

FOLLOW-ON BIOLOGICS, DATA EXCLUSIVITY, AND THE FDA

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Congress aims to create an incentive structure in the biotechnology industry that will increase competition and drive down the costs of protein-based therapeutic drugs known as biologics.¹ Faced with these analogous goals, Congress enacted the Hatch-Waxman Act in 1984,² which successfully created incentives for the introduction of generic small-molecule drugs. The Hatch-Waxman Act implemented an accelerated Food and Drug Administration (FDA) approval process for generic drugs, allowing for substantial costs savings in drug development.³ This cost savings encourages the market entry of generic competitors, which in turn lowers costs of small-molecule drugs by as much as eighty percent.⁴

Several bills under consideration in Congress would adapt aspects of the Hatch-Waxman Act to the approval process for follow-on biologics (FOBs). The current legislation must address two key issues: (1) the requisite amount of demonstrable similarity to take advantage of an abbreviated approval process for similar biologics; and (2) the length of the period of data exclusivity that allows the original drug developer to recoup development costs.

The current legislative proposals highlight the balance that Congress must strike between innovation and competition, and between lower prices and public safety. Three key differences between biologics and small-molecule drugs suggest that a statutory framework for FOBs should depart from the Hatch-Waxman framework. First, because biologic development costs exceed those for small molecules, innovator companies may require additional time to recoup development costs. Second, technical difficulties hinder the determination of whether an FOB is truly the same as an innovator biologic. Third, the structure of a biologic will vary depending on

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1. See *Hearing on Biologics and Biosimilars: Balancing Incentives for Innovation Before the H. Comm. on the Judiciary, Subcomm. on Courts and Competition Policy*, 111th Cong. 1 (2009) [hereinafter *Eshoo Statement*] (statement of Congresswoman Anna G. Eshoo).

2. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 1984 Stat. 1538 (1984) (codified as amended in scattered sections of 21 & 35 U.S.C.).

3. 21 U.S.C. § 355(j) (2006).

4. CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 32 (1998).

the conditions of manufacture. The second and third points lead to serious safety and efficacy concerns regarding abbreviated FDA testing.

This Note surveys the major concerns lawmakers face in creating an abbreviated pathway for FOB approval. Part I defines biologics and FOBs, explains the importance of biologics, and highlights the major differences between biologics and traditional small-molecule drugs. Part II summarizes current laws regulating biologics in the United States. It also describes the existing European approval process for FOBs as well as provisions of the Hatch-Waxman Act that may serve as the template for an abbreviated FOB approval process in the United States. Part III examines the legislative proposals for instituting an abbreviated FOB approval process currently before Congress.

I. BIOLOGICS AND FOLLOW-ON BIOLOGICS

A. WHAT ARE BIOLOGICS?

Traditional drugs typically consist of small molecules produced by chemical processes. In contrast, biologics are protein-based therapeutic drugs—including many vaccines and purified proteins—produced by biological processes. Modern biologics created via biotechnology, the focus of this paper, first emerged with the FDA's approval of recombinant human insulin in 1982.⁵ Since then, over four hundred biologic drugs have been developed to treat over two hundred ailments,⁶ including heart attacks, strokes, multiple sclerosis, leukemia, hepatitis, rheumatoid arthritis, breast cancer, diabetes, congestive heart failure, lymphoma, kidney cancer, and cystic fibrosis.⁷ The biologics development pipeline also includes over six hundred new drugs, with over two hundred and fifty of these targeting cancer alone.⁸

Biologics employ a multitude of strategies to treat disease. Most early biologics treated relatively simple protein deficiencies and were produced by splicing genes into bacteria to produce proteins such as insulin, blood clotting factors, and erythropoietin human for treating disorders such as diabetes, hemophilia, and anemia, respectively.⁹ Biologics have since grown and diversified tremendously, including the following examples: (1)

5. JUDITH A. JOHNSON, FDA REGULATION OF FOLLOW-ON BIOLOGICS 1 (2009).

6. See Ingrid Kaldre, *The Future of Generic Biologics: Should the United States "Follow-On" the European Pathway?*, 2008 DUKE L. & TECH. REV. 1, 2 (2008).

7. BILLY TAUZIN, BIOTECHNOLOGY RESEARCH CONTINUES TO BOLSTER ARSENAL AGAINST DISEASE WITH 633 MEDICINES IN DEVELOPMENT 1 (2008).

8. *Id.*

9. See generally *id.*

monoclonal antibodies are laboratory-made versions of the antibodies that comprise the body's natural defense against invaders; (2) interferons affect a cell's ability to reproduce, and can treat osteoporosis, chronic granulomatous disease, genital warts, multiple sclerosis, hairy cell leukemia, and other diseases; (3) antisense technology can shut off the production of specific unwanted proteins; (4) therapeutic vaccines jump-start the immune system to fight disease; and (5) gene therapy can treat disease by augmenting, replacing, or inactivating existing genes.¹⁰

B. THE GROWTH AND EXPANSION OF BIOLOGICS IN THE UNITED STATES

The promise of biologics comes with a significant catch: biologics average twenty times the cost of small-molecule drugs.¹¹ The breast cancer drug Herceptin costs up to \$48,000 per year;¹² the colon cancer drug Avastin costs up to \$100,000 per year.¹³ Cerezyme, which treats Gaucher disease (a life-threatening enzyme deficiency), typically costs between \$200,000 and \$500,000 per year.¹⁴ For comparison, treatment of arthritis with even the most expensive small-molecule drug would cost around \$300 per year, while a biologic treatment for arthritis with Enbrel costs upwards of \$20,000 per year.¹⁵

Even with their expense, the market share for biologics is expected to grow. In 2002, biologics sales accounted for eleven percent of all U.S. drug sales.¹⁶ By 2006, spending in the U.S. on "specialty drugs," which includes biologics, totaled \$54 billion, or about twenty percent of total spending on pharmaceuticals.¹⁷ Estimates suggest that biologics will expand to twenty-six percent of the total cost of pharmaceuticals in 2010, which represents

10. *Id.*

11. Karen Tumulty & Michael Scherer, *How Drug-Industry Lobbyists Got Their Way on Health Care*, TIME, Oct. 22, 2009, <http://www.time.com/time/printout/0,8816,1931595,00.html> (last visited Jan 24, 2010).

