

Understanding and Incentivizing Biosimilars

JASON KANTER* AND ROBIN FELDMAN**

Congress recently passed the Biosimilars Act in an attempt to replicate the success that generic small molecule drugs have enjoyed under the Hatch-Waxman Act. The Biosimilars Act provides a pathway for biosimilars to achieve quicker and less expensive FDA approval than what is required for a new biopharmaceutical. There is, however, greater uncertainty and cost associated with achieving the coveted biosimilarity status. This reflects the complex production methods of biopharmaceuticals, along with the many factors that can alter the structure and function of such drugs.

This Article analyzes the Biosimilars Act and the draft guidances recently released by the FDA. The Article identifies areas of uncertainty and other aspects of the current regime that create disincentives for the development of biosimilars, as well as suggesting improvements. If we are serious about reducing the price of biological drugs and encouraging the creation of biosimilars, we will need to develop a more effective pathway for approval. This is no easy task. The greater risks associated with the production of biosimilars should prompt a fair degree of caution in establishing the pathway for approval. Balancing consumer safety with appropriate market incentives is a delicate mission. Nevertheless, under the current regime, we risk the possibility that companies will focus on developing so-called biodifferents and biobetters (new drugs designed to mimic an existing biological drug), completely forgoing the opportunity to develop biosimilars.

The loser, of course, is the consumer. It is doubtful that biobetters and biosimilars will have the same price-lowering effects as generics. These drugs will be patented, creating full exclusivity in the market, and prices will remain high in the biological drug space. It would be unfortunate if the tremendous energy and creativity invested in designing and implementing the Biosimilars Act were to have very little effect in the long run.

* University of California, Hastings College of the Law, J.D. 2012; Northwestern University, M.S. 2008; University of California, Los Angeles, B.S. 2007.

** Professor of Law and Director of the Law and Bioscience Project, University of California, Hastings College of the Law. We wish to thank Peter Barton Hutt, Vern Norviel, and members of the 2012 UC Hastings Intellectual Property Concentration Capstone Seminar for their insights and comments.

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INTRODUCTION

Modern small molecule pharmaceuticals cost a great deal of money to research and produce, and a great deal more to obtain FDA approval.¹ As a result, these pharmaceuticals often enter the consumer market at a considerable markup in order to recover investment costs. However, when the patents covering a pharmaceutical expire, generic versions of the drug rapidly enter the marketplace, increasing competition and greatly lowering costs to the average consumer.² The development of generic small molecule drugs has been encouraged through legislation such as the Drug Price Competition and Patent Term Restoration Act—also known as the “Hatch-Waxman Act.” The legislation provides financial incentives and protections for generic drug manufacturers that attempt to enter the market and challenge a brand-drug’s patents.³ While this system is far from perfect, it has maintained a balance between incentivizing new drug development and encouraging the entry of generics into the market.

In contrast, biopharmaceuticals greatly differ from their small molecule cousins. Biopharmaceuticals are far more complex, which increases the costs associated with drug development and FDA approval.⁴ Most biopharmaceuticals are proteins, although the category includes other biological products such as viruses or viral therapeutics, toxins, antitoxins, vaccines, blood, blood components, and allergenic products.⁵ Given the complexity of these products, it is more difficult to determine whether one biological drug is actually identical to another.⁶ Small structural or functional differences may exist that are undetectable with modern scientific tools.⁷ Therefore, the term “generic” does not currently apply to biological drugs copied from an original biologic. Rather, such copies are referred to as biosimilars, or follow-on biologics.⁸

1. See PhRMA, PHARMACEUTICAL INDUSTRY PROFILE 2011, 14–15 (2011); Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really \$802 Million?*, 25 HEALTH AFF. 420, 424–25 (2006); Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 165 (2003).

2. See Henry Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 28 MANAGERIAL & DECISION ECON. 491, 501 (2007).

3. See Hatch-Waxman Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2007)); 35 U.S.C. § 271(e)(2) (2006) (submission of an abbreviated new drug application is an artificial act of infringement, allowing for lawsuits over patent validity without the risk of money damages typically associated with other forms of infringement).

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

5. See 42 U.S.C. § 262(i)(1) (2006).

6. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 4–6 (2012) [hereinafter FDA, SCIENTIFIC CONSIDERATIONS].

7. *Id.*

8. *Id.* at 3.

