allow FOB manufacturers to rely on the innovators’ preclinical and clinical trials data to demonstrate that the two products are comparable.⁸ Though the biologics community agrees that Congress should establish a regulatory pathway for FOBs,⁹ it disagrees on the amount and extent of testing the FDA should require.¹⁰ The innovators argue that because biologics are so intricately tied to their processing and because many details of their manufacturing processes are trade secrets, the FOB and innovator products must necessarily be different. Separate clinical trials, therefore, must be conducted to ensure safety and efficacy.¹¹

3. Andrew Wasson, *Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biological Products*, DUKE L. & TECH. REV., Mar. 1, 2005, ¶ 1, ¶ 2, <http://www.law.duke.edu/journals/dltr/articles/2005dltr0004.html>.

4. Alan J. Morrison, *Biosimilars in the United States: A Brief Look at Where We Are and the Road Ahead*, 26 BIOTECHNOLOGY L. REP. 463, 464 (2007).

5. See, e.g., Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 562 (2008).

6. See Gregory N. Mandel, *The Generic Biologics Debate: Industry’s Unintended Admission That Biotech Patents Fail Enablement*, VA. J. L. & TECH., Fall 2008, ¶ 1, ¶ 8.

7. *Id.* ¶ 9.

8. See, e.g., Press Release, AARP, AARP: Biologics Bill Will Lower Prices of Most Expensive Drugs (Mar. 11, 2009), available at http://www.aarp.org/aarp/presscenter/pressrelease/articles/Biologics_Bill_Introduction.html.

9. See, e.g., Press Release, Biotechnology Indus. Org., New Proposed Biosimilars Pathway Filled With Potholes (Mar. 11, 2009), available at http://www.bio.org/news/pressreleases/newsitem.asp?id=2009_0311_02.

10. See WENDY H. SCHACHT & JOHN R. THOMAS, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES, CRS RL 33901, at 7–8 (2009) (describing the debate over the level of data and clinical trials necessary for abbreviated approval of FOBs).

11. *Id.* at 7; Mandel, *supra* note 6, ¶ 76.

To further complicate the biologics debate, the argument against waiving clinical trials has potential implications for the U.S. patent law system.¹² Current patent law requires invention disclosure sufficient to enable someone skilled in the art to make and use the invention without undue experimentation.¹³ If the biologics patent does not allow FOB manufacturers to make the same invention, but instead requires the FOB manufacturer to go through extensive clinical trials to determine the product has comparable clinical effects, then the patent would be invalid as nonenabling.

A final point of contention concerning biologics regulation is the length and scope of marketing exclusivities—a new type of intellectual property protection outside the patent system that temporarily restricts subsequent market entry by competitors. For the term of a drug's marketing exclusivity, the FDA is barred from approving a competing application for the same drug unless that applicant goes through the full regulatory process with full preclinical and clinical testing.¹⁴ The base term of a marketing exclusivity for new chemical drugs is five years.¹⁵ Innovators claim a longer marketing exclusivity for new biologics is required because the complex nature of biologics requires longer development and approval processes.¹⁶

As the biologics debate continues, the pressure on the FDA to establish an abbreviated pathway continues to mount. The international community has already pushed forward with FOB regulation.¹⁷ If the United States does not act soon, it risks losing its technological edge.¹⁸ This Note will discuss how biologics patents conflict with existing U.S. laws and whether Congress should act. It will examine domestic and international approaches to biologics regulatory approval and develop a proposal on how Congress should move forward. Part I of this paper provides a background on biologics. Part II provides an overview of the FDA regulatory process for new drugs and of provisions in the Hatch-Waxman Act that established patent term restoration for new drugs and accelerated FDA approval for chemical generics. Part III analyzes the debate over whether the science exists to reliably show FOBs are comparable to innovator biologics. Part IV explains why many biologics patents may be invalid for lack of enablement and considers whether Congress should revise the Patent Act to ensure the validity of these patents. Part V contrasts the European Union and Canadian approaches to FOB approval with two bills currently in Congress.

12. See Mandel, *supra* note 6, ¶ 70.

13. Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984).

14. JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 348 (2005).

15. *Id.* at 350.

16. Kiernan Murphy & Kaitlin Mara, Industry Pushes for Biosimilars Approval Process; Some IGOs Take Notice (Feb. 24, 2009), <http://www.ip-watch.org/weblog/2009/02/24/industry-pushes-for-biosimilars-approval-process-some-igos-take-notice/>.

17. Gary C. Messplay & Colleen Heisey, *Follow-On Biologics: The Evolving Regulatory Landscape*, BIOEXECUTIVE INT'L, May 2006, at 42, 44.

18. Linda Hull Felcone, *The Long and Winding Road to Biologic Follow-Ons*, BIOTECHNOLOGY HEALTHCARE, May 2004, at 20, 29.

Part VI describes the various types of marketing exclusivities and discusses the policy considerations behind awarding marketing exclusivities. Part VII will then detail a proposed framework for expedited FOB approval and marketing exclusivities for biologics.

Table of Acronyms

Acronym	Word in Meaning
ABLA	Abbreviated Biologics Licensing Application
ANDA	Abbreviated New Drug Application
BLA	Biologics Licensing Application
EMA	European Medicines Agency
EU	European Union
FDCA	Federal Food, Drug and Cosmetics Act
GPhA	Generic Pharmaceutical Association
NBE	New Biologic Entity
NCE	New Chemical Entity
NDA	New Drug Application
OSC	Other New Significant Changes
PHSA	Public Health Service Act
SIFO	Selectively Interchangeable Follow-Ons
USPTO	U.S. Patent and Trademark Office

I. OVERVIEW OF FDA APPROVAL

Medicinal products may not be sold without marketing approval by the FDA.¹⁹ Traditional small-molecule chemical drugs are regulated by the FDA under the Federal Food, Drug and Cosmetics Act (FDCA) and go through the New Drug Application (NDA) process.²⁰ Due to the importance of quality control of the manufacturing process, most biologics fall under the regulation of the Public Health Service Act (PHSA).²¹ Under the PHSA, a proposed biologic is evaluated pursuant to a biologics licensing application (BLA) rather than an NDA.²² The BLA and NDA processes have been harmonized such that the review processes are nearly identical.²³ To obtain FDA approval under NDA or BLA, the innovator must show that the proposed product meets safety and

19. Mandel, *supra* note 6, ¶ 19.

20. 21 U.S.C. § 355 (2006).

21. 42 U.S.C. § 262(a)(1) (2006); Gitter, *supra* note 5, at 563–64.

22. Mandel, *supra* note 6, ¶ 33.

23. *Id.* ¶ 38.

efficacy standards through submission of extensive preclinical testing and clinical trials data.²⁴

The lengthy FDA approval process often imposes significant delays to market entry for both new and generic drugs. The amount of time from preclinical testing to FDA approval averages eight-and-a-half years, with a high of twenty years.²⁵ Throughout the approval process, the clock is running on the twenty-year patent term even though the patent proprietor has yet to realize a profit from the invention.²⁶ By the time the patent proprietor finally obtains authorization from FDA to sell his product, he may only have a few years of patent protection left. At the expiration of the patent term, subsequent entities wishing to sell the now-unpatented invention must obtain separate FDA marketing approval for their generic products.²⁷ To avoid patent infringement, the process of obtaining FDA approval of the generic version can only be initiated after the expiration of the patent term.²⁸

Hostile circumstances for the market entry of both new and generic drugs led to campaigns by both the brand name and generic industries to lobby Congress to modify the drug regulatory scheme.²⁹ Pharmaceutical research firms argued that the effective reduction in patent term acted as a barrier to new drug development.³⁰ Drug discovery has a particularly high failure rate, and large investments are often lost in the development of products that never realize commercial success.³¹ To recoup these losses and make a viable profit, companies charge higher prices for those products that survive FDA scrutiny—a burden shouldered squarely by the public.³² They argued that allowing the patent owner to reclaim the patent term lost during the product marketing approval processes would restore the incentive structure designed to mitigate the enormous cost and risk of new drug development.³³ In support of generic drug makers, some policymakers contended that requiring separate preclinical

24. THOMAS, *supra* note 14, at 7–9 (describing the approval process from initial testing to approval of the NDA).

25. Michael Dickson & Jean Paul Gagnon, *Key Factors in the Rising Cost of New Drug Discovery and Development*, 3 NATURE REVS. 417, 418 fig.1 (2004).

26. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669–70 (1990).

27. Mandel, *supra* note 6, ¶ 23.

28. *Id.*

29. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 357–58 (2007) (describing the lobbying efforts by pioneer and generic drug companies leading up to the passage of the Hatch-Waxman Act).

30. *Patent Fairness Act of 1999: Hearing on H.R. 1598 Before the H. Subcomm. on Courts and Intellectual Property of the H. Comm. on the Judiciary*, 106th Cong. 2–3 (1999) (statement of the Biotechnology Industry Organization), available at <http://www.bio.org/ip/positions/tstm070199.asp>.

31. Matthew Avery, *Continuing Abuse of the Hatch-Waxman Act by Pharmaceutical Patent Holders and the Failure of the 2003 Amendments*, 60 HASTINGS L.J. 171, 171–72 (2008).

32. Sarah Eurek, *Hatch-Waxman Reform and Accelerated Market Entry of Generic Drugs: Is Faster Necessarily Better?*, DUKE L. & TECH. REV., Aug. 13, 2003, ¶ 1, <http://www.law.duke.edu/journals/dltr/articles/2003dltr0018.html>.