12. *Id.*

13. Kathleen Jaeger, *Creating a Workable Biogenics Pathway for Patients*, 5 J. OF GENERIC MEDS. 1, 1 (2007).

14. *Id.*

15. Zach Patton, *Complex Rx: Biologic Meds Are the Wonder Drugs of Our Time. Can We Afford Them?*, GOVERNING MAG., 2007, <http://www.governing.com/archive/archive/2007/oct/drugs.txt> (last visited Jan. 24, 2010).

16. *Id.*

17. JOHNSON, *supra* note 5, at 2.

spending of around \$99 billion in the U.S.¹⁸ By 2012, experts expect half the drugs approved by the FDA to be biologics.¹⁹

C. COMPLICATIONS TO PRODUCING “GENERIC” FOLLOW-ON BIOLOGICS

Because biologics are protein-based drugs, significant differences exist between biologics and typical small-molecule drugs in terms of both complexity and manner of production. While small-molecule drugs normally comprise just dozens of atoms, biologics can easily consist of millions of atoms. Most importantly, unlike small-molecule drugs made via chemical synthesis, biologics are made via biological processes inside living organisms.²⁰ Biological production leads to higher production cost and complexity.²¹ Biological production introduces a measure of unpredictability in the structure of the therapeutic drugs, and variations in the manufacturing conditions results in variation of the biologic structure. For example, minor structural variations will arise between two supposedly identical biologics because of differences in processing conditions and starting materials.²² In short, the sensitivity of biological production to manufacturing conditions far exceeds that of chemical production.

FOBs possess structural similarity but often lack structural identity with the innovator biologic. By comparison, small-molecule generics often achieve structural identity with their innovator drug. The complexity of the biologic molecules, production in living organisms, and sensitivity of end-product structure to changes in the manufacturing process render exact FOB replication nearly impossible.²³

Moreover, due to the large size and complex structure of biologics, current scientific analysis cannot resolve all discrete structural differences

18. *Id.*

19. Val Brickates Kennedy, *Generic Versions of Biologic Medications Are Coming: Congress Considering Plan to Allow ‘Biosimilars’ to Come to Market*, MARKETWATCH, Sept. 3, 2009, <http://www.marketwatch.com/story/generic-versions-of-biologic-medications-coming-2009-08-28>.

20. See WENDY H. SCHACHT & JOHN R. THOMAS, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 2 (2009).

21. See Michal Nowicki, *Basic Facts about Biosimilars*, 30 KIDNEY BLOOD PRESSURE RESEARCH 267, 268 (2007).

22. See *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Comm. on Energy and Commerce, Subcomm. on Health*, 110th Cong. 8 (2007) [hereinafter *Woodcock Statement*] (statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, Food and Drug Administration).

23. See *Hearing before the S. Comm. on Health, Education, Labor and Pensions*, 110th Cong. 2 (2007) [hereinafter *Rossignol Statement*] (statement of Nicolas Rossignol).

between an FOB and an innovator biologic for a direct comparison.²⁴ At most, scientific analysis can determine that an FOB is similar to the innovator biologic. In short, because FOBs can only achieve similarity rather than identity, FOBs cannot become “generic” biologics.

Structural similarity does not guarantee identical therapeutic properties because small differences in structure affect the functioning of the biologic.²⁵ Even though an FOB may have structural similarity to the innovator biologic, treat the same medical condition, and utilize the same mechanism of action, subtle differences may nevertheless lead to variations in safety or efficacy compared to the innovator.²⁶

That FOBs differ at least slightly with the innovator biologic creates unique regulatory concerns absent for small-molecule drugs. One such concern is immunogenicity: the ability of the biologic to stimulate an immune response in the body.²⁷ Even though clinical tests may find an innovator biologic safe and effective, the different manufacturing process employed by an FOB manufacturer could render that FOB ineffectual or even dangerous

24. As Janet Woodcock, the Deputy Commissioner and Chief Medical Officer of the FDA testified before Congress:

Current technologies, such as peptide mapping, protein sequencing, and mass spectroscopy enable manufacturers to determine, with certainty, the amino acid sequence of a recombinant protein. However, the amino acid sequence is the most rudimentary characteristic of a protein. Conclusive analysis of other aspects of a protein’s structure requires much more sophisticated technologies and is fraught with uncertainties that are proportional to the size and complexity of the protein itself. Such complexities include: folding of the protein’s amino acid chain into highly organized structures, post-translational modification of the protein with a broad range of biochemical additions (e.g., glycosylation, acetylation, phosphorylation, etc.), and association of multiple protein molecules into aggregates. It is the combination of the protein’s amino acid sequence and its structural modifications that give a protein its unique functional characteristics. Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product. Although this currently may be possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.

Woodcock Statement, *supra* note 22, at 10.

25. See Simon D. Roger, *Biosimilars: How Similar or Dissimilar Are They?*, 11 NEPHROLOGY 341, 342 (2006).

26. See *Woodcock Statement*, *supra* note 22, at 12.

27. *Id.* at 10–12.

when used.²⁸ Currently, only expensive and time-consuming clinical trials are able to detect whether the subtle structural differences among biologics will lead to changes in safety or efficacy.²⁹

Biological production methods also raise concerns about interchangeability. Interchangeability refers to the ability to safely substitute an FOB for the innovator biologic in the course of treatment.³⁰ Interchangeability does not present a significant issue for small-molecule generics because generics are structurally identical to the innovator. Because FOBs lack structural identity with the innovator, they may also lack interchangeability. Therefore, clinical trials must specifically address the interchangeability of FOBs.

II. REGULATION OF BIOLOGICS

Because of the high cost of biologics, Congress is exploring legislation to facilitate the development of FOBs.³¹ Many policymakers expect that accelerated approval for FOBs would create an economically favorable environment for their production and bring down the costs of innovator biologics via competition in the marketplace. In essence, Congress hopes to emulate the successes of the Hatch-Waxman Act,³² which led to increased incentives for the pharmaceutical industry to produce generic drugs and cost reductions up to eighty percent.³³

Congress is currently considering a number of bills. Estimates of the potential savings vary,³⁴ but the Obama Administration estimates that an FOB approval pathway would lead to government savings of \$9.2 billion

28. *See id.*

29. *See id.*

30. Affordable Health Care for America Act, H.R. 3962, 111th Cong., at 1558 (2009).

31. *See Esboo Statement, supra* note 1, at 1.

32. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 1984 Stat. 1538 (codified as amended in scattered sections of 21 & 35 U.S.C.).

33. Drug prices decline in relation to the number of generic competitors in the market. With one generic competitor the generic price is approximately sixty percent of the innovator's original price. With ten generic competitors the price may drop to thirty-four percent, and with twenty competitors the price may drop to just twenty percent. CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY 32 (1998), <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf> (last visited Sep 28, 2009).

