

NOTE

FDA APPROVAL OF GENERIC BIOLOGICS: FINDING A REGULATORY PATHWAY

*Kathleen R. Kelleher**

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Biologics are becoming increasingly important for the potential treatment of widespread diseases such as cancer, anemia, and diabetes. As hundreds of biologics are going off-patent, the market has become ripe for the introduction of generic biologics. A regulatory pathway for biogenerics, however, is virtually non-existent. The purpose of this paper is thus to analyze how a successful legislative pathway for generic biologics might be designed. The current regulatory scheme, economic concerns, health and safety concerns, and the need to provide proper incentives for innovation are analyzed. Finally, recent Congressional bills are outlined and critiqued, through which the structure of a successful pathway for biogeneric approval can be understood.

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* J.D., expected May 2008, University of Michigan Law School; M.Eng., 2005, Materials Science and Engineering, Massachusetts Institute of Technology; S.B., 2004, Materials Science and Engineering, Massachusetts Institute of Technology. Many thanks to Professor Rebecca Eisenberg for her help with this Note.

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INTRODUCTION

Biologics are an important part of America's health care system today. They are used for the treatment of such serious or life-threatening diseases as lung cancer, colorectal cancer, diabetes, and anemia.¹ So far, over 150 new biologics have been approved by the FDA, which have provided care for over 325 million patients.² The FDA, however, has long been reluctant to approve generic biologics. As early as 1974, the FDA emphasized that every biologic must go through rigorous clinical trials before approval because "all biological products are to some extent different and thus must be separately proven safe, pure and effective. . . . There is no such thing as a 'me-too' biologic."³ Such reluctance has become more apparent today as hundreds of biologics are going off patent, but only a handful of generic biologics have been approved.⁴ At the heart of the FDA's reluctance to approve generic biologics is the inherent difficulty in determining whether generic biologics are as safe and effective as their pioneer counterparts. As the FDA struggles to find safe and effective generic biologics, however, the average cost of critical biologics continues to soar at a rate far surpassing that of traditional drugs.⁵ The challenge is thus to find a way to get biogeneric products approved while still maintaining the safety and efficacy standards set forth by the FDA. This paper will explore the generic biologic market, the challenges associated with the current regulatory framework, and how a successful legislative pathway for generic biologics might be designed.

1. Backgrounder on Biologics, http://www.waxman.house.gov/pdfs/summary_generic_biologics_9.29.06.pdf (last visited Oct. 18, 2007).

2. *Id.*

3. Wayne. H. Matelski, *Generic Biologics: Outline of Legal and Regulatory Issues*, 760 PRACTICING L. INST. PATS. COPYRIGHTS TRADEMARKS & LITERARY PROP COURSE HANDBOOK SERIES 291, 300 (2003) (quoting Preamble to FDA's Final Regulations Implementing the Freedom of Information Act, 39 Fed. Reg. 44,602 44,641 (Dec. 24, 1974)).

4. See David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 199 (2005).

5. See Backgrounder on Biologics, *supra* note 1.

I. BIOLOGICS

Biologics are complex substances that are derived from living sources. Defined under the Public Health Service Act (PHSA), a biological product is characterized as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”⁶ Examples of biologics include insulin, some vaccines, and monoclonal antibodies, which can be useful for the treatment of cancer, anemia, diabetes, hepatitis, and multiple sclerosis.⁷ Biologics are in contrast to traditional drugs, which are chemically synthesized.

Biologic product sales are continually increasing, with U.S. product sales in 2005 jumping 17.2% to \$32.8 billion and expected sales in 2006 to top \$56 billion.⁸ Furthermore, global sales are forecast to reach \$105 billion by 2010.⁹ Over the past ten years, the patents of more than a dozen high-profit biologics have expired, resulting in over \$11.5 billion in combined annual sales of off-patent biologics.¹⁰ Despite the patent expirations, biologics manufacturers continue to enjoy an effective monopoly due to the lack of generics on the market.

The market is thus ready for the introduction of biogeneric products. However, there are significantly greater barriers to market entry for generic biologics than for generic chemical entities, including both enhanced marketing strategies to overcome consumer hesitation regarding biologic materials and higher investment requirements. See Figure 1.

6. 42 U.S.C. § 262(i) (2004).

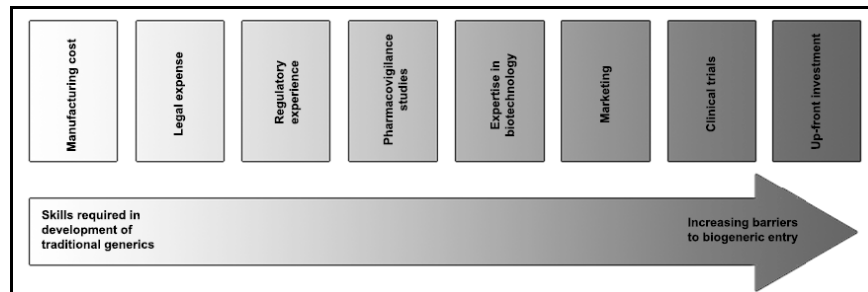
7. Alix Weisfeld, *How Much Intellectual Property Protection Do the Newest (and Coolest) Biotechnologies Get Internationally?*, 6 CHI. J. INT'L L. 833, 834 (2006).