33. Douglas Robinson, *Recent Administrative Reforms of the Hatch-Waxman Act: Lower Prices Now in Exchange for Less Pharmaceutical Innovation Later?*, 81 WASH. U. L.Q. 829, 830 (2003).

studies and clinical trials for a drug that has already undergone the FDA's rigorous approval process was a duplication of effort and waste of valuable resources.³⁴ The cost of obtaining separate FDA marketing approval was a deterrent for companies wanting to produce generic equivalents.³⁵ They also argued that forcing generic drug makers to wait until after patent expiration to commence the lengthy FDA approval process, in effect, created a de facto term extension that further inhibited the public's access to affordable medicine.³⁶

In 1984, Congress addressed the tension between the interest in promoting drug discovery through strong patent protection and the desire to facilitate market entry of lower cost generics by passing the Drug Price Competition and Patent Term Restoration Act, commonly referred to as the Hatch-Waxman Act.³⁷ The resulting statute balances the interests of the pioneer drug industry, the generic drug industry, and patients seeking access to the best available medicines.³⁸ The Hatch-Waxman Act is regarded as highly successful, providing substantial cost savings on lifesaving medicines while spurring an increase in drug innovation.³⁹

The patent term restoration provisions of the Hatch-Waxman Act allow the innovator to reclaim a portion of the patent term that is lost as a result of seeking FDA approval of the new drug product. The restoration term, however, may not exceed a total effective patent term after the extension of more than fourteen years.⁴⁰ However, the statute limits the extent to which these rights are actually restored. Though FDA approval of a product may involve multiple patents, the applicant may obtain a patent term extension for only one of them.⁴¹ Also the patent term extension does not restore the full scope of traditional patent rights. The rights granted during the extension term are limited to uses that subjected the drug to FDA regulatory approval delays in the first place.⁴²

Arguably the most significant consequence of the Hatch-Waxman Act is the implementation of expedited pathways for FDA generic drug approval. Under the Abbreviated New Drug Application (ANDA) process, generic manufacturers

34. THOMAS, *supra* note 14, at 308.

35. See JOHN THOMAS, PROPRIETARY RIGHTS IN PHARMACEUTICAL INNOVATION: ISSUES AT THE INTERSECTION OF PATENTS AND MARKETING EXCLUSIVITIES, CRS RL 33288, at 6 (2006).

36. See Eurek, *supra* note 32, ¶ 2 (noting that generic drug companies must wait for innovators' patents to expire before initiating FDA approval process, creating a significant delay for market entry of the generic product).

37. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. §§ 271(e), 335 (2006)).

38. See Eurek, *supra* note 32, ¶ 2.

39. LAURENCE J. KOTLIKOFF, STIMULATING INNOVATION IN THE BIOLOGICS INDUSTRY 10 (2008), available at http://people.bu.edu/kotlikoff/New%20Kotlikoff%20Web%20Page/Kotlikoff_Innovation_in_Biologics21.pdf. The study was funded by Teva Pharmaceuticals, one of the largest generic pharmaceutical companies in the world.

40. THOMAS, *supra* note 14, at 285. Under the Act, a patent proprietor may obtain an extension equal to one-half of the period between the Investigational New Drug Application and the New Drug Application plus the entirety of the FDA review period. *Id.*

41. *Id.* at 284-85.

42. *Id.* at 300.

may obtain FDA approval for their drugs before the patent on the associated branded product expires.⁴³ Rather than having to reproduce the full-scale safety and efficacy testing and analysis associated with the NDA process, ANDA applicants wishing to market a generic drug simply need to demonstrate therapeutic equivalence—demonstrating that the proposed generic is both pharmaceutically equivalent (same active ingredient, strength, and dosage form) and bioequivalent to a previously FDA-approved drug.⁴⁴ A generic drug is “bioequivalent” to a reference drug if the two products “do not differ significantly with respect to the rate and extent to which their active ingredients become available at their site of action on or in the body.”⁴⁵ Having demonstrated therapeutic equivalence, the ANDA applicant may rely on the safety and efficacy data paid for and submitted by the original manufacturer.⁴⁶

A second pathway for expedited generic drug approval is through the use of section 505(b)(2) applications.⁴⁷ A section 505(b)(2) application contains full safety and efficacy data, but the application relies at least partly on data that was not developed by the applicant, which usually consists of published scientific literature.⁴⁸ Unlike the strict standard of bioequivalence for ANDAs, section 505(b)(2) permits the approval of a generic drug that is a modified version of the innovator drug, provided the applicant submits studies supporting the change.⁴⁹

The Hatch-Waxman Act’s ANDA and section 505(b)(2) processes essentially force innovators to share their safety and efficacy data with generic competitors. Drafters of the Act built in a mechanism for compensating innovator drug manufacturers for this loss—a new type of intellectual property right known as marketing exclusivities. Marketing exclusivities prevent the FDA from approving a competing application for the term of the exclusivity.⁵⁰ They are awarded to successful NDA applicants if certain criteria are met. Certain kinds of marketing exclusivities bar ANDA and section 505(b)(2) applicants from relying on the NDA’s data for the duration of the exclusivity. These mechanisms will be discussed in more detail in Part V.

Biologics approved under PHSa are explicitly included in the patent term extension provisions.⁵¹ However, the FDA’s statutory interpretation excludes almost all biologics from the ANDA and section 505(b)(2) pathways on the

43. Mandel, *supra* note 6, ¶ 26.

44. David Bickart, *Developments in Pharmaceutical and Biotech Patent Law*, in PRACTISING LAW INSTITUTE, PHARMACEUTICAL AND BIOTECH PATENT LAW 208, 215 (2008).

45. *Id.* at 218.

46. THOMAS, *supra* note 14, at 311.

47. *Id.*

48. *Id.*

49. *Id.* at 312.

50. *Id.* at 349.

51. 35 U.S.C. § 156(f)(2)(A) (2006). “The term ‘drug product’ means the active ingredient of a new drug, antibiotic drug, or *human biological product* (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act).” *Id.* (emphasis added).

grounds that the provisions were intended to amend FDCA, not PHSA.⁵² According to the FDA, absent congressional action, it does not have the authority to extend the abbreviated regulatory scheme to biologics licensed under PHSA.⁵³ A Senate report directing the FDA to harmonize the BLA and NDA processes specifically excludes FOBs and explicitly states that ANDA does not apply to biologics.⁵⁴ Therefore, a FOB manufacturer seeking marketing approval must wait until the innovator's patents expire before it can start the BLA approval process, and it must develop its own safety and efficacy findings.⁵⁵ The FDA makes a narrow exception for certain smaller, less complex biologics that receive NDA approval under FDCA authority—this small category of biologics products is eligible for the section 505(b)(2) pathway but remains precluded from ANDA.⁵⁶ To further complicate matters, the FDA has no clear guidelines to determine which biologics qualify for NDA as opposed to BLA.⁵⁷

II. WHETHER “CLOSE ENOUGH” IS GOOD ENOUGH

The inquiry into whether potential follow-on manufacturers can reliably establish sameness or comparability to the pioneer biologics product must be addressed before an abbreviated pathway for FOB approval may even be considered. Biologics are usually nonuniform mixtures of complex, high molecular weight proteins and various biological impurities such as bacteria and viruses.⁵⁸ Biologics have a unique sensitivity to environmental and manufacturing conditions due to the complexity of the protein molecules and the living cells that produce them.⁵⁹ As a result, different biologic products with similar molecular compositions may behave differently in different individuals, and substitution could result in adverse effects.⁶⁰

This difficulty is “at the heart” of the debate over whether a FOB, sometimes called a biosimilar or biogeneric, can ever be truly equivalent and interchange-

52. Gitter, *supra* note 5, at 575–76. The FDA will not approve section 505(b)(2) applications for biologic products originally approved under PHSA, which includes most biologics. *Id.* at 580.

53. *Id.* at 580.

54. Mandel, *supra* note 6, ¶ 43 (citing S. REP. NO. 105-43 (1997)).

55. *Id.* ¶ 44.

56. Gitter, *supra* note 5, at 576. In approving the section 505(b)(2) application for the FOB, Omnitrope, the FDA warned that the agency's action did not mean that other “more complex and/or less well understood” FOBs could obtain FDA approval using the same pathway. *Id.* at 580.

57. A. Taylor Corbitt, *The Pharmaceutical Frontier: Extending Generic Possibilities to Biologic Therapies in the Biologics Price Competition and Innovation Act of 2007*, 18 DEPAUL J. ART TECH. & INTELL. PROP. L. 365, 379–80 (2008).

58. Gitter, *supra* note 5, at 575–76; Kaldre, *supra* note 1, ¶ 11.

59. Michael Kleinberg & Kristen Wilkinson Mosdell, *Current and Future Considerations for the New Classes of Biologicals*, 61 AM. J. OF HEALTH-SYSTEM PHARMACY 695, 695 (2004); Kaldre, *supra* note 1, ¶¶ 11–13.

60. Scott Gottlieb, *Biosimilars: Policy, Clinical, and Regulatory Considerations*, 65 AM. J. OF HEALTH-SYSTEM PHARMACY S2, S5 (2008).

able with the pioneer product.⁶¹ The innovator and generics industries, policymakers, and academics strongly disagree as to whether the current state of technology permits the interchangeability of innovator and FOB products. Those in support of an ANDA-like system, including some FDA officials, argue that FOBs “can achieve comparability [with the pioneer biologic] even if they are manufactured using different processes, at least with respect to recombinant products created through genetic engineering.”⁶² According to the Generic Pharmaceutical Association (GPhA), there are two types of characterization: absolute and comparative.⁶³ Absolute characterization is the norm for traditional chemical drugs and involves a comprehensive analysis of the molecule at the atomic level.⁶⁴ The GPhA claims that using comparative characterization to compare a FOB to a reference innovator product “in all meaningful ways” is a sufficient means to characterize FOBs without the need for full preclinical and clinical testing.⁶⁵ The GPhA contends that principles of comparability have been well established and the technology exists to characterize and determine comparability of most biologics.⁶⁶ The critical aspects of identity, potency, safety, quality, and purity can be determined by employing a suite of comparative characterization methods, using the innovator product as the reference.⁶⁷ The FDA has shown some support for this argument by stating publicly that the technology to accurately characterize biologics using comparability methods, rather than clinical trials, already exists for simpler FOBs.⁶⁸

Comparability is a lower standard than bioequivalence. If comparability methods establish a FOB’s similarity to a reference biologic, this does not mean that the FOB is interchangeable with the reference product.⁶⁹ More data would be needed to show that the FOB would produce the same clinical results.⁷⁰

Opponents of an ANDA-like pathway for FOBs argue that because “the process is the product, and the product is the process,”⁷¹ FOBs are, at most, similar to the innovator product and must be evaluated on a case-by-case basis.⁷² The composition and efficacy of a FOB product may be difficult to

61. Morrison, *supra* note 4, at 465.

62. Gitter, *supra* note 5, at 602–03.

63. *Id.* at 592.