34. JOHNSON, *supra* note 5, at 3.

over the next ten years.³⁵ Total consumer savings in that time may reach between \$71³⁶ and \$108 billion.³⁷

A. CURRENT REGULATION—THE PUBLIC HEALTH SERVICE ACT

The FDA currently approves “biological products” under the regulatory framework provided by the Public Health Service (PHS) Act of 1944.³⁸ This pathway for biologic approval resembles the approval process for small-molecule drugs under the Federal Food Drug and Cosmetic (FDC) Act.³⁹

Although the original innovator faces similar hurdles for approval of biologics (under the PHS) and drugs (under the FDC), subsequent applicants seeking to reference the innovator drug under the two regimes face significantly different requirements. Approval of a new drug under both pathways begins with an FDA application, followed by clinical trials to determine safety and efficacy.⁴⁰ Clinical trials progress from small-scale human testing to large scale human testing with costs increasing at each level.⁴¹ For small-molecule drugs under the FDC, the Hatch-Waxman Act created an abbreviated approval process for the subsequent market entrant where the second entrant could rely on the innovator’s clinical data.⁴² No such provision exists for biologics under the PHS. Thus the subsequent biologic market entrant must bear costly and time-consuming trials prior to FOB approval.⁴³

B. A LEGISLATIVE TEMPLATE—THE HATCH-WAXMAN ACT

The Hatch-Waxman Act is a “balancing of interests.”⁴⁴ On one side, innovator drug companies hope to profit after sinking tremendous amounts of money on the development of new drugs. On the other side, generic drug companies seek to bring generic drugs to the market. In the middle, the public benefits both from the lowering of costs for older drugs via

35. HOUSE BUDGET COMM., SUMMARY OF THE PRESIDENT'S FISCAL YEAR 2010 BUDGET (2009).

36. JOHNSON, *supra* note 5, at 3.

37. Tumulty & Scherer, *supra* note 11.

38. 42 U.S.C. § 262 (2006).

39. JOHNSON, *supra* note 5, at 6.

40. 42 U.S.C. § 262(a)(2)(C) (2006).

41. Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 472 (2007).

42. 21 U.S.C. § 355(j) (2006).

43. JOHNSON, *supra* note 5, at 6.

44. See Arie M. Michelsohn, “Follow-On” Biologics: *What Will It Take?*, 5 THE SCITECH LAWYER (2008), available at <http://www.abanet.org/scitech/docs/michelsohn.pdf>.

competition and from the development of new therapies by innovator drug companies.⁴⁵

Under the Hatch-Waxman framework, when an innovator drug initially enters the market, two mechanisms help an innovator enjoy a period of market exclusivity: patent extension and data exclusivity. During this period, innovators recoup development costs through supracompetitive profits. Balanced against this, the Hatch-Waxman framework also encourages generic competition with an abbreviated FDA approval process that bypasses costly clinical trials. In an ideal situation, an innovator enjoys just enough market exclusivity to justify the expense of drug development, after which the market opens to competition that drives down costs.

The Hatch-Waxman Act offers innovators the possibility of patent extension.⁴⁶ A patent provides its owner with the right to exclude others from making, using, or selling the patented invention.⁴⁷ In the drug industry patents cover drug compositions, manufacturing processes, or methods of use. Patents are usually filed in the initial stages of drug discovery and last twenty years from the date of filing. However, clinical trials may take over six years, and FDA approval may require a year or two more.⁴⁸ Therefore, a substantial portion of patent life may lapse before the drug reaches the market. To compensate, the Hatch-Waxman Act can add up to five years of patent term extension for the time lost seeking FDA approval.⁴⁹ As a result, an average innovator small-molecule drug retains around eleven to thirteen years of patent protection after FDA approval.⁵⁰

45. *See id.*

46. The Hatch-Waxman Act allows patent term extension due to FDA approval time for both small-molecule drugs under the FDC Act and biologics under the PHS Act. *See* Pub. L. 98-417, 1984 Stat. 1538 § 201 (1984).

47. 35 U.S.C. § 271(a) (2006) (“Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent therefore, infringes the patent.”).

48. *See* DiMasi & Grabowski, *supra* note 41, at 475.

49. The Hatch Waxman Act allows for restoration of half the time spent in clinical trials and the full time spent by the FDA during final approval. The Hatch Waxman Act also caps the maximum patent life after restoration at fourteen years, so the full five year restoration is not available if the manufacturer retains a patent term of greater than nine years prior to Hatch Waxman patent term extension. 35 U.S.C. § 156 (2006).

50. Henry G. Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 28 *MANAGERIAL & DECISION ECON.* 491, 495–96 (2007).

In addition to patent extension, the Hatch-Waxman Act provides a five year period of data exclusivity for new drugs.⁵¹ While the Hatch-Waxman Act grants generic manufacturers the ability to borrow the innovator's clinical trial data, this grant is not immediate. The data exclusivity period requires that generic manufacturers wait five years after the approval of the new innovator drug before filing an application that relies on the innovator's clinical data for approval.⁵² During the data exclusivity period, the innovator enjoys a form of market protection from generic competition. Without access to the innovator's data, the high cost of clinical trials can deter market entry by generic manufacturers. If a competitor proceeds with its own clinical trials, however, that competitor can still enter the market.⁵³

Compared to an average effective patent life of around twelve years, data exclusivity persists for a relatively short amount of time. Therefore, patent protection acts as the primary means by which small-molecule drug innovators prohibit entry of generic competition into the marketplace. Only when a drug has a very limited patent term remaining after FDA approval does data exclusivity provide meaningful market protection.

For generics manufacturers, the Hatch-Waxman Act established a pathway to attain abbreviated approval. Specifically, § 505(j) of the FDC Act allows generic drug makers to rely on an innovator drug manufacturer's FDA filings to demonstrate safety and effectiveness, provided that the generic is "bioequivalent" to the innovator drug.⁵⁴ A generic achieves bioequivalence if a subsequent applicant shows identical chemical structure for the active ingredient, as well as other characteristics like dosage and therapeutic formulation, and the generic manufacturer can rely on the innovator's clinical trials in the application process.⁵⁵ Since showing bioequivalence costs far less than conducting clinical trials on humans, the Hatch-Waxman Act excuses the generic applicant from a substantial burden in drug development.