Congress recently approved the Biologics Price Competition and Innovation Act of 2009 (“Biosimilars Act”) in an attempt to replicate its small molecule generics success in the biopharmaceutical market.⁹ This legislation provides a pathway for biosimilars to achieve quicker and less expensive FDA approval than what is required for a new biopharmaceutical.¹⁰ However, there is greater uncertainty and cost associated with achieving the coveted biosimilarity status.¹¹ This reflects the complex production methods of biopharmaceuticals, along with the many factors that can alter the structure and function of such drugs.¹²

To combat some of the uncertainties in the Biosimilars Act, the FDA released several draft guidances in February 2012.¹³ These guidances provide scientific and quality considerations in demonstrating biosimilarity. They outline the FDA’s “totality of the evidence” approach to biosimilar approval and provide a method for the characterization of proposed biosimilars.¹⁴

While the Biosimilars Act and its associated guidelines indicate that the approval process for biosimilars will be easier and less costly than that of a pioneer biopharmaceutical drug, they provide few clear parameters for a biosimilar manufacturer to rely on, give only a vague outline for FDA approval requirements, and imply that the biosimilar approval process will be far more expensive and time consuming than that of generic small molecule drugs. Given the greater costs and increased uncertainty associated with biosimilar approval, investment in the development of such drugs will likely be inhibited, resulting in lower availability of biosimilars and thus higher costs to consumers. While some uncertainty and additional costs are inevitable given today’s scientific tools, the biosimilar market would benefit from clearer, more quantitative parameters in future Biosimilars Act guidances, better litigation procedures under the Biosimilars Act, and greater legislative exclusivity protections¹⁵ of biosimilar manufacturers.

9. See 42 U.S.C. § 262(k). Small molecule generic drugs have become commonplace in the United States, with annual sales greater than \$51 billion. DAVID HARDING, GAINING MARKET SHARE IN THE GENERIC INDUSTRY THROUGH ACQUISITIONS AND PARTNERSHIPS 2 (2010).

10. 42 U.S.C. § 262(k).

11. FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 4–6.

12. *Id.*

13. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PROTEIN PRODUCT 9–10 (2012) [hereinafter FDA, QUALITY CONSIDERATIONS]; FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 4–6. See generally FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 (2012) [hereinafter FDA, BIOSIMILARS].

14. FDA, QUALITY CONSIDERATIONS, *supra* note 13, at 6; FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 8.

15. Since the passage of Hatch-Waxman in 1984, Congress has provided generic drug applicants

This Article analyzes the Biosimilars Act and the draft guidances, identifying areas of uncertainty and other aspects of the current regime that create disincentives for the development of biosimilars. If we are serious about reducing the price of biological drugs and encouraging the creation of biosimilars, we will need to develop a more effective pathway for approval. This is no easy task. The greater risks associated with the production of biosimilars should prompt a fair degree of caution in establishing the pathway for approval. Balancing consumer safety with appropriate market incentives is a delicate mission. Nevertheless, under the current regime, companies are more likely to focus on the development of so-called biodifferents and biobetters (new drugs designed to mimic an existing biological drug), completely forgoing the opportunity to develop biosimilars. Biodifferents are drugs that are distinct from the FDA-approved biologic, and biobetters are a subset of biodifferents that have better efficacy than the FDA-approved biologic. Biodifferents and biobetters go through the same regulatory approval process as original biopharmaceutical drugs. Should companies choose to develop biodifferents and biobetters rather than biosimilars, the exercise of creating the legislative and regulatory structure for biosimilars will have been largely in vain.

I. GENERIC APPROVAL UNDER THE HATCH-WAXMAN ACT

Congress' treatment of small molecule generics and the relative success of the generic market serve as important points of comparison when evaluating the incentives presented under the Biosimilars Act. In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, often referred to as the "Hatch-Waxman Act."¹⁶ The Hatch-Waxman Act provides for the submission of Abbreviated New Drug Applications ("ANDAs") seeking approval of generic versions of established drugs.¹⁷ This process allows generic drug manufacturers to rely on safety and efficacy data previously submitted to the FDA by a reference product sponsor if the generic applicant can provide enough evidence to show that its drug is sufficiently identical to the reference drug.¹⁸ The FDA's guidances regarding the Hatch-Waxman Act are fairly specific, and define a generic drug to be identical to the original drug

with a 180-day exclusivity period as an incentive for the generic drug manufacturers to challenge patents. David E. Korn et al., *A New History and Discussion of 180-Day Exclusivity*, 64 *FOOD & DRUG L.J.* 335, 335 (2009).