64. *Id.*

65. *Id.* at 591–92.

66. GENERIC PHARM. ASS’N, BIOPHARMACEUTICALS (“FOLLOW-ON” PROTEIN PRODUCTS): SCIENTIFIC CONSIDERATIONS FOR AN ABBREVIATED APPROVAL PATHWAY 10 (2004), available at <http://www.gphaonline.org/sites/default/files/GPhA%20White%20Paper%20on%20Generic%20Biopharmaceuticals.pdf>.

67. *Id.* at 11–12.

68. Gitter, *supra* note 5, at 595.

69. Steven Sklar, Corporate Counsel, Leydig, Voit & Mayer, Ltd., Congress Debates The Future of Generic Biologics (Sept. 2007), http://www.leydig.com/publications/articles_publications-25.

70. *Id.*

71. Hogan & Hartson LLP, *Regulation of “Biosimilars” in the European Union*, EU BULLETIN, Jun. 18, 2004, at 2, http://www.hhlaw.com/files/Publication/f8bed036-dc7b-42c6-a4a0-b2776a956014/Presentation/PublicationAttachment/078fe85f-a0d5-4ccc-a96f-afec79554fbd/1475_040618_reg_biosimilars_eubulletin.pdf.

72. Biotechnology Indus. Org., BIO Principles on Follow-On Biologics (Mar. 26, 2007), <http://bio.org/healthcare/followonbkg/Principles.asp>.

characterize, requiring the manufacturer to conduct clinical trials, immunogenicity testing, and, if necessary, postmarketing clinical studies and evaluation.⁷³

In particular, immunogenicity—the potential for an immune response in a patient—is notoriously difficult to characterize because the potential for an immune response is influenced by many factors.⁷⁴ Though immune responses are not always adverse, they can sometimes produce serious complications and potentially worsen the condition the drug was intended to treat.⁷⁵ Though immunogenicity can be a major concern, both sides agree that this is the case only in rare instances.⁷⁶ Furthermore, some have expressed concern about immunogenicity for both innovator and FOB products.⁷⁷ The FDA currently employs an array of scientific and analytical methods to evaluate innovator products to determine their immunogenicity.⁷⁸ The same can be done for FOBs.⁷⁹

Weighing the evidence, it would seem that science has progressed to the point that assessments of “relative sameness” between protein drug products may be achieved.⁸⁰ Even now, innovator companies apply comparability principles to obtain FDA approval when implementing changes to their manufacturing processes.⁸¹ The FDA could use these comparability protocols and apply to FOBs the same criteria for equivalence.⁸² As technology continues to advance, characterization techniques will become more sophisticated, and manufacturers will be able to assess the safety and efficacy of their products with higher degrees of confidence.

III. BIOLOGICS PATENTS ON SHAKY GROUND

The debate over interchangeability between innovator products and FOBs reveals an incongruity between the U.S. patent regime and many biologics patents. Innovator companies rely heavily on patents to protect their biologics

73. *Id.*; see Kaldre, *supra* note 1, ¶ 11 (discussing the complexity of biologics).

74. Meenu Wadhwa & Robin Thorpe, *Unwanted Immunogenicity: Implications for Follow-On Biologics*, 41 *DRUG INFO. J.* 1, 3 (2007).

75. See Gopi Shakar et al., *Scientific and Regulatory Considerations on the Immunogenicity of Biologics*, 24 *TRENDS IN BIOTECHNOLOGY* 274, 274 (2006).

76. Gitter, *supra* note 5, at 605.

77. *Id.* at 604.

78. *Id.* at 604–05.

79. *Id.* at 605.

80. *The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 10 (2004) (statement of Dr. Lester M. Crawford, then-Acting Commissioner, FDA).

81. Erwin A. Blackstone & Joseph P. Fuhr Jr., *Generic Biopharmaceutical Drugs: An Economic and Policy Analysis*, *BIOTECHNOLOGY HEALTHCARE*, Feb. 2007, at 43, 45, available at <http://www.biotechnologyhealthcare.com/journal/fulltext/4/1/BH0401043.pdf>.

82. See *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 80 (2007) (statement by Dr. William Schwieterman, independent consultant) (“[T]he evidence clearly demonstrates that comparability processes soundly support the approval of biogenerics without the need for large and questionable clinical trials . . .”); *GENERIC PHARM. ASS’N*, *supra* note 66, at 7.

products from competing market entrants.⁸³ The question of whether biologics would be considered patentable subject matter was rendered moot in light of the Supreme Court's pronouncement that "anything under the sun that is made by man" is patentable.⁸⁴ However, concerns regarding the patentability of biologics remain.

To qualify for patent protection, patent applicants must satisfy the enablement requirement; that is, the patent specification must be sufficient to inform one skilled in the art of how to make and use the subject invention for its intended purpose.⁸⁵ The enablement requirement presents a unique problem for inventions that involve living materials, such as biologics products, because a written account with complete taxonomic description may be insufficient to enable others to make and use the biological invention.⁸⁶ In these cases, the U.S. Patent and Trademark Office (USPTO) allows submission of physical samples of the patented invention to publicly accessible depositories in order to satisfy the enablement requirement.⁸⁷ These samples may be the final product itself or the starting material required to make and use the invention that would not otherwise be available.⁸⁸

Unfortunately, the depository does not completely resolve the enablement issue for biologics patents. Ironically, the best case against adequate enablement comes from the patent holders themselves. The pioneer biologics industry often contends that generic biologics products are not truly generic in the traditional sense because they can never actually be identical to the innovator's version.⁸⁹ Since the details of the innovator's finely tuned manufacturing process are often a trade secret, each subsequent manufacturer's process will necessarily vary at least slightly, resulting in a different product that should require an independent showing of safety and effectiveness before being approved for patient use.⁹⁰ This argument dooms the patents underlying the brand name drug.

The Patent Act's enablement requirement has been interpreted to require the patent specification to provide enough information such that another may make and use the claimed invention without undue experimentation.⁹¹ If subsequent parties are indeed unable to reliably reproduce the biologics product without access to additional trade secret information, then the patent is not enabling and

83. Rebecca Eisenberg, *The Shifting Functional Balance of Patents and Regulation*, 19 HEALTH AFF. 119, 120 (2001).

84. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (internal citations omitted).

85. The enablement requirement is embodied in 35 U.S.C. § 112 (2006), which reads, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same . . ."; see also Mandel, *supra* note 6, ¶ 22.

86. THOMAS, *supra* note 14, at 208.

87. *Id.*

88. Mandel, *supra* note 6, ¶ 72.

89. See, e.g., Biotechnology Indus. Org., *supra* note 72.

90. *Id.*

91. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

is, therefore, invalid.⁹² Analyzed from a different perspective, the innovator companies argue that the characteristics of the patented invention require FOB applicants to conduct extensive clinical trials to show that the innovator biologics product and FOB are equivalent.⁹³ Though the “undue experimentation” standard is highly fact specific,⁹⁴ common sense dictates that requiring human clinical trials to make and use the patented invention would qualify. Even if subsequent technologies enabled complete characterization of a biologics product and made clinical trials of FOBs unnecessary, the patent would not be salvaged because these technologies would not be considered when evaluating whether the enablement requirement is satisfied.⁹⁵

Given how lucrative the biologics industry is, it is foreseeable that an entity will attempt to invalidate these seemingly questionable patents granting monopolies over biologics products. The Federal Circuit has addressed enablement in several biotechnology cases and has adhered to a high standard for patents in this field.⁹⁶ If this trend continues, many biologics patents could be invalidated, which would set back the development of new medicines.⁹⁷ While this may sound troubling, weakening the enablement requirement would create more problems. The grant of a temporary monopoly is part of society’s bargain with the inventor in order to encourage full and complete disclosure of innovations for the advancement of science.⁹⁸ Allowing innovators to obtain monopolies without enabling others to make and use the invention would distort this balance and actually slow innovative research by limiting access to information on the latest technological advances.

Innovators routinely obtain separate patents for the end product and the manufacturing process of that product. As a possible solution to the enablement problem, properly tailored process patents could be used to protect aspects of the manufacturing process that are currently kept as trade secrets. Innovators argue that process patents provide insufficient protection because, due to the complexity of the manufacturing process, biologics process patents would need to be narrowly tailored.⁹⁹ The resulting patent would provide minimal protection because others could easily design around the patent to avoid infringement liability.¹⁰⁰ The judge-made doctrine of equivalents was established to prevent others from avoiding infringement by making minor, insubstantial changes to

92. Mandel, *supra* note 6, ¶ 74.

93. Biotechnology Indus. Org., *supra* note 72.

94. See *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (laying out the eight-factor test to determine whether experimentation is unduly burdensome, commonly known as “the *Wand* factors”).

95. See *In re Wright*, 999 F.2d 1557, 1562–63 (Fed. Cir. 1993).

96. Bruce S. Manheim Jr., Patricia Granahan & Kenneth J. Dow, ‘Follow-On Biologics’: Ensuring Continued Innovation in the Biotechnology Industry, 25 HEALTH AFF. 394, 399 (2006).

97. See Mandel, *supra* note 6, ¶ 75.

98. Dale L. Carlson, Katarzyna Przychodzen & Petra Scamborova, *Patent Linchpin for the 21st Century?—Best Mode Revisited*, 45 IDEA 267, 269 (2005).

99. Manheim, *supra* note 96, at 398.

100. *Id.*

the patented process.¹⁰¹ Although the Federal Circuit recently limited the doctrine of equivalents by ruling that it cannot be used to reclaim patent scope conceded during patent prosecution, the doctrine still imposes infringement liability for insignificant changes.¹⁰² Narrowing the scope of the claims to avoid prosecution history estoppel limitations is a strategic choice made by the patent applicant. The patentee should be made to bear the consequences of this decision.

If Congress were to relax the enablement requirement or begin creating industry-based exceptions to patent requirements, the public would suffer the anticompetitive effects of a monopoly without getting anything meaningful in return. Rather than dilute the enablement requirement and weaken the entire patent system, innovators should be required to disclose the details of their manufacturing process, sufficient to enable others to make and use the identical biologics product. Though innovators may balk at the idea of being required to disclose trade secrets, doing so in order to meet the minimum requirements of the Patent Act is a fair price to pay for a twenty-year statutory monopoly.