In the Hatch-Waxman regime, an innovator must list each patent relevant to its drug with the FDA. For the subsequent applicant, applicants must file one of four certifications, known as Paragraph I through Paragraph IV certifications, in order to gain the benefit of an abbreviated approval process. A Paragraph I certification is filed if the innovator failed to file that

51. 21 U.S.C. § 355(j)(5)(F)(ii) (2006). A drug qualifies for five years of data exclusivity if the FDA has not previously approved that drug's "active moiety." *See* 21 C.F.R. § 314.108 (2009).

52. *See* 21 U.S.C. § 355(j)(5)(F)(ii).

53. Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 189 (1999).

54. 21 U.S.C. § 355(j)(2) (2006).

55. *See id.*

patent.⁵⁶ A Paragraph II certification is filed if the innovator's patent has expired.⁵⁷ A Paragraph III certification is filed if the innovator has a valid patent and the subsequent applicant would like to approval on the date after patent expiry.⁵⁸ A Paragraph IV certification is filed if the innovator's patent is either invalid or not infringed by the subsequent applicant.⁵⁹ A Paragraph IV certification also adds the incentive of a 180 day market exclusivity period to the first applicant to successfully challenge the innovator's patent in court.⁶⁰ This award not only encourages generic manufacturers to file first, but also encourages design-around innovation as well as the challenge of invalid patents.⁶¹

The Hatch-Waxman Act undoubtedly promotes the introduction of generics into the United States market. Generics comprised only nineteen percent of prescriptions when the Hatch-Waxman Act took effect in 1984.⁶² Now, generics represent sixty-nine percent of United States prescriptions.⁶³ Estimates suggest that consumers save around \$8 to \$10 billion dollars through the use of generics.⁶⁴ As a result, the Hatch-Waxman Act serves as an attractive legislative template for an abbreviated approval process for FOBs.

C. ANOTHER LEGISLATIVE TEMPLATE—REGULATION OF BIOSIMILARS IN THE EUROPEAN UNION

In 2005, the European Medicines Agency (EMA), the European equivalent of the U.S. FDA, published guidelines for the abbreviated approval of FOBs (termed "biosimilars").⁶⁵ In April 2006, the EMA authorized the human growth hormone Omnitrope as the first biosimilar in the European Union, and twelve additional authorizations followed.⁶⁶ Although biosimilars only recently entered the market in Europe, early

56. 21 USC § 355(j)(2)(A)(vii) (2006).

57. *Id.*

58. *Id.*

59. *Id.*

60. 21 U.S.C. § 355(j)(5)(B) (2006).

61. FED. TRADE COMM'N, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 7* (2002).

62. *Id.*

63. The US Generic Drugs Industry Overview, <http://www.themedica.com/articles/2009/04/the-us-generic-drugs-industry.html> (last visited Jan 25, 2010).

64. *Id.*

65. EUR. MEDS. AGENCY, *GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS* (2005).

66. Mateja Urlep, *Biosimilars: Succeeding in the Market of the Future*, PHARMA FOCUS ASIA (2009) http://www.pharmafocusasia.com/research_development/biosimilars.htm. (last visited Nov. 16, 2009).

indications show twenty-five to thirty percent price reductions for certain biologics.⁶⁷

The EMEA regulations arose because “[d]ue to the complexity of biological/biotechnology-derived products[,] the generic approach is scientifically not appropriate for these products.”⁶⁸ Instead, the EMEA follows the “similar biological medicinal products” approach, which is based on a comparability exercise.⁶⁹ In demonstrating similarity to a reference innovator biologic, the biosimilar manufacturer must (1) show analytical data comparing the biosimilar against the reference biologic, and (2) demonstrate comparable safety and efficacy.⁷⁰

The EMEA determines the need for clinical studies of safety and efficacy on a case-by-case basis.⁷¹ However, the EMEA publishes a tiered system of guidance documents to supplement this general framework.⁷² These guidance documents describe the specific requirements manufacturers must meet for approval of biosimilars. The top tier consists of quality, clinical, nonclinical, and additional overarching guidelines that apply to all biosimilars.⁷³ The middle tier contains product guidance documents for classes of biologics such as vaccines and antibodies.⁷⁴ Finally, at the lowest tier, the EMEA provides guidelines describing the data requirements for the approval of specific proteins, such as recombinant human erythropoietin, recombinant human granulocyte colony-stimulating factor, recombinant human insulin, and recombinant human growth hormone.⁷⁵

In Europe, biologics innovators enjoy ten years of data exclusivity, with the possibility of a one year extension.⁷⁶ Also, the biosimilar authorization process in Europe only covers similarity between an innovator biologic and

67. See Thomas Gryta, *Hospira Learning Valuable Lessons In European Biosimilar Market*, DOW JONES ONLINE, Oct. 1, 2009, <http://www.nasdaq.com/aspx/company-news-story.aspx?storyid=200910011307dowjonesdjonline000653> (last visited Jan. 24, 2010).

68. EUR. MEDS. AGENCY, *supra* note 65, at 4.

69. *Id.*

70. European Generic Medicines Association, *Frequently Asked Questions about Biosimilar Medicines*, <http://www.egagenerics.com/FAQ-biosimilars.htm> (last visited Nov 21, 2009).

71. See James C. Greenwood, *Follow on Biologics (FOBs): How Has Europe Approached FOBs (“Biosimilars”)?*, <http://www.bio.org/healthcare/followonbkg/Europe.asp> (last visited Jan. 24, 2010).

72. See Nowicki, *supra* note 21, at 269.

73. See EUR. MEDS. AGENCY, *supra* note 65, at 5.

74. See *id.* at 6–7.

75. See Nowicki, *supra* note 21, at 269.

76. See Greenwood, *supra* note 71, at 1.

the follow-on biosimilar, and does not address interchangeability.⁷⁷ The EU process leaves the interchangeability assessment for biosimilars to individual governments. In fact, countries such as France, Italy, and the Netherlands have explicitly stated that biosimilars will not be substitutable.⁷⁸

III. UNITED STATES LEGISLATION REGULATING FOLLOW-ON BIOLOGICS

The Hatch-Waxman Act is credited with reducing prices for small-molecule drugs, increasing access to these drugs, and hastening the pace of innovation in the drug industry.⁷⁹ Because of the success of the Hatch-Waxman framework, Congress will likely create an analogous model to facilitate FOB entry and reduce the costs of biologics for patients.