8. Gregory Roumeliotis, *FDA Under Pressure to “Open the Floodgates” for Biogenerics* (2006), <http://www.in-pharmatechnologist.com/news/ng.asp?n=69925-fda-biogenerics-insulin-hgh-omnitrope>; Weisfeld, *supra* note 7, at 834.

9. Mark Belsey et al., *Biosimilars: Initial Excitement Gives Way to Reality*, NATURE REVIEWS DRUG DISCOVERY, July 2006, at 535.

10. Meredith Wadman, *Copycats Gear up to Dog Biotech Brands*, NATURE, Oct. 5, 2006, at 496.

FIGURE I
BARRIERS TO THE DEVELOPMENT OF BIOGENERICS¹¹



The most significant barrier to entry for generic biologics is the current regulatory scheme. As a result of their complex manufacturing process, biological products vary significantly in complexity, size, and heterogeneity from chemically synthesized drugs.¹² Such complexity has made finding a generic pathway for biologics under the current system difficult. Without an approval process for generic biologics, the costs and barriers to market entry for generic biologics are essentially insurmountable.

II. CURRENT REGULATORY FRAMEWORK

A. *Public Health Service Act vs. Food, Drug, and Cosmetic Act*

The current regulatory scheme for biologics is not well-suited to handle generic entry. Most biologics are not regulated as new drugs under the Food, Drug, and Cosmetic Act (FDCA), but are instead licensed under section 351 of the Public Health Service Act (PHSA) and evaluated by the Center for Biologics Evaluation and Research (CBER).¹³ Under the PHSA, a biologics license (BLA) must be obtained for all biologics, which requires a showing that the product is safe and pure, and that the facility for manufacturing is designed to assure such characteristics.¹⁴ The PHSA does not currently contain a provision for generic approval.

11. Belsey, *supra* note 9, at 536.

12. See Metalski, *supra* note 3, at 301.

13. See 42 U.S.C. § 262 (2007).

14. *Id.*

Some biologics, however, such as insulin and human growth hormone, are regulated as new drugs under the FDCA.¹⁵ While there is no clear explanation for why these biologics are regulated under the FDCA, such delegation to the FDA does seem reasonable under the FDCA's definition of a "drug," which includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man."¹⁶ This regulation of biologics under the FDCA suggests that the FDCA provisions regarding generic entry of traditional drugs, called the Hatch-Waxman provisions, could potentially be suitable for the regulation of biologics.

B. Hatch-Waxman 505(j)

The first possible route for generic biologic approval under the Hatch-Waxman Act is through section 505(j) of the FDCA, under which a generic applicant is permitted to file an abbreviated new drug application (ANDA). An ANDA will be accepted by the FDA without proof of safety and efficacy if the generic manufacturer can show, among other requirements, bioequivalence between the generic and pioneer drug.¹⁷ Bioequivalence allows some variation in the route of administration, strength, or dosage form, but always requires possession of the "same" active ingredient.¹⁸ The courts have generally left the determination of "sameness" under section 505(j) solely in the hands of the FDA, noting that the FDA is entitled to a "high level of deference" for "evaluations of scientific data within its area of expertise."¹⁹ While the FDA originally interpreted "sameness" rather leniently,²⁰ the term is now generally interpreted to require absolute chemical identity.²¹ Such equivalence is often inapplicable to inherently complex and variable biological products. Furthermore, the FDA appears to have foreclosed the applicability of ANDAs to biologics approved under the PHSA when it stated that "an abbreviated application will usually be reserved for duplicates of drug

15. Andrew Wasson, *Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biological Products*, 2005 DUKE L. & TECH. REV. 0004, ¶ 9, <http://www.law.duke.edu/journals/dltr/articles/2005dltr0004.html>.

16. 21 U.S.C. § 321(g)(1)(B) (2004).

17. 21 U.S.C. § 355(j) (2004).

18. *See id.*

19. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)).

20. *See id.* at 1318.

21. *See* Melissa R. Leuenberger-Fisher, *The Road to Follow on Biologics: Are We There Yet?*, 23 BIOTECHNOLOGY L. REP. 389, 395 (2004).

products previously approved under a full application.”²² Thus, 505(j) has been effectively eliminated as a means for generic biologics approval.

C. Hatch-Waxman 505(b)(2)

A more commonly used section of the Hatch-Waxman Act for getting approval for generic biologics has been section 505(b)(2) of the FDCA. The generic version of a small number of biologics, such as a recombinant follitropin beta (Follistim®), recombinant human glucagon (Glucagen®), and human growth hormone (Omnitrope), have already successfully gained approval through this section.²³ Section 505(b)(2) provides a sort of hybrid between a new drug application (NDA) and an ANDA, whereby applicants may rely on the investigations conducted by a third party, including the pioneer manufacturer, to show the safety and efficacy of their own products.²⁴ While the applicant is required to prove the “relevance and applicability” of any previous clinical findings, he is not required to perform many of the trials himself and, thus, avoids much of the cost associated with obtaining FDA approval of a new drug. Furthermore, the statutory language of 505(b)(2) nowhere requires bioequivalence, though the products must be similar enough that the safety and efficacy standards can be legally and scientifically applicable to a new drug.²⁵ This section is therefore, perhaps, a more likely regulatory pathway for getting biogenerics to the market because it allows more leeway for the natural variation of biological products.