The enablement problem for biologics is intertwined with the comparability issue. The amount of detail required in the patent specification would depend on whether the FDA adopts a comparability standard and the characterization techniques applicable to the particular biologic. If the FDA adopts a comparability standard for FOB approval, then the scope of the biologics patent may be as broad as the characterization methods at the time permit. Where characterization methods are adequate, innovators would not be required to specify the exact conditions—only enough to provide others with the information necessary to make a comparable product that can be sufficiently characterized without the need for extensive clinical trials testing. This would spur development of more advanced technology to characterize complex biologics products. Innovators would still enjoy broad patent protection, and FOB manufacturers would be able to bypass full-scale clinical trials. This would reduce research and development (R&D) costs for FOBs, which, in turn, would drive down the price to consumers.

IV. EXISTING APPROACHES TO BIOSIMILARITY

While the United States contemplates whether to adopt a comparability standard for FOBs, other jurisdictions have already moved forward with abbreviated approval pathways for FOBs. The European Union has already deemed the advanced characterization techniques available today to be sufficient to justify a similarity standard.¹⁰³ In 2004, the European Union passed a directive that gave the European Medicines Agency (EMA)—the European Union’s equivalent of the FDA—the authority to grant marketing authorization for “similar biological

101. THOMAS, *supra* note 14, at 464.

102. *Festo v. Shoketsu Kinzoku Kogyo Kabushiki*, 344 F.3d 1359, 1366–67, 1374 (Fed. Cir. 2003). This is known as prosecution history estoppel.

103. *See* Kaldre, *supra* note 1, ¶ 20.

medicinal products.”¹⁰⁴ An entity seeking to market a FOB product may utilize the EMEA’s “centralised procedure,” the European Union’s application process for obtaining marketing approval for any medicinal product.¹⁰⁵ Traditional generics are evaluated under the bioequivalence standard, but due to the characterization problems unique to biologics, the EMEA established a biosimilars approach to FOB approval based on comparability principles.¹⁰⁶ Under this regime, the applicant must demonstrate that there are “no meaningful differences” in safety or efficacy between the biosimilar (the proposed FOB) and the reference innovator biologic (the patented biologic).¹⁰⁷ The applicant must comply with product-specific guidelines that are issued by EMEA through extensive consultation procedures.¹⁰⁸ Generally, extensive comparability exercises are required to establish the quality, safety, and efficacy of the product itself; and the applicant must demonstrate the consistency and robustness of the manufacturing process.¹⁰⁹ The applicant must also demonstrate comparable immunogenicity, which often requires preclinical testing and clinical trials.¹¹⁰

The European Union’s approach accepts that differences will persist between biologics products from different manufacturers, and provides the EMEA with flexibility to determine the extent and nature of testing required to establish biosimilarity.¹¹¹ Approval for each proposed biosimilar is a case-by-case analysis, and the amount of data required depends on the “state of the art of analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences.”¹¹² The applicant may not be required to repeat full safety and efficacy testing, but EMEA retains the discretion to require the full array of clinical and preclinical data if the biologic’s structure is too complex to establish equivalence adequately.¹¹³ For example, EMEA guidelines specifically state that certain routine toxicology studies are generally not required for biosimilars, and clinical trials may not be necessary if other studies sufficiently

104. Paul Chamberlain, *Biogenerics: Europe Takes Another Step Forward While the FDA Dives for Cover*, 9 DRUG DISCOVERY TODAY 817, 818 (2004); see also Council Directive 2004/27, 2004 O.J. (L 136) 34 (EC).

105. See European Meds. Agency [EMA], Human Medicines, <http://www.ema.europa.eu/index/indexh1.htm> (last visited Aug. 12, 2009).

106. EMA, Comm. for Medicinal Prods. for Human Use (CHMP), *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues*, at 4, EMA Doc. CHMP/BWP/49348/2005 (Feb. 22, 2006).

107. EMA, Questions and Answers on Biosimilar Medicines (Similar Biological Medicinal Products), EMA Doc. 74562/2006 Rev. 1 (Oct. 22, 2008).

108. R. F. Kingham & E. Lietzan, *Current Regulatory and Legal Considerations for Follow-On Biologics*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 633, 634 (2008).

109. EMA, *supra* note 106, at 3–4.

110. Kaldre, *supra* note 1, ¶ 21.

111. See EMA, *supra* note 107.

112. EMA, CHMP, *Guideline on Similar Biological Medicinal Products*, at 4, EMA Doc. CHMP/437/04 (Oct. 30, 2005).

113. Messplay & Heisey, *supra* note 17, at 44.

demonstrate the biosimilar's clinical comparability.¹¹⁴ The EMEA has approved only two biosimilars since the framework was established; therefore, it is too soon to gauge the impact of the European Union's biosimilar pathway on healthcare and industry.¹¹⁵ However, experts believe that, with accrued experience, the EMEA will be able to optimize its guidelines to handle the risks associated with biosimilars.¹¹⁶

Demonstrating that a FOB product is biosimilar to a reference biologic does not mean it is interchangeable with—and, thereby, substitutable for—the reference biologic. Under the European Union's framework, whether a biosimilar is interchangeable with the reference biologic is a decision made by each individual member state.¹¹⁷ A FOB manufacturer may still face significant obstacles to commercial success, depending on the particular member state's policy attitude towards interchangeability of biologics. To date, no member state has approved the substitution of a biologic.¹¹⁸

Canada's approach to establishing a mechanism for FOB approval is to issue guidance documents at the agency level, rather than amend existing legislation. In 2008, Health Canada—the department of the Canadian government responsible for national public health policy¹¹⁹—issued revised draft guidance on the approval of “subsequent entry biologics” (SEBs).¹²⁰ A SEB is defined as “a biologic drug that would enter the market subsequent to, and ‘similar’ [sic] to an innovator product authorized for sale in Canada.”¹²¹ A SEB relies on information for the reference biologic drug that is deemed relevant due to the demonstration of similarity between the SEB and the reference drug.¹²² A similarity determination means: “1) that the existing knowledge of both products is sufficient to predict that any differences in quality attributes should have no adverse impact upon safety or efficacy of the SEB; and 2) that the non-clinical and clinical data previously generated with the reference biologic drug is relevant to the SEB.”¹²³ The SEB applicant must show that the active ingredient, the dosage form, strength, and route of administration are the same for the

114. EMEA, CHMP, *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues*, at 4–6, EMEA Doc. CHMP/BMWP/42832/2005 (Feb. 22, 2006).

115. Kaldre, *supra* note 1, ¶¶ 22–23.

116. Andrzej Wiecek & Ashraf Mikhail, *European Regulatory Guidelines for Biosimilars*, NEPHROLOGY DIALYSIS TRANSPLANTATION, October 2006, at v17, v19.

117. Suzanne M. Sensabaugh, *Biological Generics: A Business Case*, 4 J. GENERIC MED. 186, 188 (2007), available at <http://www.palgrave-journals.com/jgm/journal/v4/n3/pdf/4950067a.pdf>.

118. Kingham & Lietzan, *supra* note 108, at 634.

119. See About Health Canada Main Page, <http://www.hc-sc.gc.ca/ahc-asc/index-eng.php> (last visited Aug. 12, 2009).

120. HEALTH CAN., DRAFT GUIDANCE FOR SPONSORS: INFORMATION AND SUBMISSION REQUIREMENTS FOR SUBSEQUENT ENTRY BIOLOGICS (SEBs) § 1.1 (Mar. 27, 2009), <http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/2009-03-seb-pbu-notice-avis-eng.php>.

121. *Id.* § 1.4.

122. *Id.*

123. *Id.* § 2.3.1.4.

SEB and reference biologic.¹²⁴ The approach to manufacturing must also be the same; a SEB with the same active ingredient, but manufactured under a different process, will not be eligible for the abbreviated pathway.¹²⁵

Under the draft guidance, a SEB application must contain the full chemistry and manufacturing data package that would be required for a new biologic drug.¹²⁶ Additionally, a SEB applicant must conduct a direct or indirect comparison with the reference biologic drug, including analytical and biological characterization.¹²⁷ The comparability exercises are used to show that the SEB and reference biologic drug have similar quality attributes, thus supporting a conclusion that they are similar in terms of safety and efficacy.¹²⁸ Some nonclinical and clinical data will be required for SEB approval.¹²⁹ The extent and nature of testing needed will be a case-by-case determination based on “the existing knowledge of the reference [biologic], and on the nature of the indication being claimed.”¹³⁰ It will also depend on the availability of analytical techniques to detect differences between the SEB and reference product.¹³¹ The consultation period for the draft guidance document has closed, and it remains to be seen how Health Canada will proceed.¹³² Until Canada formally establishes a SEB regulatory framework, SEB manufacturers have to go through the full drug approval process as if the SEB were any other new biologic drug.¹³³ Canada’s draft guidance specifically states that SEB approval is not a declaration of therapeutic or pharmaceutical equivalence to the reference biologic product, implying that the products are not interchangeable.¹³⁴

The United States lags behind the European Union and Canada in establishing an abbreviated pathway for biologics approval. A legislative battle is being waged by both sides of the biologics debate. As of March 2009, three biologics bills had been introduced in the 111th Session of Congress.¹³⁵ The Promoting Innovation and Access to Life-Saving Medicine Act¹³⁶ was introduced in the

124. *Id.* § 2.1.3.

125. *Id.* § 1.2.

126. *Id.* § 2.3.1.

127. *Id.* §§ 2.1.4, 2.3.1.4. The reference drug must have been previously authorized for sale in Canada.

128. *Id.* § 2.3.1.1.

129. *Id.* § 1.5.

130. *Id.* §§ 1.5 & 2.1.2.

131. *Id.* § 2.3.1.1.

132. The consultation period closed on May 26, 2009. Health Can., Notice—Release of a Revised Version of the Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (Mar. 27, 2009), <http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/2009-03-seb-pbu-notice-avis-eng.php>.