In November 2009, the United States House of Representatives passed House Bill 3962, the Affordable Health Care for America Act, which includes a provision for the abbreviated approval of FOBs.⁸⁰ In December 2009, the Senate passed the Patient Protection and Affordable Care Act, House Bill 3590,⁸¹ which contained almost identical language on an abbreviated approval pathway for FOBs.⁸²

Proposals to regulate FOBs must address two key issues. The first concerns the balance between public safety and FOB development costs. Current technology requires the use of expensive clinical trials to determine the safety and efficacy of an FOB. The legislative proposals task the FDA with determining the clinical testing needed for approval. This testing should protect the public but also permit FOB developers to realize a cost savings during development.

The second issue concerns the balance between lowering costs for established biologics and ensuring continued investment toward innovation. Encouraging the entry of FOBs into the market creates competition that drives down prices, but at the same time innovator companies require an exclusivity period sufficient to justify their considerable upfront investments.

77. See *Rossignol Statement*, *supra* note 23, at 7.

78. See *Urlep*, *supra* note 66.

79. See FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 4 (2009).

80. Affordable Health Care for America Act, H.R. 3962, 111th Cong. (2009).

81. Patient Protection and Affordable Care Act, H.R. 3590, 111th Cong. (2009).

82. Since the text is nearly identical the House bill provisions will be referenced in this Note for simplicity.

A. FOB DEVELOPMENT COSTS VS. SAFETY

1. *Bioequivalence and Biosimilarity*

For small-molecule generics, the Hatch-Waxman Act allows the FDA to rely on the innovator drug manufacturer's findings on safety and efficacy, requiring a subsequent generic applicant only to demonstrate "bioequivalence" between its generic and the referenced drug.⁸³ To show bioequivalence, the generic applicant must first demonstrate that the generic drug has the same active ingredient, route of administration, dosage form, strength, and proposed labeling as the original innovator drug.⁸⁴ Then, the generic manufacturer must show that the rate and extent of absorption of the generic drug does not significantly differ from that of the reference drug when administered at the same dosage.⁸⁵ Once the generic demonstrates bioequivalence with the innovator drug, the generic may rely on prior data for approval under the assumption that the generic is as safe and effective as the innovator drug.⁸⁶

Because of the size and complexity of biologics, however, current technology cannot show bioequivalence in an FOB.⁸⁷ While available analyses can reliably compare the protein sequence of an FOB and the innovator biologic, that sequence does not reveal the biologic's complete structure. A biologic's therapeutic properties also depend on structural factors such local folding, three dimensional folding, the addition of modifications,⁸⁸ and the clumping of individual biologics proteins into aggregates.⁸⁹ Current techniques cannot detect and compare these more complex structures and modifications. Therefore, FOB producers cannot show that an FOB has the identical active ingredient as the innovator biologic.⁹⁰

Other duplication methods for biologics are unlikely to succeed. Even an attempt to copy each of an innovator biologic's production steps would not guarantee an identical FOB product. Even small variations in manufacturing conditions cause structural differences in the biologics produced.⁹¹ Because

83. 21 U.S.C. § 355(j)(2) (2006).

84. *Id.*

85. *Id.*

86. *See* Mossinghoff, *supra* note 53, at 191.

87. *See* FEDERAL TRADE COMM'N, *supra* note 79, at 8.

88. Post-translational modifications include phosphorylation, glycosylation, and acetylation. *See Woodcock Statement, supra* note 22, at 10.

89. *Id.*

90. *See id.* at 8.

91. *See* Roger, *supra* note 25, at 342.

the FOB manufacturer usually lacks access to the innovator's exact manufacturing process or cell lines, structural differences between the FOB and the innovator will generally occur.⁹² For example, the European Union approved the FOB growth hormone Valtropin, which referenced the innovator biologic Humatrope. Even though the EMEA found Valtropin to be similar to Humatrope, because different cell lines were used for the production of the two products (yeasts for Valtropin and *Escherichia coli* for Humatrope), the two require different precautions and indications.⁹³

Because existing technology cannot show bioequivalence, the currently proposed legislation calls only for "biosimilarity." Biosimilarity occurs when the "biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" provided that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency."⁹⁴

The legislative proposals require clinical trials for FOBs in order to demonstrate safety, purity, and potency. As a consequence, although a showing of similarity can save clinical testing expenses compared to a full series of clinical trials, demonstrating similarity nevertheless requires substantially more expense than demonstrating bioequivalence of small-molecule generics.⁹⁵ While small-molecule generic drug manufacturers can show bioequivalence through simple analytic testing, FOB manufacturers must perform expensive and time-consuming studies on clinical safety and efficacy. Additionally, because clinical testing ideally takes place after product manufacturing processes are finalized, FOB manufacturers also must bear the expense of seeking approval and validation of their commercial manufacturing facilities at or before initiation of clinical trials.⁹⁶

2. Immunogenicity

Immunogenicity, the ability to stimulate an immune response in the body, is a major safety concern for biologics. This issue poses a comparatively trivial obstacle to traditional drug development because small

92. See Woodcock et al., *The FDA's Assessment of Follow-on Protein Products: A Historical Perspective*, 6 NATURE REVS. DRUG DISCOVERY 437, 437 (2007).

93. See Nowicki, *supra* note 21, at 270.

94. Affordable Health Care for America Act, H.R. 3962, 111th Cong., at 1558 (2009).

95. See FED. TRADE COMM'N, *supra* note 79, at 9.

96. See *id.*

molecules are far less likely to generate an immune response than proteins.⁹⁷ Immune reactions to biologics can range from the production of detectable, but not clinically significant, antibodies, to an immune response that compromises drug safety or effectiveness.⁹⁸ If the immune system produces neutralizing antibodies, these antibodies will bind to the biologic and reduce the biologic's effectiveness. Even worse, hypersensitivity responses include symptoms such as severe allergic reactions, rashes, fevers, or kidney problems. For example, several patients developed a rare brain condition after taking Efallzumab, a biologic used to treat psoriasis.⁹⁹ In another case, because of a subtle change in the manufacturing process of recombinant erythropoietin, patients developed epoetin-resistant anemia requiring blood transfusions, immunosuppressive treatment, and, eventually, kidney transplantation.¹⁰⁰ Thus, immune responses present a serious concern because they may reduce a biologic's efficiency or even become life threatening for patients.

To assure safety for FOBs, immunogenicity tests will need to be done for each individual FOB.¹⁰¹ The inevitable structural differences between the innovator biologic and the FOB mean that even after an innovator biologic is known to be safe and effective in terms of immunogenicity, there is no assurance that the corresponding FOB will not create immune-mediated problems.¹⁰² This individualized testing for immunogenicity can represent substantial costs for FOB manufacturers.