Such an approach seemed promising in *Berlex Laboratories, Inc. v. FDA*, where the District Court of D.C. confirmed that biological products could be legally approved under section 505(b)(2).²⁶ The court in *Berlex* upheld the FDA’s approval of Avonex, a “generic” of Berlex’s interferon beta-1a product. The FDA’s approval was based upon evidence of comparability between the two products that included physicochemical comparability, similarity of vivo activities, and equivalent pharmacokinetics in humans.²⁷ The FDA’s decision regarding Avonex, and the district court’s approval of it, was of particular importance because it marked the first time that the FDA had found two different cell lines to be similar. However, this decision essentially marks the first and only time that the FDA has taken such a position. Since

22. Dudzinski, *supra* note 4, at 197 (citing New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7466, 7497 (Feb 22, 1985) (codified at Abbreviated Application, 21 C.F.R. § 314.55)).

23. *Id.* at 199.

24. *See* 21 U.S.C. § 355(b)(2) (2004).

25. Dudzinski, *supra* note 4, at 214.

26. 942 F. Supp. 19 (D.D.C. 1996).

27. *Id.* at 22.

then, the FDA has steadfastly refused to approve generic versions of complex biologic products under section 505(b)(2).²⁸

Aside from the FDA's hesitancy to approve complex biologics under 505(b)(2), use of this regulatory pathway poses another problem for generic biologics: use of the provision would require that biologics either be approved as "new drugs" under the FDCA or that the Hatch-Waxman provisions extend to biologics approved under the PHSA. Most biologics, however, are approved under the PHSA. And while an extension of the Hatch-Waxman to the PHSA does not seem contradictory to statutory language, as section 262(j) of the PHSA emphasizes that the FDCA still applies to biological products that are also regulated under the PHSA,²⁹ the FDA has so far refused to take such a view. As the agency recently emphasized, "there is no abbreviated approval pathway . . . for produce products licensed under section 351 of the Public Health Service Act."³⁰ Section 505(b)(2) is consequently an unlikely pathway for generic approval of biologics.

III. LEGISLATION

A. Need for New Legislation

A recent decision by the District Court of D.C. in *Sandoz Inc. v. Leavitt* had many generic manufacturers believing that there was soon to be a pathway for getting generic biologics through the approval process.³¹ By ordering the FDA to respond to Sandoz's application for approval of Omnitrope, a generic biologic used to treat growth disorders, the court attempted to force the FDA to deal with the growing confusion surrounding approval of generic biologics. However, while the FDA approved Omnitrope, it has aggressively appealed the district court's decision to the Federal Circuit.³² Furthermore, in granting its approval, the agency asserted that it was approving Omnitrope not as a generic biologic, but as a relatively simple "follow-on protein product."³³ The FDA emphasized that the approval did "not establish a pathway for approval of follow-on products for biological products . . . nor does it mean that more complex and/or less well understood proteins approved as

28. See Omnitrope Questions and Answers, <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm> (last visited Nov. 4, 2007).

29. 42 U.S.C. § 262(j) (2003).

30. Omnitrope Questions and Answers, *supra* note 28.

31. 427 F. Supp. 2d 29 (D.D.C. 2006).

32. *Id.*, appeal filed, No. 1:05CV01810, available at www.orangebookblog.com/files/Omnitrope.pdf.

33. Omnitrope Questions and Answers, *supra* note 28.

drugs under the [FDCA] could be approved as follow-on products.”³⁴ Its warning was reaffirmed in July, 2006 when the agency refused to approve an ANDA for Natestch’s generic version of Miacalcin, a protein-based nasal spray.³⁵

As the leader of one interest group notes, “[i]t has become clear that the FDA will not act on its own to create . . . an abbreviated pathway for all biologic medicines, so it is essential that Congress provide legislative direction.”³⁶ Duplicate non-clinical and clinical testing for similar products is both inefficient and unethical, and the lack of potential generic competition stifles innovation in the biologics industry. Furthermore, the failure to find an abbreviated process for generic biologics has limited generic market entry and led to prohibitively high prices for vital medical products. Taken together, these factors warrant new Congressional legislation. In designing such a statute, however, Congress will have to be mindful of the delicate balance between economic concerns, health and safety concerns, and the creation of proper incentives for innovation.