133. Health Can., Questions and Answers to Accompany the Release of the Subsequent Entry Biologics Guidance Document, http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/2009-03-seb-pbu_qa-qr-eng.php (last visited Aug. 12, 2009).

134. HEALTH CAN., *supra* note 120, § 1.3.4; Health Can., *supra* note 133.

135. Posting of Donald Zuhn to Patent Docs, <http://www.patentdocs.org/2009/04/third-followon-biologics-bill-introduced.html> (Apr. 1, 2009, 23:52 EST).

136. H.R. 1427, 111th Cong. (2009).

House by Representative Henry Waxman, with a companion Senate bill subsequently introduced by Senator Charles Schumer.¹³⁷ The two bills heavily favor the generic biologics industry and are endorsed by various consumer, labor, and business groups.¹³⁸ Representative Waxman's bill was soon followed by Representative Anna Eshoo's bill, the Pathway for Biosimilars Act,¹³⁹ which takes a much more proinnovator approach.¹⁴⁰ The Pathway for Biosimilars Act has received strong support from the academic and research communities.¹⁴¹

The Promoting Innovation and Access to Life-Saving Medicine Act (the Waxman bill) creates an abbreviated regulatory pathway for biologics to expedite the market entry of affordable biotech drugs.¹⁴² Under the Waxman framework, to obtain marketing approval for a FOB, the applicant must establish biosimilarity—meaning that there are “no clinically meaningful differences” in safety, purity, and potency between the biological product and the reference product.¹⁴³ The applicant must also show that the two products have highly similar structures and have the same mechanism(s) of action, if known.¹⁴⁴ The legislation requires that the biosimilarity determination be based on data derived from nonclinical and clinical studies.¹⁴⁵ The bill grants the FDA broad discretion in determining the level and extent of test data required, but explicitly instructs the Agency to avoid “duplicative and unethical clinical testing.”¹⁴⁶

Under the Waxman bill, application for “biogeneric” status—which means the FOB is interchangeable with the reference product—is separate from a biosimilarity determination.¹⁴⁷ To be considered interchangeable with a reference product, the FOB must demonstrate that (1) the FOB and reference product are biosimilar and (2) a patient can be switched between the products without an increased risk of adverse effects.¹⁴⁸ The FDA may give the FOB the same name

137. S. 726, 111th Cong. (2009).

138. *Consumer, Business and Labor Groups Endorse Bipartisan Senate Bill Authorizing Biogenerics*, PR NEWSWIRE, Mar. 26, 2009, available at http://www.redorbit.com/news/health/1661113/consumer_business_and_labor_groups_endorse_bipartisan_senate_bill_authorizing/.

139. H.R. 1548, 111th Cong. (2009).

140. Lynne Taylor, *New U.S. Biogenerics Bill Offers 14 Years' Market Exclusivity*, March 20, 2009, <http://www.eatg.org/eatg/Global-HIV-News/EMEA-FDA/New-US-biogenerics-bill-offers-14-years-market-exclusivity>.

141. Press Release, Rep. Anna Eshoo, Reps. Eshoo, Inslee, and Barton Introduce Pathway for Biosimilars Act (Mar. 17, 2009), available at http://eshoo.house.gov/index.php?option=com_content&task=view&id=581&Itemid=79.

142. See Press Release, Rep. Henry A. Waxman, Bipartisan Group of Members Introduces “Promoting Innovation and Access to Life-Saving Medicines Act” (Mar. 11, 2009), available at <http://waxman.house.gov/News/DocumentSingle.aspx?DocumentID=115183>.

143. H.R. 1427, 111th Cong. § 3(a)(2) (2009); see also H. Comm. on Energy & Commerce, Detailed Outline of the Promoting Innovations and Access to Life-Saving Medicine Act (March 11, 2009), available at http://energycommerce.house.gov/Press_111/20090311/hr1427_detailedsummary.pdf (last visited Apr. 2, 2009).

144. H.R. 1427 § 3(a)(2).

145. *Id.*

146. *Id.*

147. See H. Comm. on Energy & Commerce, *supra* note 143.

148. *Id.*

as the reference drug, even if they are found not to be interchangeable.¹⁴⁹ As with the biosimilarity determination, the biogeneric determination must be based in nonclinical and clinical data, but the FDA has broad discretion in determining the type and extent of additional testing required.¹⁵⁰

The Pathway for Biosimilars Act (the Eshoo bill) provides an abbreviated pathway for FOB approval under more rigid criteria than the Waxman bill. Before an application may be accepted, the FDA must issue guidance for the approval of biosimilars with respect to the product class, after opportunity for public comment.¹⁵¹ The FOB application must demonstrate biosimilarity through (1) analytical studies showing that the proposed FOB is “highly similar” to a reference product; (2) animal studies, including toxicity assessments; and (3) clinical studies “sufficient to demonstrate safety, purity, and potency for *each condition of use* for which the reference product is approved.”¹⁵² The FDA has the discretion to waive one or more of these requirements if it determines they are unnecessary.¹⁵³ The FDA may not, however, waive an immunogenicity study unless it has published a final guidance, after public comment, containing scientific evidence that the current state of the art allows for determining immunogenicity without the need for clinical trials for that particular product class.¹⁵⁴

Not surprisingly, the Eshoo bill provides a more rigid mechanism for determining interchangeability. The FOB applicant must show the product is biosimilar to the reference product and can be expected to produce the same clinical effects for “*the condition or conditions* prescribed, recommended, or suggested” for the reference product.¹⁵⁵ The FDA may not approve a FOB’s interchangeability unless it has published final guidance, after public comment, supported by evidence that the current state of the art makes interchangeability determinations scientifically feasible.¹⁵⁶ Approved FOBs, regardless of interchangeability, must have unique packaging and labeling that distinguishes the FOB from the reference biologic.¹⁵⁷

V. MARKETING EXCLUSIVITIES

A marketing exclusivity is a type of intellectual property protection that operates outside of the patent regime.¹⁵⁸ During the term of a drug’s marketing

149. H.R. 1427, 111th Cong. § 3(a)(2) (2009); Hogan & Hartson LLP, *Waxman Bill Creates Risks, Opportunities*, PHARMACEUTICAL AND BIOTECHNOLOGY UPDATE, Mar. 16, 2009, http://www.hhlaw.com/files/Publication/eff54d95-647b-4157-8520-0539f8301935/Presentation/PublicationAttachment/a63a8b58-2f97-4997-bdae-140582431d50/PharmaBioUpdate_March2009.pdf.

150. H.R. 1427 § 3(a)(2).

151. H.R. 1548, 111th Cong. § 101(a)(2) (2009).

152. *Id.* (emphasis added).

153. *Id.*

154. *Id.*

155. *Id.* (emphasis added).

156. *Id.*

157. *Id.*

158. THOMAS, *supra* note 14, at 349.

exclusivity, the FDA may not grant approval of a competing marketing application for the same drug.¹⁵⁹ Marketing exclusivities are particularly powerful because, by barring FDA approval, the competing product may not be marketed at all.¹⁶⁰ This perfect monopoly protection is automatic and does not require the entity holding the market exclusivity to act—a sharp contrast to patent rights, which are *only* enforced when the patent holder prevails in a legal action.¹⁶¹ The policy behind marketing exclusivities is to incentivize pharmaceutical research entities to engage in ambitious, cutting-edge research for the development of new drugs and to develop greater understanding about existing drugs.¹⁶²

The Hatch-Waxman Act established multiple types of FDA-administered exclusivities,¹⁶³ but this paper will focus on two: the “new chemical entity” and “other significant changes” marketing exclusivities. Products that qualify for a “new chemical entity” (NCE) marketing exclusivity may not include a previously FDA-approved active ingredient.¹⁶⁴ The FDA will not accept competing applications for a drug that has been granted an NCE exclusivity for a period of five years, effectively preventing generic competition from reaching the market for five years plus the time required for the FDA to complete its review process.¹⁶⁵ The FDA typically takes seventeen months to approve a generic drug application,¹⁶⁶ which means a typical NCE exclusivity effectively lasts almost six-and-a-half years.

An “other new significant changes” (OSC) marketing exclusivity is awarded to an NDA or supplemental NDA if it is approved for a new indication or dosage form for a previously approved drug.¹⁶⁷ To qualify, the application must contain new clinical investigations that were sponsored or conducted by the applicant.¹⁶⁸ An OSC marketing exclusivity prevents the FDA from approving a competing marketing approval application for a period of three years. Unlike the NCE exclusivity, the FDA may accept and grant tentative approval for competing applications during the term of the OSC exclusivity; however, it must withhold final marketing approval until the exclusivity has run its course.¹⁶⁹ Neither the NCE nor the OSC marketing exclusivity prevents the FDA from approving NDAs with full preclinical and clinical trials data.¹⁷⁰ The two

159. *Id.* at 348.

160. Eisenberg, *supra* note 29, at 355.

161. THOMAS, *supra* note 35, at 20.

162. *Id.* at 14.

163. THOMAS, *supra* note 14, at 349.

164. 21 U.S.C. § 355(j)(5)(F)(iv) (2006). This also applies to any salt or ester of a previously FDA-approved active ingredient. § 355(j)(5)(F)(v).

165. THOMAS, *supra* note 14, at 350.

166. Martin Sipkoff, *FDA Approach to Generics May Be a Mixed Blessing*, MANAGED CARE, Feb. 2008, at 20, available at http://www.nxtbook.com/nxtbooks/medimedia/managedcare_200802/ (last visited Aug. 22, 2009).

167. Bickart, *supra* note 44, at 291.

168. *Id.* at 291–92.

169. THOMAS, *supra* note 14, at 353.

170. *Id.*

marketing exclusivities effectively delay FDA approval for generic drug manufacturers who wish to rely on the innovator's previously submitted safety and efficacy data.¹⁷¹

In addition to marketing exclusivities for innovator drug companies, the Hatch-Waxman Act also provides marketing exclusivities for generics manufacturers as an incentive to develop cheaper alternatives to approved pharmaceuticals.¹⁷² The first generic applicant is awarded a 180-day exclusivity during which the FDA may not issue final marketing approval to subsequent ANDA applicants.¹⁷³ This essentially creates a "duopoly" between the brand name company and the first generic applicant during the 180-day term.¹⁷⁴ After the generic marketing exclusivity term expires, other generic competitors may enter the market, resulting in a sharp drop in prices.¹⁷⁵

The length of marketing exclusivities for biologics, if they should be awarded at all, is one of the most controversial issues surrounding FOB legislation.¹⁷⁶ A shorter marketing exclusivity term favors earlier market entry of cheaper FOB products, while a longer term focuses on incentivizing the development of new biologics products.¹⁷⁷ Determining the optimal approach to marketing exclusivity for biologics requires a careful weighing of different policy arguments.