In addressing immunogenicity, the current bills leave the proper amount of clinical safety data required to FDA discretion on a case-by-case basis.¹⁰³ Earlier versions of the bills included more stringent requirements for the FDA, and recommended that the FDA publish product class guidance documents which would detail immunogenicity requirements during clinical trials.¹⁰⁴

97. See Letter from Frank M. Torti, M.D., M.P.H., Principal Deputy Comm'r and Chief Scientist, FDA, to the Honorable Frank Pallone, Jr., Chairman, House Subcomm. on Health, Comm. on Energy and Commerce, at 1 (Sept. 18, 2008).

98. See *Woodcock Statement*, *supra* note 22, at 11.

99. MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: IMPROVING INCENTIVES IN THE MEDICARE PROGRAM, 108 (2009).

100. Nowicki, *supra* note 21, at 270.

101. See *Woodcock Statement*, *supra* note 22, at 12.

102. See *id.*

103. Affordable Health Care for America Act, H.R. 3962, 111th Cong., at 1531 (2009).

104. Pathway for Biosimilars Act, H.R. 1548, 111th Cong., at 18 (2009).

3. *Interchangeability*

Interchangeability refers to the ability of an FOB to directly substitute for the innovator biologic. For example, if a patient begins treatment with the innovator biologic, the introduction of an FOB may lead a patient to consider a switch to the FOB. Similarity between the FOB and the innovator assures that the FOB has similar safety and efficacy, but this only represents safety and efficacy for the FOB working independently. There is still an “interchangeability” issue because of the potential for unforeseen reactions when a patient switches to an FOB after starting with the innovator biologic.¹⁰⁵ The true test for safety when switching between the reference biologic and the FOB occurs during interchangeability tests in clinical trials.

Interchangeability may play a critical role in the market for an FOB because a determination of interchangeability would greatly ease market penetration. Without interchangeability, both physicians and patients would remain skeptical about the safety and efficacy of substituting an FOB for an innovator biologic.¹⁰⁶ Demonstrable interchangeability played a significant role in physician behavior when small-molecule generics entered the market. Manufacturers of generic small-molecule drugs benefit from state substitution statutes that allow pharmacists to dispense generics when presented with a prescription for a branded drug, unless directed otherwise by the physician or the consumer.¹⁰⁷ Additionally, pharmacy chains prefer dispensing the generic because generics typically carry higher margins.¹⁰⁸ Together, these two factors can lead to a loss of market share for a branded small-molecule drug within one year of the entry of generics.¹⁰⁹

An FOB achieves interchangeability with the reference biologic if the “risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alteration or switch.”¹¹⁰ If an FOB is interchangeable with the reference product, the FOB “may be substituted for the reference product without intervention of the health care provider who prescribed the reference product.”¹¹¹ The FDA

105. See *Woodcock Statement*, *supra* note 22, at 12.

106. See FED. TRADE COMM’N, *supra* note 79, at 16–17.

107. See *id.* at 13.

108. See FED. TRADE COMM’N, PHARMACY BENEFIT MANAGERS: OWNERSHIP OF MAIL-ORDER PHARMACIES 74–75 (2005).

109. See FED. TRADE COMM’N, *supra* note 79, at 13.

110. Affordable Health Care for America Act, H.R. 3962, 111th Cong., at 1533 (2009).

111. *Id.* at 1558.

determines interchangeability, like biosimilarity and immunogenicity, on a case-by-case basis.¹¹²

4. *Role of the FDA*

In the bills under consideration in Congress, the FDA would retain substantial control of the FOB approval process. Specifically, the FDA would determine which clinical trials are necessary for approval.

Allowing the FDA to assess the need for clinical data would provide more flexibility than predefined statutory mandates for clinical testing. In general, the amount and type of new data necessary to demonstrate the safety and effectiveness of an FOB will depend on the level of demonstrable similarity between the FOB (either structurally, functionally, or clinically) and the corresponding approved biologic. Clinical uses and the amount and type of accumulated clinical experience regarding the approved product will influence the amount and type of data required by the FDA for FOB approval.¹¹³ With its experience in the approval of biologics, the FDA would be the agency best suited to consider and weigh the multiple factors that influence the appropriate scope of clinical trials.

However, the best way to evaluate an FOB application may not involve case-by-case determination. To be sure, case-by-case determinations enjoy the important advantage of flexibility and adaptability to advancing technologies. But, because immunogenicity and similarity are largely unpredictable with current technology, public safety may demand the certainty provided by strict statutory guidelines requiring specific clinical trials.¹¹⁴ Innovator drug manufacturers would also benefit from the predictability that such a system could provide.

The current bills accordingly implement a compromise between statutory requirements and case-by-case assessment. The bills call on the FDA to produce guidance documents, similar to those under the EMEA, that would provide FOB manufacturers with categorical estimates of the requirements for FDA approval, while still allowing the FDA to make case-specific determinations as necessary.¹¹⁵ Although producing guidance documents may substantially burden the FDA,¹¹⁶ the FDA supported this approach.¹¹⁷ The

112. *Id.* at 1532–33.

113. *See Woodcock Statement, supra* note 22, at 9.

114. *See Kaldre, supra* note 6, at 33.

115. *See Affordable Health Care for America Act, H.R. 3962, 111th Cong., at 1540 (2009).*

116. *See JOHNSON, supra* note 5, at 12.

117. *See generally Woodcock et al., supra* note 92.

FDA has long analyzed related protein products, from the first therapeutic proteins purified from natural sources through the rise of recombinant proteins in the 1980s.¹¹⁸ Another context in which the FDA has demonstrated expertise in directly comparing protein products is when a biologic's manufacturing processes requires modification. This may arise in contexts such as a new manufacturing plant, a change in equipment used at a current plant, or a change in the steps of manufacture.¹¹⁹ The FDA must approve modifications to the manufacturing process, and this entails an evaluation of the current protein product against the product of the previous manufacturing process.¹²⁰ In 1999, the FDA published a draft guide for abbreviated approval under § 505(b)(2) of the FDC Act, which covers small-molecule drugs similar, but not identical, to the reference innovator drug.¹²¹ Although unfinished, these guidelines could serve as a basis for drafting new FOB guidelines. In sum, the FDA has considerable experience and expertise with the analytical and regulatory issues surrounding biosimilarity.