B. *Economic Concerns*

As Representative Henry Waxman stated in September 2006, “[u]nder our current law, biologic products are effectively given a near-complete monopoly The time has come to break this monopoly. Congress can no longer stand by and watch as our reliance on biologics increases, and the cost of these medicines continues to soar.”³⁷ Because biologics are not faced with generic competition, manufacturers are able to charge up to \$100,000 annually per patient for their products.³⁸ In fact, in 2005, the cost of biologics increased by 17.5%, compared to 10% for traditional drugs.³⁹ These prices have severely inflated health care costs, as evidenced by the fact that the five largest Medicare Part B drug expenditures are all for biologics (including Epogen, Aranesp, Procrit, Remicade, and Neulasta).⁴⁰

Economists have argued that pharmaceutical monopolistic practices create deadweight loss to society that range from \$3 billion to \$5 billion

34. *Id.*

35. Roumeliotis, *supra* note 8.

36. Letter from Travis B. Plunkett, Legislative Dir., Consumer Fed’n of Am., to Henry A. Waxman, U.S. House of Representatives (Sept. 28, 2006) (available at http://www.waxman.house.gov/pdfs/letter_consumer_federation_biologics_9.28.06.pdf).

37. Wadman, *supra* note 10, at 496.

38. See Kathleen Jaeger, *FDA Needs to support Generic Biologics* PHARMACY TIMES, June 2006, at 40, available at <http://www.pharmacytimes.com/Article.cfm?Menu=1&ID=3584>.

39. Backgrounder on Biologics, *supra* note 1, at 2.

40. *Id.* at 1.

dollars.⁴¹ Generic substitution can, however, protect society from some of this deadweight. Fifty-six percent of all prescriptions dispensed in the United States are generics, but they account for only 13% of health care expenditures.⁴² A study by the Congressional Budget Office estimated that the net benefit of savings from generic substitution of prescription drugs per year can range between \$8 billion to \$10 billion dollars.⁴³ Thus, if generic biologics have the same effect on healthcare as traditional pharmaceutical generics, the introduction of generic biologics could save the country billions of dollars.

Some economists, however, have challenged the notion that access to biogenerics will cut prices for consumers. Although generics generally become available for about one-twentieth of the regular price,⁴⁴ the cost of producing and testing biogenerics is likely to be much higher than for traditional drugs. The cost associated with getting a biogeneric to market could be tens of millions of dollars, as compared to a couple of million dollars for traditional generics.⁴⁵ In addition to the higher cost associated with biogeneric development, biologics tend to have smaller target markets for which incentives to entry may not be as high, and they tend to be used to treat life-threatening diseases, for which managed care organizations are often less likely to utilize price control measures.⁴⁶ As a result, some economists argue that very few biogeneric companies are likely to emerge, making price drops for consumers unlikely in the near future.⁴⁷ Such concerns, however, may be misplaced. The European Union, which already has a system in place for biogeneric approval, estimates that it will save \$2.8 billion from the market entry of only a few products.⁴⁸ Similarly, Australia, which also has a fast-track mechanism in place for generic biologics, has been successful in decreasing the cost of human growth hormone by 25%.⁴⁹ Therefore, the economic savings on biogenerics displayed in the EU and Australia certainly seem to favor development of a regulatory pathway for generic biologics.

41. Joshua W. Devine et al., *Follow-on Biologics: Competition in the Biopharmaceutical Marketplace*, 46 J. AM. PHARMACISTS ASSOC. 193, 199 (2006).

42. Kathleen Jaeger, President/CEO, Generic Pharm. Ass'n, Windhover FDA/CMS Summit (Dec. 5, 2006), available at <http://www.gphaonline.org/AM/Template.cfm?Section=Media&Template=/CM/HTMLDisplay.cfm&ContentID=3048>.

43. Backgrounder on Biologics, *supra* note 1, at 3.

44. Wadman, *supra* note 10, at 497.

45. Henry Grabowski et al., *The Market for Follow-On Biologics: How Will it Evolve?*, 25 HEALTH AFFAIRS 1291, 1293 (2006).

46. *Id.* at 1294–95.

47. *Id.*

48. Jaeger, *supra* note 42.

49. *Id.*

C. Health and Safety Concerns

Because the economic stakes in the biologics industry are so high, it can be difficult to tell which of the health and safety concerns raised by the various industries are valid. Nonetheless, health and safety concerns are particularly significant for biogenerics as a result of the inherent difference between biologics and traditional drugs. When two chemically-synthesized drugs are proven bioequivalent, their safety and efficacy can be assumed because two identical drugs will consistently produce the same reactions. However, biologics do not have such characteristics. Rather, all biologics possess the potential for immunogenicity,⁵⁰ which can cause both serious side-effects and a loss in efficacy.⁵¹ Even small and undetectable changes can cause significant immune reactions. Slight changes in sequence, glycosylation, process-related impurities, formulation, and storage and handling can all increase immunogenicity.⁵² Because reference biologics will generally have manufacturing processes that are protected by trade secrets, comparable biologics manufacturers will naturally have a different manufacturing process, which could lead to small but significant variations in the safety and efficacy of the final product.⁵³ Therefore, the ability to properly characterize biologics is critical in determining comparability.