In the European Union, all medicinal products, including biologics, are governed by the same marketing exclusivity regime, the so-called "8+2+1" rule.¹⁷⁸ The innovator may obtain marketing exclusivity for eight years during which the EMEA may not accept an application for a competing generic medicinal product;¹⁷⁹ this is functionally the same as an NCE exclusivity. The EMEA may not grant marketing approval to a generic product until ten years after the innovator's receipt of marketing approval (the "+2").¹⁸⁰ The marketing exclusivity period may be extended for another year if the innovator obtains marketing approval for a new indication.¹⁸¹ Unlike the OSC exclusivity in the United States, an innovator may obtain this extension only once for a given medicinal product, and the innovator must have obtained approval for a new indication; new strengths, dosage forms, and routes of administration would not qualify.¹⁸² However, during the "+1" period, the generic manufacturers may

171. THOMAS, *supra* note 35, at 7.

172. THOMAS, *supra* note 14, at 354.

173. *Id.*

174. *Id.*

175. *Id.*

176. Emily Waltz, *Western Biotechs Ponder Follow-On Possibilities*, 26 NATURE BIOTECHNOLOGY 962, 962 (2008).

177. *The Generic Biologics Debate Heats Up with Introduction of Rival House Bill*, LIFE SCIENCES ALERT (Crowell & Moring LLP, Washington, D.C.), Mar. 24, 2009, <http://www.crowell.com/NewsEvents/Newsletter.aspx?id=1189>.

178. THOMAS, *supra* note 14, at 637.

179. THOMAS, *supra* note 35, at 15–16.

180. *Id.* at 16.

181. *Id.*

182. *Id.*

not market the product for either old or new indications.¹⁸³

Canadian regulation provides for a “6+2” marketing exclusivity for all innovative drugs, including biologic drugs.¹⁸⁴ Under this regulation, a competitor relying on the innovator drug as the reference drug may not submit an application until six years after the date of marketing approval of the innovator drug.¹⁸⁵ Final marketing approval for the application will not be granted until eight years after the date of marketing approval of the reference biologic drug.¹⁸⁶

While Canada and the European Union treat biologics as any other innovative drug in the context of marketing exclusivities, the bills currently in Congress would establish a separate marketing exclusivity regime for biologics. The Waxman bill lays out a structure of market exclusivities that appears to mirror that of the Hatch-Waxman Act, but there are several striking differences.¹⁸⁷ The Waxman bill provides for a five-year marketing exclusivity for most innovator biologics, but it is substantially weaker than the five-year NCE marketing exclusivity applicable to traditional, small-molecule drugs established under the Hatch-Waxman Act.¹⁸⁸ Under the proposed marketing exclusivity for new biologics, the FDA may accept and process FOB applications but must withhold grant of final approval until the exclusivity has run.¹⁸⁹ The biosimilar applicant and the FDA may begin relying on data contained in the innovator’s application when the innovator receives approval.¹⁹⁰ This, in effect, precludes a de facto patent term extension like the one created by the NCE marketing exclusivity.¹⁹¹ In some instances, an innovator biologic may obtain a three-year exclusivity similar to an OCS exclusivity, but only if the applicant conducted new clinical investigations that resulted in a “significant therapeutic advance.”¹⁹² Generally, new indications for previously approved biologics will be granted a six-month extension of marketing exclusivity, and only one extension may be granted for a particular biologic.¹⁹³ The bill contains an adjustment provision that would shorten the extension to just three months for commercially successful biologics with annual sales exceeding \$1 billion.¹⁹⁴

The sharpest difference between the Waxman and Eshoo bills is the length of

183. THOMAS, *supra* note 14, at 637.

184. HEALTH CAN., DATA PROTECTION UNDER C.08.004.1 OF THE *Food and Drug Regulations* § 3 (2009).

185. *Id.* § 3.1.

186. *Id.* § 3.2.

187. See James N. Czaban & Robert J. Scheffel, Wiley Rein LLP, Waxman Bill Brings Controversial New Concepts and Questions to Biosimilars Debate (Mar. 13, 2009), <http://www.wileyrein.com/publications.cfm?sp=articles&id=4587>.

188. Hogan & Hartson LLP, *supra* note 149, at 1–2.

189. Czaban & Scheffel, *supra* note 187.

190. *Id.*

191. *Id.*

192. H.R. 1427, 111th Cong. § 3(a)(2) (2009).

193. *Id.*

194. *Id.*

marketing exclusivities. The Eshoo bill grants innovators a twelve-year marketing exclusivity, and the FDA may not accept a competing FOB application for at least four years.¹⁹⁵ The base twelve-year term may be increased to fourteen years if the innovator secures FDA approval for “a significant improvement, compared to marketed products.”¹⁹⁶ The proposed twelve- to fourteen-year marketing exclusivity could exceed the patent term remaining after FDA approval, lengthening the monopoly by the time period the exclusivity extends beyond patent protection.¹⁹⁷ This would increase the term of monopoly protection to about thirty years, which is 50% longer than standard patent protection, and 30% longer than monopoly protection for brand name chemical drugs.¹⁹⁸ The effect of marketing exclusivities on the market is currently limited because most run concurrent to and expire before the corresponding patents.¹⁹⁹ If the Eshoo bill is passed, marketing exclusivities could potentially extend the statutory monopoly years beyond patent expiration.

Awarding what amounts to a second effective patent term that is automatically enforced by the FDA would be a gross overcorrection to a problem Congress has addressed. Congress has already enacted provisions within the Hatch-Waxman Act to compensate research entities for the patent term lost while seeking FDA approval.²⁰⁰ The justification put forth by innovators for such a sharp increase in data protection for biologics is that, by the time the innovator finally secures FDA approval and is able to market the product, the limited term of patent protection is insufficient to obtain an adequate return on investment before FOBs enter the market and deflate prices.²⁰¹ However, market entry of FOB products has not resulted in the same price deflation as traditional generics. When Sandoz launched a FOB recombinant human growth hormone called Omnitrope in Germany, the price was only 20% lower than that of the innovator product.²⁰² In Australia, Omnitrope is priced approximately 25% less than the innovator product.²⁰³ Studies show that for the United States, FOBs will sell for only 10%–20% less than the innovator product, a much less drastic price drop than the 40%–80% typically seen for chemical generics.²⁰⁴ Hence, even after entry of FOB products, innovators should still be able to realize substantial profits.

195. H.R. 1548, 111th Cong. § 101(a)(2) (2009).

196. *Id.*

197. KOTLIKOFF, *supra* note 39, at 6.

198. Laurence Kotlikoff, Op-Ed, *Clearing the Way for Low-Cost Biogenerics*, BOSTON GLOBE, Oct. 26, 2008, available at http://www.boston.com/bostonglobe/editorial_opinion/oped/articles/2008/10/26/clearing_the_way_for_low_cost_biogenerics/.

199. THOMAS, *supra* note 35, at 13.

200. Codified in 35 U.S.C. § 156 (2006).

201. *Pathway for Biosimilars Act Protects Patients, Promotes Competition, Preserves Innovation and Creates Quality Jobs, Lilly Says*, PR NEWSWIRE, Mar. 17, 2009, <http://www.bloomberg.com/apps/news?pid=conewsstory&refer=conews&tkr=LLY%3AUS&sid=acyg5iSk5xz4>.

202. Sensabaugh, *supra* note 117, at 189.

203. *Id.*

204. *See, e.g.,* SCHACHT & THOMAS, *supra* note 10, at 23.

The Eshoo bill proposes extending the monopoly to safeguard incentives to develop new biologics.²⁰⁵ A 2007 Duke study concluded that it would take between 12.9 and 16.2 years before the innovator breaks even and obtains the investors' expected rate of return on new biologics.²⁰⁶ The study suggests aligning marketing exclusivity terms with the break-even times to encourage biologics innovation.²⁰⁷ However, the break-even time is highly sensitive to certain assumptions underlying the economic model in the Duke study,²⁰⁸ and the study's findings have been criticized as inaccurate due to flawed assumptions.²⁰⁹ An alternate study, funded by Teva Pharmaceuticals, utilized the same analytical framework under a different set of assumptions and concluded that a seven-year marketing exclusivity would be sufficient.²¹⁰ The sharp contrast in results utilizing the same model undercuts the persuasiveness of the break-even time argument by either side.

Conversely, offering shorter data protection for biologics would fail to compensate for the additional risks undertaken by biologics innovators. Even utilizing the same marketing exclusivity framework for both biologics and small-molecule drugs would overlook the fundamental differences between the two. The average cost of developing a new biologic is \$1.2 billion,²¹¹ compared to \$802 million for traditional pharmaceutical drugs.²¹² Furthermore, the Duke study found that while biologics have a higher rate of clinical success overall, they have a lower risk of success in late-stage clinical trials,²¹³ meaning biologics are more likely to fail after substantial resources have already been invested. On average, the FDA takes longer to approve innovator biologics—and, therefore, depletes more of the patent term—than traditional chemical drugs.²¹⁴ A study by Tufts University found that the process of clinical development and FDA review takes about eight months longer for a biologics product than traditional pharmaceutical products.²¹⁵ While an eight-month delay may seem minimal, this loss in effective patent term while waiting for regulatory

205. See, e.g., Crowell & Moring LLP, *supra* note 177.

206. Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERY 479, 486 (2008), available at <http://fds.duke.edu/db?attachment-25—1301-view-503>.

207. *Id.* at 487.

208. *Id.* at 486.

209. Posting of Donald Zuhn to Patent Docs, <http://www.patentdocs.org/2008/11/white-paper-from-former-house-ways-and-means-economist-finds-7year-data-exclusivity-period-to-be-suf.html> (Nov. 20, 2008, 23:49 EST).