Under the proposed framework, an FDA rejection would, for practical purposes, signify the loss of millions of dollars of investment in FOB development and clinical trials. Even in cases where the FDA grants approval, the amount and extent of the required clinical trials would be subject to considerable FDA discretion. As a result, the FDA would wield substantial power over drug innovation policy in the United States.¹²²

The central role proposed for the FDA in an approval process that implicates perhaps billions of dollars prompts some concerns regarding the agency's decision making processes. Under the "agency capture" theory, a regulatory body may, through close ties or political pressure, become controlled by the industry it regulates, resulting in that regulatory body serving the special interests of the industry instead of serving the public.¹²³ In the past, the FDA has shown "relaxed" standards for the approval of generics compared to the standards for innovators.¹²⁴ In a recent case, the

118. *Id.* at 438.

119. 21 C.F.R. § 314.70 (2009).

120. Woodcock et al., *supra* note 92, at 438–41.

121. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2), DRAFT GUIDANCE (1999).

122. See Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 360 (2007).

123. See Andrew E. Costa, *Negligence Per Se Theories in Pharmaceutical & Medical Device Litigation*, 57 ME. L. REV. 51, 87 (2005).

124. See Mossinghoff, *supra* note 53, at 191.

FDA even acknowledged that political pressure influenced its approval of Menaflex, a knee repair device.¹²⁵

5. *Effect on Market Pricing*

Although the proposed bills allow for FDA discretion in determining the necessity and scope of clinical trials for safety and efficacy, it is unlikely that the FDA will allow approval of any FOB without at least some clinical testing. Current technology can only determine the similarity of an FOB to its reference innovator through clinical trials. Neither preclinical nor nonhuman studies can fully predict immunogenicity.¹²⁶ Although severe immune reactions may escape detection even in clinical trials,¹²⁷ public safety demands at least some level of human clinical trials for immunogenicity.

As a result of these safety concerns, the effectiveness of an abbreviated FOB approval pathway depends heavily on the scope of clinical trials required by the FDA. Even relatively small trials of biologics in a few hundred patients would likely cost tens of millions of dollars and take several years to complete.¹²⁸ One study surmises clinical trials for FOBs would cost eight to one hundred times more and take twice as long as development for a generic small-molecule drug.¹²⁹ For European approvals, clinical trial costs ranged between \$10 and \$40 million. This contrasts with the \$1 to \$2 million cost and approximately two year time span necessary to demonstrate bioequivalence for generic small-molecule drugs.¹³⁰

Thus, clinical trials for immunogenicity and interchangeability will add tremendous expenses for FOB manufacturers. Moreover, some FOBs may even require *more* clinical trials than their reference innovator biologic.¹³¹ Testing for a new FOB would require testing of the FOB not only against the innovator biologic but also against each previous FOB referencing the same innovator for potential cross-reactions.

125. *Knee Device Approval Exposes Pressure on FDA*, MSNBC, Sept. 25, 2009, http://www.msnbc.msn.com/id/33025867/ns/health-more_health_news/ (last visited Dec 23, 2009).

126. See Nowicki, *supra* note 21, at 270.

127. MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 99, at 108.

128. See Henry Grabowski, Iain Cockburn & Genia Long, *The Market For Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1293 (2006).

129. See Neil Turner, *Biogenerics: A Difficult Birth?*, IMS, http://www1.imshealth.com/web/content/0,3148,64576068_63872702_70261000_71026746,00.html (last visited Oct 27, 2009).

130. See Grabowski et al., *supra* note 128, at 1293.

131. See Christopher Webster et al., *Biologics: Can There Be Abbreviated Applications, Generics, or Follow-On Products?*, BIOPHARM INT'L 28 (2003).

High costs for clinical trials pose serious hurdles for the companies seeking to create FOBs. The Federal Trade Commission (FTC) predicts that clinical testing will lead to high development costs, reducing the number of companies seeking to develop FOBs to a small pool of large companies.¹³² Additionally, the potential price reduction for biologics may only be ten to thirty percent.¹³³ This represents a substantial savings, but cannot match the savings of up to eighty percent seen after generic competitors enter the market for small-molecule drugs.

B. PRESERVING INNOVATION INCENTIVES VS. PUBLIC SAVINGS

Data exclusivity acts as a separate, complementary protection to patents for innovator drug manufacturers. When the innovator initially applies for FDA approval, it submits data from its testing of safety and efficacy. Data exclusivity prevents a subsequent competitor from relying on this data for its own FDA approval for a specified time period.¹³⁴ Competitors must either wait for the exclusivity period to end or finance the high costs to replicate the data themselves.¹³⁵ In effect, the high cost barrier to creating clinical testing data protects innovators from the entry of competitors, and this results in a time period in which the innovator usually enjoys exclusive control of the market.¹³⁶

Patents typically protect innovations in the biotechnology industry. However, the patent system for biologics innovators suffers from numerous drawbacks. With increasing development times for new drugs and the tendency for the PTO to issue composition of matter patents in the early stages of development, innovator biologics companies may find themselves in a situation with little or no patent term left to protect their investment when the product enters the market.¹³⁷ On average, biologics require ten to fifteen years¹³⁸ to progress from initial discovery to FDA approval.¹³⁹ As an example, the biologic cancer drug Avastin required fifteen years to reach patients.¹⁴⁰ Unable to rely on composition of matter patents, a biologics innovator would need to depend on secondary process patents and method

132. See FED. TRADE COMM'N, *supra* note 79, at 15.

133. *Id.* at 23.

134. See JOHNSON, *supra* note 5, at 13.

135. See Eisenberg, *supra* note 122, at 360.

136. See *id.*

137. See *id.* at 348.

138. For comparison, a patent has a life of twenty years from filing. 35 U.S.C. § 154(a)(2) (2006).

139. Tauzin, *supra* note 7, at 59.

140. Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERY 479, 481 (2008).

of use patents. But competitors can easily design around these types of patents.¹⁴¹ Even more, questions of patent validity and infringement create significant uncertainty.

Data exclusivity can address these perceived inadequacies of the patent system for the innovator biologics companies. For drugs with long development times and thus little useful patent life, data exclusivity provides a measure of protection to bring these drugs to market. Data exclusivity indirectly addresses design-around issues because the competitor cannot rely on the innovator's clinical data. Even if the FOB manufacturer could design around an innovator's patent, high financial barriers created by clinical trials restrict the entry of FOB manufacturers. Furthermore, FOB manufacturers cannot challenge data exclusivity as they could a patent, which renders the protection provided by data exclusivity effectively stronger than that provided by patents.¹⁴²

The trade off for any form of exclusivity, whether patent or data, is decreased competition.¹⁴³ By imposing the financial barrier of clinical trials on competitors, data exclusivity would give innovators a relatively assured time period to enjoy exclusive control of the market and allow planned recovery of development costs. During this time, prices would remain relatively high for consumers due to lack of competition in the market.