16. See Hatch-Waxman Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2007)).

17. *Id.*

18. *Id.*

when pharmacokinetic studies show that the generic's average bioequivalence falls within an 80–125% range.¹⁹

The Hatch-Waxman Act also provides an opportunity for generic manufacturers to challenge patents that protect a brand drug without exposing the generics to hefty damages from actually producing and selling a version of the patented drug.²⁰ It allows generic manufacturers to artificially infringe a brand manufacturer's patents, avoiding the accrual of actual damages and forcing the brand manufacturers to choose either to initiate a lawsuit or forfeit their rights to do so in the future.²¹ Additionally, Hatch-Waxman provides a 180-day period of exclusivity to the first generic manufacturer that submits an ANDA artificially infringing a reference product's patents, thus incentivizing patent challenges and generic entry into the market.²²

To balance the additional pressure on brand-name manufacturers, Hatch-Waxman creates a period of brand exclusivity, preventing approval of generic drugs until five years after brand approval.²³ Furthermore, Hatch-Waxman provides patent term restoration to brand-name manufacturers, which extends the lifetime of patents covering drugs that obtain FDA approval through the Investigational New Drug and New Drug Application processes.²⁴

The Hatch-Waxman Act has been relatively successful in creating a system that is well defined for investors, incentivizing both new drug development and generic entry. For example, the market share of generic drugs has risen from nineteen percent of all pharmaceutical sales

19. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS 20 (2003); see James D. Henderson & Richard H. Esham, *Generic Substitution: Issues for Problematic Drugs*, 94 S. MED. J. 16, 20 (2001) (“Typically, the data from a single-dose, 2-way crossover bioavailability study are analyzed using a complex statistical model that allows evaluation of the least squares means of the bioavailability parameters and their standard errors. These results are then used to construct the 90% CI for the differences in parameter means. A 90% CI is used, since a 5% statistical error is allowed at both the upper and the lower limits; therefore, the total error is 10%, generating the 90% CI. When the current rule was adopted in 1986, if both the upper and lower limits of the CI were within 20% of the reference mean (80% to 120%), the generic product was declared bioequivalent to the reference product. In 1992, the FDA issued a guidance in which the use of log-transformed data and an upper limit of 125% were adopted.”).

20. 21 U.S.C. § 355.

21. *Id.*

22. *Id.*

23. *Id.* § 355(j)(5)(B)(iv).

24. *Id.* Additionally, the Investigational New Drug process allows a drug developer to obtain an exemption from the FDA that permits it to transport the experimental drug for the conduct of clinical trials. FOOD & DRUG ADMIN., INVESTIGATIONAL NEW DRUG (IND) APPLICATION, <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm> (last updated June 6, 2011).

in 1984 to over half of all such sales today.²⁵ Furthermore, after patent expiration, most popular small molecule drugs experience swift generic competition.²⁶ This added competition from generics saves consumers billions of dollars each year.²⁷ Despite the Hatch-Waxman Act's strong encouragement of generic entry, the system has not resulted in reduced incentives to create new branded drugs. In fact, research and development spending has increased steadily over the past decade, reaching nearly \$67.4 billion in 2010.²⁸

While regulations concerning approval of biosimilars undoubtedly require different considerations from those of generics, the success of the Hatch-Waxman Act provides a reasonable example of balanced incentives for both brand and follow-on drug development. As such, the Act serves as a useful measuring stick for examining the biosimilar legislation and regulations.

II. NATURAL PROCESS VARIATION AND COMPLEXITY IN BIOPHARMACEUTICAL DEVELOPMENT

One major factor in determining what incentives biosimilars will require is the relative complexity of such drugs. Biological drugs are often much more elaborate than the average small molecule drug, creating greater costs and difficulty both in accurately mimicking a brand-name biopharmaceutical and in demonstrating just how similar a follow-on biologic actually is.²⁹ This complexity arises not only from the greater relative molecular size of biopharmaceuticals, but also from the structural variation resulting from protein folding and post-translational modifications.³⁰ These difficulties are further increased by the unique production processes that must be employed to manufacture such drugs.³¹ As a result, biosimilar manufacturers have an innate disadvantage when compared with generic manufacturers, which may necessitate greater statutory or administrative incentives for encouraging biosimilar development.

As mentioned previously, biopharmaceutical drugs are enormously large and complex molecular structures compared to typical small molecule drugs. A good example of the relative size of these medications

25. Ernst R. Berndt & Murray L. Aitken, *Brand Loyalty, Generic Entry and Price Competition in Pharmaceuticals in the Quarter Century After the 1984 Waxman-Hatch Legislation*, 18 INT'L J. ECON. BUS. 177, 181-82 (2011) (noting a current generic market share of 74.5%).