210. ALEXANDER BRILL, PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS: A CRITIQUE 4, 11 (2008), http://www.tevad.com/Brill_Exclusivity_in_Biogenics.pdf.

211. Tufts Ctr. for the Study of Drug Dev., *Average Cost To Develop a New Biotechnology Product Is \$1.2 Billion*, Nov. 9, 2006, <http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69>.

212. Tufts Ctr. for the Study of Drug Dev., *Innovative R&D Strategies Remain Key to Developing New Medicines*, Jan. 5, 2005, <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=51>.

213. Grabowski, *supra* note 206, at 482.

214. See ELAINE WHITMORE, DEVELOPMENT OF FDA-REGULATED MEDICAL PRODUCTS: PRESCRIPTION DRUGS, BIOLOGICS, AND MEDICAL DEVICES 47 fig. 4.1, 48 fig. 4.2 (2004).

215. Tufts Ctr. for the Study of Drug Dev., *supra* note 212.

review is worth about \$312 million in product sales.²¹⁶

Unlike European Union and Canadian laws, the Waxman and Eshoo bills are both sympathetic to the additional risks incurred by FOB manufacturers and contain marketing exclusivity provisions for the first FOB manufacturer that demonstrates interchangeability with a reference biologic product.²¹⁷ Neither the European Union nor Canada awards any type of marketing exclusivity to generic drug and FOB manufacturers. In contrast, the Waxman bill contains a 180-day marketing exclusivity for the first FOB applicant to demonstrate interchangeability with a reference product.²¹⁸ During this time, the FDA cannot make another interchangeability determination for the same reference product, regardless of whether the subsequent application is from a generic manufacturer or the original innovator.²¹⁹ Under the Eshoo bill, the first FOB applicant to demonstrate interchangeability receives a two-year marketing exclusivity beginning either when interchangeability is determined or if marketed afterward, when the marketing first commences.²²⁰ During this period, the FDA will not make an interchangeability determination for the same reference product.²²¹ Because the interchangeability determination is separate and subsequent to biosimilarity approval, there may be several comparable biologics on the market seeking an interchangeability designation. A longer marketing exclusivity for the first interchangeable FOB would incentivize development of fully substitutable FOBs where it otherwise may not be economically viable.

The cost of developing FOBs is substantially higher than the cost of developing a traditional generic drug. For FOBs, this cost is estimated to be \$10–\$80 million, whereas for a traditional generic drug, this cost is \$1–\$2 million.²²² Additionally, some experts believe that due to the inherent complexity of biologics products, FOBs will likely also take longer than small-molecule generics to get FDA approval even if an abbreviated pathway is established, providing a de facto monopoly extension without legislative intervention.²²³

VI. PIECING IT TOGETHER: A PROPOSED FRAMEWORK FOR BIOLOGICS

A. BIOSIMILARITY

Each of the widely divergent approaches to abbreviated pathways for FOB approval discussed in the previous section represents a perceived compromise

216. See DRUG AND BIOLOGICAL DEVELOPMENT 18 (Ronald P. Evens ed., 2007) (writing that lost sales awaiting regulatory review costs the company an average of \$1.3 million per day).

217. See H.R. 1427, 111th Cong. § 3(a)(2) (2009); H.R. 1548, 111th Cong. § 101(a)(2) (2009).

218. Posting of Kurt R. Karst to FDA Law Blog, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/03/rep-waxman-introduces-followon-biologics-bill-legislation-hews-closely-to-hatchwaxman-exclusivity-pa.html (Mar. 11, 2009, 11:15 EST).

219. *Id.*

220. H.R. 1548 § 101(a)(2).

221. *Id.*

222. Sensabaugh, *supra* note 117, at 189.

223. See, e.g., KOTLIKOFF, *supra* note 39, at 4.

and balance among the interests of innovators, follow-on manufacturers, and consumers. The question remains: What approach should the United States adopt? Establishing a biosimilarity standard that requires a high degree of comparability, as opposed to the inflexible bioequivalence standard, makes the most sense for biologics. Biologics are made from living cells, as opposed to traditional chemical synthesis, so establishing equivalence would require extremely rigorous testing and clinical trials.²²⁴ U.S. policymakers should take into consideration that while most biologics today may require clinical trials to demonstrate comparable safety, efficacy, and immunogenicity,²²⁵ some experts believe researchers will eventually develop the capability to fully reverse engineer naturally derived biologics products.²²⁶ As science continues to advance rapidly, it would be impractical to enforce a bioequivalence standard for biologics and bind the FDA to the scientific understanding as it exists today.²²⁷ The biosimilarity standard adopted by the United States should provide the FDA with the flexibility to adapt to evolving technology, rather than make it wait for the law to catch up.

The standard proposed in the Waxman bill provides the highest degree of flexibility, affording the regulatory agency broad discretion in determining what type of data is required.²²⁸ Canada's draft guidance is more stringent and requires a showing that the active ingredient, dosage form, strength, route of administration, and approach to manufacture are the same for both the SEB and reference biologic.²²⁹ It places the burden on the applicant to show that the knowledge and technology exist to detect potential product differences.²³⁰ The European Union requires substantial testing to demonstrate immunogenicity, quality, safety, and efficacy.²³¹ It also requires the applicant to show that the manufacturing process is comprehensive and reliable.²³² At the far end of the spectrum is the Eshoo bill, which places enormous emphasis on a regimented system of FDA formal guidance after a period of public comment.²³³

A flexible similarity standard incorporating elements of each approach would strike the proper balance between the innovator biologic and follow-on manufacturing industries. Under this proposed model for an abbreviated biologics

224. Mark J. Belsey et al., *Biosimilars: Initial Excitement Gives Way to Reality*, 5 NATURE REV. DRUG DISCOVERY 535, 535 (2006).

225. Cathy Dombrowski, *Most Biosimilars Would Need Clinical Trials, ASCO Tells House Panel*, PINK SHEET, Jun. 9, 2008, available at <http://www.fdalegislativewatch.com/2008/06/most-biosimilar.html>.

226. Gitter, *supra* note 5, at 604.

227. See H. COMM. ON ENERGY AND COMMERCE, Q'S AND A'S ON THE "PROMOTING INNOVATION AND ACCESS TO LIFE-SAVING MEDICINE ACT" 1 (2009), http://energycommerce.house.gov/Press_111/20090311/Generic%20Biologics%20Q%20and%20A.pdf.

228. H.R. 1427, 111th Cong. § 3(a)(2) (2009).

229. HEALTH CAN., *supra* note 120, §§ 1.2, 2.1.3.

230. *Id.* § 2.3.1.4.

231. Kaldre, *supra* note 1, ¶ 21.

232. EMEA, *supra* note 106, at 4.

233. H.R. 1548, 111th Cong. § 101(a)(2) (2009).

licensing application (ABLA) pathway, the biosimilarity standard requires two showings. First, the applicant must show there are no clinically meaningful differences, including in immunogenicity, between the proposed FOB product and the reference innovator biologic for each condition of use for which FOB approval is sought. This means there are no increased risks in terms of efficacy or safety associated with the FOB as compared to the reference product.²³⁴ The applicant must demonstrate that the two products have highly similar structures and the same mechanisms of action, if known.²³⁵ Second, the applicant must establish the consistency and robustness of the manufacturing process.²³⁶ To rely on either or both the preclinical and clinical data from the innovator, the applicant would have to overcome a presumption that such studies are required for each biologic.²³⁷ The ABLA applicant may do so by convincing the FDA that (1) the technology exists sufficiently to characterize the particular product class to ensure the product's quality, safety, and efficacy and (2) clinical and preclinical data of the reference biologic is relevant to the proposed FOB due to similarities between the two products.²³⁸ The FDA would have broad discretion in determining whether to accept the applicant's argument and waive one or more of the testing requirements.²³⁹ The FDA may issue guidance documents laying out the preclinical and clinical testing requirements for particular product classes. The FDA would also have discretion, on a case-by-case basis, to determine whether the FOB application contains sufficient information to demonstrate biosimilarity.

The ABLA applicant may rely only on the innovator's publicly available preclinical and clinical data. This model would not force innovators to reveal trade secrets to their follow-on competitors. However, this stance is rooted in the assumption that the enablement requirement of biologics patents is dutifully enforced, as discussed in Part III. If innovators are forced to adhere to the enablement requirement and disclose details about their manufacturing processes, then the patent, combined with other publicly available data contained in FDA applications, should allow ABLA applicants to conduct comparability studies.

The policy reasoning behind this ABLA framework is that allocating the initial burden to the applicant to convince the FDA that appropriate techniques exist to predict the effects of differences between the FOB and reference biologic is the most efficient solution. The ABLA applicant would be in the best position to know what state-of-the-art technology exists for characterizing the product class associated with his product because he likely used the technology during the course of product development. This model places a great deal of

234. See H.R. 1427, 111th Cong. § 3(a)(2) (2009) (but incorporating the explicit immunogenicity requirement of the Eshoo bill).

235. See H.R. 1427 § 3(a)(2).

236. See EMEA, *supra* note 106, at 4.

237. See H.R. 1548 § 101(a)(2).

238. See HEALTH CAN., *supra* note 120, § 2.3.1.4.

239. See H.R. 1427 § 3(a)(2).

responsibility in the hands of the FDA's technical experts. They are the primary gatekeepers and must ground their biosimilarity determinations in technical data and generally accepted scientific principles. If this framework were to be implemented today, it would likely be difficult for ABLA applicants to waive clinical studies entirely. As science continues to develop, the FDA should issue clear guidance documents for particular product classes based on experience and collective knowledge accrued from previous decisions. These documents will serve as roadmaps for future ABLA applicants, expediting FDA decisions regarding clinical trial waivers. This feature incorporates the emphasis on formal guidance documents found in the European Union's system and the Eshoo bill, but uses the documents to facilitate future FOB approval, rather than bar application if FDA has not yet issued the guidance document. As a result, well-characterized FOBs will enter the market much faster and at a lower cost, without risking public safety.