Relatively small molecules can be characterized fairly easily through the use of mass spectrometry, infrared spectrometry, nuclear magnetic resonance, x-ray crystallography, and other physical methods.⁵⁴ However, larger biologic molecules can be much more difficult to characterize in detail because they are more variable and complex when they contain active macromolecules.⁵⁵ Analytical tests such as chemical and physical assays can be a starting point for determining the structure, identity, purity, and stability of more complex biologics. While such methods may not always be capable of identifying the functional characteristics of biological products, bioassays may help identify specific functional attributes.⁵⁶ Unfortunately, even the relation between the structure and function of biologics in many instances may not clearly relate to

50. See Matelski, *supra* note 3, at 301.

51. Christian Combe et al., *Biosimilar Epoetins: An Analysis Based on Recently Implemented European Medicines Evaluation Agency Guidelines on Comparability of Biopharmaceutical Proteins*, 25 PHARMACOTHERAPY 954, 955 (2005); Matelski, *supra* note 3, at 301.

52. Combe et al., *supra* note 51, at 955.

53. See Leuenberger-Fisher, *supra* note 21, at 398.

54. Arman H. Nadershahi & Joseph M. Reisman, *Generic Biotech Products: Provisions in Patent and Drug Development Law*, BIOPROCESS INT'L, Oct. 2003, at 26, 27.

55. *Id.* at 27–28.

56. Leuenberger-Fisher, *supra* note 21, at 399.

the safety and efficacy of the product.⁵⁷ Accordingly, the ability to clearly predict the immunogenicity of a biologic entirely through non-clinical means does not exist.

Clinical trials remain the best markers of biologic immunogenicity. However, clinical trials can be extremely expensive. Furthermore, even clinical trials may not be effective in understanding all safety and efficacy concerns, particularly because immune responses to biologics can vary from product to product. Given the uncertainty surrounding the health and safety of biogenerics, any new legislation should give the FDA considerable discretion to establish the scientific criteria necessary to define biosimilarity, and hence, health and safety of a biologic, on a case-by-case basis.

D. Hatch-Waxman Lessons

The mechanisms of the Hatch-Waxman Act have been carefully crafted to balance the need for lower-priced and safe drugs with proper incentives for innovation and development. Aside from the similarity and bioequivalence provisions that affect health and safety concerns regarding generics, the Hatch-Waxman Act provides several provisions that are meant to protect or incentivize either the pioneer or the generic manufacturer. Such provisions are an important consideration in developing a regulatory pathway for generic biologics.

1. New Chemical Entity Exclusivity

The Hatch-Waxman Act gives a five-year data exclusivity period for new chemical entities.⁵⁸ Under the provisions for new chemical entity exclusivity, a generic manufacturer is prohibited from filing an ANDA for five years after the innovator's approval. This prohibition, however, is reduced to four years if the generic manufacturer files a paragraph IV certification stating either that the generic does not infringe a patent or that the innovator patent is invalid.⁵⁹ This provision of the Hatch-Waxman Act was meant to alleviate concerns that a generic pathway would prohibit innovators from realizing the benefits of their investments. Between this new chemical exclusivity and the patent term extensions granted under the Patent Act (which are already applicable to biologics),⁶⁰ the Hatch-Waxman Act appears to have been successful in at least keeping innovators' incentive to invest stable, as brand name pharmaceutical sales and

57. *Id.*

58. 21 U.S.C. § 355(j)(5)(F)(ii) (2000).

59. 21 U.S.C. § 355(j)(5)(F)(ii) (2000); 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2000).

60. 35 U.S.C. § 156(f)(2) (2004).

revenues continued to multiply following the enactment of the legislation.⁶¹

The inherent differences between biologics and traditional drugs may counsel towards even greater exclusivity protection for innovator biologic drugs than for traditional drugs. Biologics cost more to produce than traditional drugs, and thus a five-year market exclusivity similar to the Hatch-Waxman provision may not be long enough to incentivize the development of biologics. Furthermore, while traditional new drugs are generally protected by patents, biologics may be less effectively protected by the patent system. The complexity of most biologics may allow a biogeneric manufacturer to design around an innovator's patents, but still secure regulatory approval through its "biosimilarity" to the pioneer biologic.⁶² Furthermore, the patentability of some biological materials is extremely narrow due to stringent specification and enablement requirements.⁶³ As such, new legislation needs to appropriately protect the innovator investment in biologic products. Some have suggested that a 12-year market exclusivity for pioneer biologics would be optimal because traditional drugs generally have slightly under 12 years of market exclusivity due to patent protection.⁶⁴ Others, of course, would suggest that such an "extension" would be excessive and that the 5-year exclusivity granted to traditional drugs would be more than enough to encourage development in the profitable biologics market. Regardless, new legislation for biogenerics should certainly include some form of new entity exclusivity.

2. 30-Month Stay

Under Hatch-Waxman provisions, if an infringement action is brought against a generic manufacturer, the FDA is required to stay approval of a generic product for thirty months or until a court decision, whichever is shorter.⁶⁵ This provision is meant to provide the innovator with an opportunity to protect its patent rights before the FDA permits generic entry. This provision has been highly criticized, however, because it has arguably led to frivolous patent suits as innovators attempt to keep generic competitors off of the market. A study by the Federal Trade Commission (FTC) demonstrated that such arguments may be well-founded, as 73% of the court cases analyzed resulted in decisions for the

61. Devine, *supra* note 41, at 197.

62. Bruce S. Manheim Jr. et al., "Follow-On Biologics": *Ensuring Continued Innovation in The Biotechnology Industry*, 25 HEALTH AFFAIRS 394, 398 (2006).