But the current legislation ultimately seeks to increase competition, thereby expanding access to biologics and driving down costs.¹⁴⁴ This implicates the delicate balance between innovation and competition.¹⁴⁵ Therefore, the proper time span for data exclusivity is a critical issue in the current legislative debate. An optimum time for exclusivity theoretically occurs when the benefits of encouraging biologics development equal the costs of delaying competition.¹⁴⁶ An analysis of the costs involved in biologics development estimates that an innovator company may need 12.9 to 16.2 years to break even on the costs of development for a biologic drug.¹⁴⁷ Based on these studies, the current biologics legislation in Congress calls for a data exclusivity period of twelve years.¹⁴⁸

141. *See id.* at 480.

142. *See* ALEX M. BRILL, PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS: A CRITIQUE 6 (2008).

143. *See* Grabowski, *supra* note 140, at 481.

144. *See Esboo Statement, supra* note 1, at 1.

145. *See Woodcock Statement, supra* note 22, at 5.

146. *See* Grabowski, *supra* note 140, at 481.

147. *Id.* at 487.

148. *See* Affordable Health Care for America Act, H.R. 3962, 111th Cong., at 1537 (2009).

The twelve-year exclusivity period in the current FOB bills represents a major change from the Hatch-Waxman framework. This extended grant of data exclusivity for the innovator biologic manufacturer could potentially shift the principal form of protection in the biologics market from patents to data exclusivity. Unlike the generic small-molecule drug industry where patent protection generally outlasts the period of data exclusivity, for biologics, the data exclusivity period may run even longer than patent protection. This is potentially troubling as data exclusivity is unchallengeable in court.

The opponents of extended data exclusivity include the FTC and generic drug makers. The FTC argues that Hatch-Waxman-like incentives such as exclusivity would not encourage any more innovation than that already encouraged by patent protection and market forces.¹⁴⁹ Patents disallow the same free riding on discoveries that exclusivity would provide, and there is no evidence that patents in biologics are more easily invalidated or designed around.¹⁵⁰ Generic drug manufacturers call a twelve-year exclusivity period “arbitrary and excessive” unjustifiably delaying access to affordable competition and choice for consumers.¹⁵¹ A prior proposal in the House of Representatives, House Bill 1427, called for a much shorter period of five years, identical to the length of data exclusivity in the Hatch-Waxman Act.¹⁵²

Another criticism of the “12.9 to 16.2 years to break even” analysis argues that a break even period should not necessarily equate to a data exclusivity period. Even after competitor FOB entry, an innovator would almost certainly retain a sizable market share and generate profit, although those profits would likely decrease.¹⁵³ Therefore, setting a data exclusivity period at the break-even point may overcompensate the innovator company.¹⁵⁴

On the other hand, a recent analysis suggests that patent protection may inadequately protect even small-molecule drugs. Currently, the Hatch-Waxman framework incentivizes patent challenges that, in turn, may result in

149. See FED. TRADE COMM’N, *supra* note 79, at 38.

150. See *id.* at 36.

151. Jaeger, *supra* note 13, at 2.

152. JOHNSON, *supra* note 5, at 13–14.

153. For example, Eprex, the innovator epoetin alpha in Germany, still retained about half of the market almost a year after entry of biosimilars. See HOSPIRA, HOSPIRA RESPONSES TO FTC QUESTIONS ON BIOSIMILARS (2009), <http://www.ftc.gov/os/comments/healthcarecompissues/090519hospirasupplementonbiosimilars.pdf>.

154. See BRILL, *supra* note 142, at 10.

reduced patent life for innovator companies.¹⁵⁵ For example, the osteoporosis drug Fosamax lost about four years of patent life after a patent challenge.¹⁵⁶ A recent increase in patent challenges has been correlated with a decrease in one indicator of innovation in the drug industry: FDA drugs approvals of new molecular entities.¹⁵⁷ In order to encourage innovation and assure innovator drug companies a period to recoup development costs, commentators have recommended an increase of the data exclusivity period for small-molecule drugs to ten or twelve years.¹⁵⁸ Criticism of the five year length of Hatch-Waxman data exclusivity for small-molecule drugs as inadequate strengthens the justification for a twelve year length of data exclusivity for biologics.

IV. CONCLUSION

The production of biologics and subsequent FOBs represents a unique industry with unique concerns. Innovator companies fear that the patent system will not adequately protect their investments in biologics, either because patents will be designed around or because of a lengthier development timeline. Therefore, data exclusivity may provide the mechanism for the market protection required to foster innovation and assure innovators an opportunity to earn back their investments. Under the currently proposed legislative framework, biologics innovators will enjoy twelve years of data exclusivity, a length of time supported both by an economic break even analysis and by experience in the small-molecule drug industry. Although there are criticisms of the exact economic modeling, to foster innovation it is reasonable to base the data exclusivity period directly on the time required to recoup investments.

Problems unique to FOBs also include the inability to determine bioequivalence compared to the innovator biologic and the safety concern of immunogenicity. Both can potentially lead to much higher development costs for FOBs compared to small-molecule generics. The amount of these increased development costs will be directly proportional to the level of clinical testing required for each FOB approval by the FDA.

Ultimately, the future of FOBs lies with the FDA. The FDA will set the bar for clinical trials, controlling entry into the market. If set too high, clinical

155. See Grabowski & Kyle, *supra* note 50, at 497.

156. Matthew J. Higgins & Stuart J.H. Graham, *Balancing Innovation and Access: Patent Challenges Tip the Scales*, 326 *SCIENCE* 370, 371 (2009).

157. Bethan Hughes, *2007 FDA Drug Approvals: A Year of Flux*, 7 *NATURE REV. DRUG DISCOVERY* 107, 107 (2008).

158. Higgins & Graham, *supra* note 156, at 371.

testing costs will stifle FOBs, meaning no costs savings or actual increased access to drugs for the public. If set too low, reduced costs will facilitate market entry by FOBs, but at the risk of compromising both safety and innovation. In other words, the FDA will not only regulate FOB safety, but the growth of the entire biologics industry. Congress should consider if the FDA is equipped to make these kinds of decisions before delegating the FDA this level of discretionary power.