Moving away from a standard of bioequivalence to one of biosimilarity has patent law implications. Under the Hatch-Waxman regime, an ANDA applicant must essentially concede its product is the "same" as the pioneer product, which necessarily implicates patents covering the original product.²⁴⁰ Therefore, the ANDA itself reinforces the underlying patent rights by bolstering the patent proprietor's case in the event of patent infringement litigation.²⁴¹ Under a biosimilarity standard, the applicant is not claiming his product is the "same," merely that it is comparable.²⁴² In a patent infringement case, he could successfully assert that the FOB does not infringe any of the innovator's patents. This problem extends more from the nature of biologics products themselves than the biosimilarity standard. Though making the case against an ABLA applicant may be more difficult than against an ANDA applicant, the standard of proof for a patent infringement claim remains the same. If the biologics patents are properly enabling (as discussed in Part III), then the intricacies of the process may require a narrowly tailored set of claims, and the patent may be harder to defend. It is entirely possible that the FOB manufacturer designed around the innovator's patent to create a highly similar product.²⁴³

Ultimately, FDA approval and the patent system are distinct systems with different goals. As discussed in Part III, however, the two regimes may be used in tandem to facilitate speedy and effective approval of FOBs while still protecting patent rights. Reinforcing the enablement requirement in the patent regime could spur development of more advanced characterization techniques that allow patentees to meet the "undue experimentation" standard and preserve the scope of their patents. FOB applicants may use those same techniques to meet FDA standards without extensive preclinical and clinical testing.

240. Manheim, *supra* note 96, at 396.

241. *See id.*

242. *See id.* at 401.

243. *See id.*

In the proposed ABLA framework, there would be a two-tier system of interchangeability. This optional process may take place concurrent with or subsequent to obtaining marketing approval as a biosimilar.²⁴⁴ The top tier is for biogenerics, which are interchangeable for each condition of use described, recommended, or suggested for the reference product.²⁴⁵ A biogeneric determination would require the applicant to show that (1) his product is biosimilar to the reference biologic; and (2) for multiple-dose treatments, the patient may be switched from one product to the other without an increased risk of adverse effects for all indications for which the reference biologic is approved. An approved biogeneric would be assigned a generic or similar name, which would facilitate marketing of the product. A biogeneric is, by definition, interchangeable for all indications for which the reference product is approved, meaning there is minimal risk to public safety because of confusion between a similarly named biogeneric and the innovator product.

The lower tier of interchangeability would be called “Selectively Interchangeable Follow-Ons,” or SIFOs. A SIFO determination requires the applicant to show that (1) the product is biosimilar to the reference biologic and (2) for multiple dose treatments, the patient may be switched from one product to the other without an increased risk of side effects for only certain indications for which the reference product has been approved. Due to safety concerns arising from the possibility that a SIFO may be prescribed for an unapproved indication, SIFOs will be assigned a unique name, distinct from that of the reference biologic, and the product itself must be labeled so as to indicate clearly which clinical uses have been approved for interchangeability. The product packaging for a SIFO should be easily distinguished from that of the reference biologic so as to minimize confusion.

Just as for biosimilarity, the FDA has broad discretion to determine whether the criteria for biogeneric or SIFO designation have been met, but the decision must be based on available scientific data.²⁴⁶ This flexible approach would allow the FDA to adapt to rapidly changing technology. The two-tiered structure will facilitate market entry of biogenerics because the FOB manufacturer could take advantage of the innovator’s marketing efforts while still allowing SIFOs to be selectively substituted. The FOB manufacturer will have to conduct its own product marketing because SIFOs are given unique names.²⁴⁷

B. PROPOSED MARKETING EXCLUSIVITY FRAMEWORK

The optimal solution to the marketing exclusivity problem would compensate research entities for taking on the investment risks in order to develop new

244. See H.R. 1427, 111th Cong. § 3(a)(2) (2009).

245. See H.R. 1548, 111th Cong. § 101(a)(2) (2009).

246. See H.R. 1427 § 3(a)(2).

247. Thomas Gryta, *Generic Biologics Face Hurdles*, WALL ST. J., Mar. 4, 2009, available at <http://online.wsj.com/article/SB123614292238326905.html>.

innovator biologics and interchangeable FOBs, but this consideration must be weighed against society's interest in promoting market competition and access to affordable medicines.

In the proposed framework, innovators that receive BLA approval may apply for a New Biologic Entity (NBE) exclusivity. To account for the 50% increase in development costs for innovator biologics, the NBE exclusivity term would be set to a base period of seven-and-a-half years, a 50% increase over the NCE exclusivity base term. The implementation of the NBE exclusivity would mimic the European Union system and essentially be a "5+2.5+1" rule. For the first five years of the NBE exclusivity, the FDA may not accept competing applications that rely on the innovator's data, namely ABLAs. After the initial five-year period of marketing exclusivity, ABLA applicants may submit applications to the FDA, but the agency will not award final approval until the full term of marketing exclusivity has run. The innovator may apply for a one-year extension if it conducts or sponsors clinical investigations resulting in a significant new indication. This extension may be granted just once per biologic product and would apply only to the new indication. The marketing exclusivity will have no impact on applicants who utilize the full BLA pathway.

This approach is intended to give the innovator sufficient time to recoup his investment, while minimizing the delay for eventual market entry by FOBs by allowing the FDA to begin ABLA regulatory review before the NBE exclusivity expires. The proposal also takes into account the reality that requiring narrower patents may discourage investment in new biologics. Awarding a longer marketing exclusivity offers an assurance of data protection that may otherwise be lacking.²⁴⁸ This certainty would reduce financial risks and encourage investment by venture capitalists and other potential investors.²⁴⁹

Marketing exclusivities granted to the first FOB manufacturer to successfully demonstrate interchangeability with a reference biologic would vary depending on the type of interchangeability designation. The first ABLA applicant to obtain lower-tier approval as a SIFO for a reference biologic would receive a six-month marketing exclusivity, during which time the FDA may not make any other SIFO determinations using the same reference biologic for the same conditions of use. The FDA, however, may make a SIFO determination for conditions of use not covered under the marketing exclusivity, and it may grant interim approval for protected conditions of use. Also, the FDA may approve applications for biogeneric determination using the same reference biologic. For example, assume that the innovator biologic is approved for indications 1, 2, 3, and 4. FOB manufacturer A obtains FDA approval as a biosimilar and positive SIFO determinations for indications 1 and 2. A is the first to receive SIFO designations for indications 1 and 2 and is awarded a six-month marketing exclusivity. Before A's marketing exclusivity expires, FOB manufacturer B

248. See SCHACHT & THOMAS, *supra* note 10, at 14.

249. *Id.*

applies for SIFO determinations for indications 2 and 3. The FDA may accept the application and grant SIFO status for indication 3. It may grant tentative approval to B for indication 2, which becomes final immediately after A's marketing exclusivity expires. This prevents B from having to file multiple SIFO applications. At any time during the term of A's marketing exclusivity, the FDA may accept and make a *biogeneric* determination as to manufacturer C's FOB, which is interchangeable for all approved indications 1, 2, 3, and 4.

The first ABLA applicant to obtain top-tier approval as a biogeneric for a reference biologic product would get a three-year marketing exclusivity, during which the FDA may not make any interchangeability determinations—biogeneric or SIFO—for the same reference product. The FDA may accept and review applications for biogeneric or SIFO designations, but any approval is effective only after the biogeneric marketing exclusivity has run. A biogeneric marketing exclusivity will have no effect on SIFO marketing exclusivities that were granted *prior to* the grant of the biogeneric marketing exclusivity. This would leave marketing exclusivities awarded for previously approved SIFOs intact. The longer marketing exclusivity is intended to incentivize development of fully interchangeable biologics, even though there may be several SIFOs already on the market.

CONCLUSION

The vague patents currently protecting many biologics products must be brought in compliance with the existing patent regime. An enabling patent is a critical component to the bargain that society has struck with the inventor in exchange for a temporary monopoly. Allowing the USPTO to continue to grant nonenabling patents hinders innovation and the progress of science. The argument that more clearly defined specifications would result in weaker patents is not compelling enough to justify changing patent laws to allow patents that do not teach others how to make or use the invention. The drafters of the Constitution gave Congress the authority to grant patent rights in order to promote innovation,²⁵⁰ not create monopolies that unfairly stifle competition. To relax the enablement requirement that would otherwise foster technical progress and innovation would result in inadequate disclosure for the sake of reinforcing monopolies. Instead, Congress should follow the Federal Circuit's lead and strictly enforce the existing enablement standard.

An abbreviated pathway for regulatory approval of FOBs is critical to providing the best available healthcare to as many consumers as possible. While currently not all biologics may be adequately characterized without clinical trials, technology will continue to progress, and new characterization methods may emerge that can fully displace the need for clinical trials. The most effective regulatory approval framework would allow the FDA to rapidly

250. U.S. CONST. art. I, § 8.

change its technical guidelines to keep pace with evolving technology without having to wait for notice and public comment. The ABLA regime proposed in this paper would give the FDA flexibility while at the same time ensuring patient safety by imposing a presumption, rebuttable by the ABLA applicant, that clinical trials are necessary and requiring the FDA to base its determinations in scientific data. The proposed two-tiered approach to interchangeability would promote the development of truly generic versions of biologics (biogenerics) while still facilitating patient access to substitutes that are only selectively interchangeable (SIFOs).

A longer marketing exclusivity would compensate research entities for investing in the discovery of new biologics, which are more costly to develop than traditional chemical drugs. However, the marketing exclusivity should not artificially create a second effective patent term. The ABLA framework handles this problem in a straightforward manner. A new biologic that is, on average, 50% more expensive to develop than a small molecule NCE will receive a 50% longer marketing exclusivity. The NBE exclusivity, however, would permit the FDA to process ABLA applications after five years to minimize the duration of the de facto monopoly that would result while the ABLA applicant awaits approval. Awarding marketing exclusivities to the first SIFO or biogeneric manufacturer provides an incentive to develop cheaper alternatives to the innovator product. Biogenerics will probably take longer to develop, meaning other SIFOs may already be on the market by the time the FDA grants approval. A longer marketing exclusivity for the first manufacturer of a biogeneric for a given reference product would provide the necessary incentive to invest in developing fully interchangeable FOBs.