63. See, e.g., *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1997); *Genentech v. Novo Nordisk A/S*, 108 F.3d 1361 (Fed. Cir. 1993).

64. Manheim et al., *supra* note 62, at 401.

65. 21 U.S.C. § 355(j)(5)(B)(iii) (2000).

generic drug companies.⁶⁶ Most of the concern regarding the 30-month stay, however, has been alleviated by recent amendments to the Hatch-Waxman Act, which restrict innovators to only one use of the 30-month stay.⁶⁷ As the FTC has noted, one 30-month stay is unlikely to significantly delay generic entry because it historically has accurately approximated the time necessary for the FDA to review and approve an ANDA.⁶⁸

Unfortunately, the stay provision of any new biologics legislation could be prone to more abuse than seen under the Hatch-Waxman Act. Because patents covering biologics may be narrower than for traditional drugs, and because the FDA will certainly continue its hands-off approach to monitoring patent listings, the potential exists for biologic innovators to bring more frivolous suits based upon weakly-related patents. As one 30-month stay is unlikely to delay generic entry, however, legislation providing a pathway for approval of generic biologics should probably include a stay provision. Without such a provision, the strength and enforceability of patent rights may be hindered, and incentive for biologics innovation may be significantly reduced.

3. 180-Day Generic Exclusivity

The Hatch-Waxman Act also gives generic exclusivity to the first generic to get approval of an ANDA through use of a Paragraph IV certification.⁶⁹ The purpose of this exclusivity was to provide an incentive for generic companies to challenge listed patents. The 180-day exclusivity, however, has also been criticized. The biggest concern has traditionally been that generic and pioneer companies are able to take advantage of the 180-day exclusivity by entering into agreements to settle pending patent infringement litigation. If the 180-day provision never began, as the statute was previously interpreted, then it could never end, thereby prohibiting any additional generic manufacturers from entering the market. Recent amendments to the Hatch-Waxman Act alleviate some of these concerns by mandating forfeiture of the 180-day exclusivity if certain “forfeiture events” occur, such as the first applicant failing to market the drug or the FTC winning a suit against the parties for antitrust violations.⁷⁰

66. Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, 13 (July 2002), available at <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>.

67. See Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066, 2448–57 (2003) (amending Fed. Food, Drug, and Cosmetic Act, 21 U.S.C. § 355, 35 U.S.C. § 271 (2000)); see also Fed. Trade Comm’n, *supra* note 66, at 39.

68. Federal Trade Comm’n, *supra* note 66, at 39, 47.

69. 21 U.S.C. § 355(j)(5)(B)(iv) (2000).

70. 21 U.S.C. § 355(j)(5)(D)(ii) (2000).

Even with the 180-day exclusivity forfeiture provision, some settlements are still being questioned under anti-trust law, though such issues are outside the scope of this paper. One further concern with the 180-day generic exclusivity has been whether the innovator can bring its own generic, called an authorized generic, to the market during the 180-day exclusivity period. However, because the legislative intent in allowing generic approval pathways is to lower consumer costs, such concerns seem unlikely to prevail.

A successful pathway for generic biologics approval will thus likely have a 180-day generic exclusivity provision for those biogenics that challenge an innovator's patents, provided that it includes forfeiture events similar to those outlined in the Hatch-Waxman Act.

E. European Approach

Lessons might also be learned from the European Union on how to develop a generic pathway for biologics. In 2005, the EU approved a regulatory path for the approval of biosimilars.⁷¹ The European Medicines Agency, Europe's equivalent of the FDA, has approved the first four drugs this year, including a generic version of human growth hormone.⁷² Almost half (44%) of pharmaceutical industry executives believe that the United States should follow the EU approach.⁷³ The European guidelines, similar to the Hatch-Waxman Act, establish two routes for submission of an abridged marketing application for biogenics, including a route for identical products and a route for "biosimilar" products. Biosimilarity under the EU guidelines can only be found by establishing comparability of quality, safety, and efficacy of the biologics.⁷⁴ Determinants for finding product comparability include the nature of the product, quality of the findings, dosage regimen, route of administration, therapeutic window identified in dose-ranging studies, mechanism of action, previous experience with immunogenic activity, extent of knowledge of structure-activity relationships, and short- vs. long-term use.⁷⁵ The guidelines therefore generally give the European Medicines Agency wide discretion in determining the similarity and safety of biogenics on a case-by-case basis. In addition to these measures, Europe has recently

71. Wadman, *supra* note 10, at 496.

72. *Progress of Biologics Slow in the United States*, DRUG STORE NEWS (August 13, 2007), available at http://findarticles.com/p/articles/mi_m3374/is_10_29/ai_n19492799.

73. Liebert, Ann. *Should U.S. Approve Follow-On Biologics?*, BIOTECHNOLOGY LAW REPORT 389, 389 (August 2006).

74. EUROPEAN MEDICINES EVALUATION AGENCY COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (EMA), *Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances* (2003), <http://www.emea.eu.int/pdfs/human/ewp/309702en.pdf>.

75. *Id.*

instituted a 10-year market exclusivity period for all pharmaceuticals, including biologics, in order to allow the innovator to reap the benefits of its research.⁷⁶

IV. CURRENT CONGRESSIONAL BILLS

A. Bill Summaries

Several bills have been introduced into Congress this year, including H.R. 1038, H.R. 1956, and S. 1695, in an attempt to find a generic pathway for biologics. The flurry of activity has many generic biologic manufacturers hoping that a regulatory pathway may be in sight, though similar proposed legislation has historically stalled.⁷⁷

All three of the current bills amend section 351 of the PHS Act to establish a process for approval of an abbreviated biological product application for products that contain the same or similar active ingredients as previously licensed biological products.⁷⁸ Under one of the proposed bills, an applicant must prove through necessary non-clinical (chemical, physical, and biological assays) and clinical studies “the absence of clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency.”⁷⁹ Though not as explicitly, the other bills likewise address the safety, purity, and potency of the biosimilar.⁸⁰ In order to meet such standards, the applicant must always demonstrate that the product is “biosimilar” to the reference product. The current bills vary on how such similarity must be shown, though they generally require “similarity” of active products, identical routes of administration, dosage, and strength, and the same mechanism of action for the same condition of use. See Table 1 for a comparison of the similarity provisions of the current bills.

76. Grabowski, *supra* note 45, at 1300.

77. Paul Elias, *Generic Drug Proponents Call FDA Ruling “First Step” to Cheaper Biotech Drugs*, SAN JOSE MERCURY NEWS, May 31, 2006.

78. H.R. 1038, 110th Cong. (2007); H.R. 1956, 110th Cong. (2007); S.1695, 110th Cong. (2007).

79. H.R. 1038.

80. H.R. 1956; S. 1695.

TABLE I
COMPARISON OF SIMILARITY REQUIREMENTS IN CURRENT
CONGRESSIONAL BILL PROVISIONS

HR 1038 Access to Life-Saving Medicine Act	HR 1956 Patent Protection and Innovative Biologic Medicines Act	S 1695 Biologics Price Competition Innovation Act
<i>Introduced Feb. 14, 2007 by Henry Waxman (D-CA)</i>	<i>Introduced April 19, 2007 by Jay Inslee (D-WA)</i>	<i>Introduced June 26, 2007 as a bipartisan effort led by Ted Kennedy (D-MA) and Orin Hatch (R-UT)</i>
Biosimilar and reference must contain highly similar principal molecular structural features, notwithstanding minor differences in heterogeneity profile, impurities, or degradation patterns.	Biosimilar and reference must be comparable at both the active and finished product levels.	Biosimilar and reference must be highly similar.
Biosimilar and reference route of administration, dosage form, and strength must be the same.	N/A	Biosimilar and reference route of administration, dosage form, and strength must be the same.
Biosimilar and reference must have the same mechanism of action for the same condition of use.	Biosimilar and reference must show comparative results of pharmacokinetics, pharmacodynamics, toxicity, and immunogenicity, comparative safety, purity, and potency profiles for the same condition of use.	Biosimilar and reference must utilize the same mechanism of action for the same condition of use.

Moreover, all of the bills have provisions to account for the complexity of biological products. One bill prohibits the FDA from refusing to find two products comparable when they: (1) differ in structure due solely to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence; (2) have “similar saccharide repeating units, even if the number of units differ and even if there are differences in post-polymerization modifications”; (3) are glycosylated and have characteristics of the above; (4) have identical sequences of polynucleotides; (5) are “closely related, complex partly definable biological products with similar therapeutic intent, such as two live viral products for the same indication.”⁸¹ Yet another bill requires the

81. H.R. 1038.

products to be “highly similar,” with the standards for similarity left entirely up to the discretion of the FDA.⁸²

The bills likewise vary in their exclusivity provisions, ranging from zero to 14 years of innovator exclusivity and zero to one year of generic exclusivity.⁸³ Furthermore, only two of the three allow the generic producer to establish interchangeability with the reference product.⁸⁴

B. Proposed Improvements to Bills

In light of the various failures and successes of the Hatch-Waxman Act and the guidance provided by the European guidelines, there are specific areas of all of the current Congressional bills that may need improvement. See Table 2 for a comparison of the Hatch-Waxman Act and the current bills.

TABLE 2
COMPARISON OF HATCH-WAXMAN AND CURRENT
CONGRESSIONAL BILL PROVISIONS

Hatch-Waxman Act	HR 1038 Access to Life-Saving Medicine Act	HR 1956 Patient Protection and Innovative Biologic Medicines Act	S 1695 Biologic Price Competition Innovation Act
Requires bioequivalence.	Requires biosimilarity & limits FDA discretion.	Requires biosimilarity & creates committee to set standards.	Requires biosimilarity & gives FDA discretion.
5-year new chemical entity exclusivity for innovator.	N/A	14-year innovator exclusivity.	12-year innovator exclusivity.
30-month stay of generic approval if patient litigation suit is filed.	N/A	N/A	No stay, but the innovator may seek a preliminary injunction to prohibit generic from manufacturing the product.
180-day generic exclusivity for generic approval under Paragraph IV.	At least 180 days of generic exclusivity for interchangeable products.	N/A	At least one year of generic exclusivity for interchangeable products.

82. S. 1695.

83. H.R. 1038; H.R. 1956; S.1695.

84. *Id.*

Hatch-Waxman Act	HR 1038 Access to Life-Saving Medicine Act	HR 1956 Patient Protection and Innovative Biologic Medicines Act	S 1695 Biologic Price Competition Innovation Act
Patents must be listed in the Orange Book.	Generic may request list of patents, and the holder of the approved reference must provide the information with 60 days, but may demand up to \$1,000 to cover the costs.	N/A	Reference applicant must provide a list of patents for which an infringement claim could be made within 60 days of receiving the generic application.

Like the Hatch-Waxman Act, both H.R. 1956 and S. 1695 grant wide discretion to the FDA to determine similarity standards. However, H.R. 1038 limits such discretion. Due to the inherent difficulty in determining the safety and effectiveness of biologics, a generic pathway might be best structured to grant the FDA wide discretion to determine whether products are comparable, but requiring, as the EU guidelines do, that the FDA consider the nature of the product, quality of the findings, dosage regimen, route of administration, therapeutic window identified in dose-ranging studies, mechanism of action, previous experience with immunogenic activity, extent of knowledge of structure-activity relationships, and the expected extent of use.

An ideal bill should adequately provide incentives for pioneer biologics manufacturers. Whereas the Hatch-Waxman Act grants five years of innovator exclusivity and the EU gives a 10-year period of exclusivity, H.R. 1038 provides no innovator exclusivity. In contrast, both H.R. 1956 and S. 1695 grant periods of exclusivity over 12 years, with the potential to renew such exclusivity for even minor changes under S. 1695.⁸⁵ Given the increased cost associated with biologics and the potential lack of patent protection for such products, a generics pathway should include at least a 5-year exclusivity period in order to protect innovator investments and provide incentive for innovation. However, a period of much more than 10 years has the potential to make generic manufacturers shy away.

Innovators are limited in their ability to protect their investments under all of the current bills because there is no 30-month stay granted during infringement suits. As one 30-month stay is unlikely to significantly delay market entry, and patent protection is fundamental to innovation, the ideal Congressional bill should include such a provision.

Finally, the ideal bill should adequately compensate generic manufacturers by providing at least some exclusivity for biologic products.

85. *Progress of Biologics Slow in the United States*, *supra* note 72.

However, whereas the Hatch-Waxman Act gives exclusivity only to those products against which infringement actions have been filed, H.R. 1038 and S. 1695 both grant exclusivity to interchangeable manufacturers regardless of whether an innovator brings an infringement suit. While such an expansive grant of exclusivity is not inherently unreasonable and might encourage generic biologics manufacturers to pursue interchangeability, it may be unnecessary, particularly given the economic incentives for pursuing generics that are already in place. In contrast, H.R. 1956 fails to provide any generic exclusivity, which is also seemingly problematic.

Thus, all of the current Congressional bills have their drawbacks. H.R. 1038 grants little discretion to the FDA to find products unsimilar and fails to give either innovator exclusivity or a stay, thereby significantly favoring generics manufacturers. In contrast, H.R. 1956 grants an extensive period of innovator exclusivity and fails to give any generic exclusivity, thereby favoring the brand-name biologics manufacturers. And finally, S. 1695, though seemingly more neutral, may grant too much innovator exclusivity, particularly if the language is read to grant additional exclusivity for minor changes to the product. As a result of these challenges, none of the current bills is likely to pass. In fact, the chances that any legislation will pass through this Congress are “extremely thin,” according to Representative Waxman himself.⁸⁶ However, despite the bills’ shortcomings and the unlikely chances of passage, the introduction and consideration of a biogenerics bill in any form signifies a promising future for generic biologic products.

CONCLUSION

Because there is currently no approval mechanism for generic biologics, it is important that Congress develop new legislation to establish such a pathway. Whatever new pathway is chosen, and whatever bill Congress ultimately passes, it must somehow weigh the costs and benefits of safety concerns and innovation with lower costs and expanded access. Judging from the differences between biologics and traditional drugs and the provisions of both the Hatch-Waxman Act and the EU guidelines, an ideal generic biologics bill would likely provide the FDA with the discretion to determine similarity of products on a case-by-case basis so that health and safety concerns can be accurately met. Moreover, the new legislation should include a new entity exclusivity period of five years or more, a 30-month stay, and a 180-day exclusivity for

86. Ed Silverman. *Generic Biologics Bill Unlikely to Pass*, PHARMALOT, Sept. 7, 2007, <http://www.pharmalot.com/2007/09/generic-biologics-bill-unlikely-to-pass/>.

those biogenerics that challenge an innovator's patent. While the current Congressional bills are a step in the right direction, they may fail to properly balance the needs of brand-name manufacturers with those of the consuming public. Therefore, Congress must continue to consider the economic, health and safety, and innovation concerns in order to successfully develop a regulatory pathway that will bring much-needed generic biologics to the market.