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

27. *Id.* at ix (noting an estimated savings of \$8-10 billion in 1994 alone).

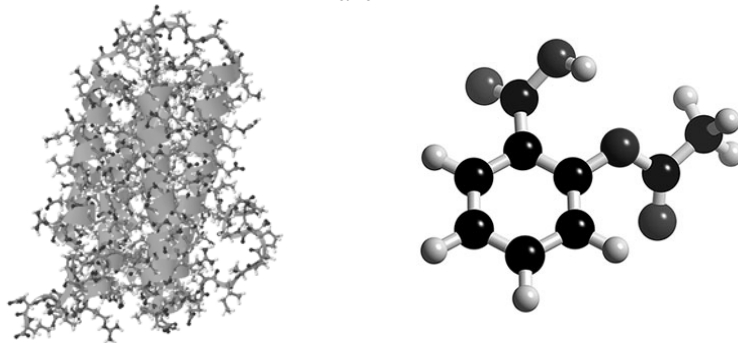
28. PhRMA, *supra* note 1 at 10-11, 16.

29. FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 4-6.

30. *Id.*

31. *Id.*

is the popular drug Epogen, produced by Amgen.³² Epogen is a replication of the human erythropoietin protein, which stimulates the production of red blood cells and is typically used to treat anemia.³³ In 2010, worldwide sales of Epogen exceeded \$2.5 billion.³⁴ The erythropoietin molecule is made up of 165 amino acids and weighs approximately 30,400 daltons.³⁵ That makes Epogen 168 times heavier than the small molecule drug Aspirin, which weighs only about 180 daltons—in comparison, Epogen appears massive in scale.³⁶ Figures 1 and 2 are



illustrations of the amino acid structure of an erythropoietin molecule (left) compared with an aspirin molecule (at right and not to scale):

FIGURES 1³⁷ & 2³⁸

32. See generally FOOD & DRUG ADMIN., PROCIT LABEL, EPOGEN LABEL (2007) [hereinafter FDA, PROCIT/EPOGEN]; AMGEN, EPOGEN, <http://www.epogen.com> (last visited Oct. 2, 2012).

33. See FDA, PROCIT/EPOGEN, *supra* note 32, at 36. “Anemia is a condition in which you don’t have enough healthy red blood cells to carry adequate oxygen to your tissues.” *Anemia*, MAYO CLINIC, <http://www.mayoclinic.com/health/anemia/DS00321> (last visited Oct. 2, 2012).

34. Brady Huggett et al., *Public Biotech 2010—The Numbers*, 29 NATURE BIOTECH. 585, 589 (2011).

35. See FDA, PROCIT/EPOGEN, *supra* note 32, at 36. A dalton is a unit of mass on the molecular scale, representing approximately 1.660×10^{-27} kg. *Convert Dalton to Atomic Mass Unit*, CONVERSION CENTER, [http://www.conversioncenter.net/mass-conversion/from-dalton-to-atomic-mass-unit-\(amu\)](http://www.conversioncenter.net/mass-conversion/from-dalton-to-atomic-mass-unit-(amu)) (last visited Oct. 2, 2012).

36. PUBCHEM, ASPIRIN-COMPOUND SUMMARY, <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2244> (last visited Oct. 2, 2012).

37. *File:HumanEPO.png*, GANFYD, <http://www.ganfyd.org/index.php?title=File:HumanEPO.png> (last visited Oct. 2, 2012).

38. *Aspirin* @ 3DCHEM.COM, 3DCHEM, <http://www.3dchem.com/molecules.asp?ID=157> (last visited Oct. 2, 2012).

Because of the greater size and complexity of protein-based drugs, they often cannot be synthesized artificially and are instead produced in living organisms such as bacteria or mammalian cell cultures.³⁹ As a result, it is more difficult to control and monitor biopharmaceutical production processes. Furthermore, natural variations and changes in such bacteria may introduce variation between two processes or even from one batch to the next. For example, mutations in the DNA of the producing organisms can result in changes in the protein sequence of the drug.⁴⁰ Generic developers do not need to contend with these process issues, and they are typically able to manufacture a small-molecule drug through a series of relatively well-characterized chemical reactions, producing a reliable outcome.⁴¹

Even if a biosimilar manufacturer manages to create a stable production system that can exactly copy the sequence of amino acids in a brand biopharmaceutical (referred to as its primary structure), the resulting biosimilar may have a very different secondary, tertiary, or quaternary structure (Figure 2), each of which helps to define the protein's effect on a living organism.⁴²

FIGURE 3⁴³

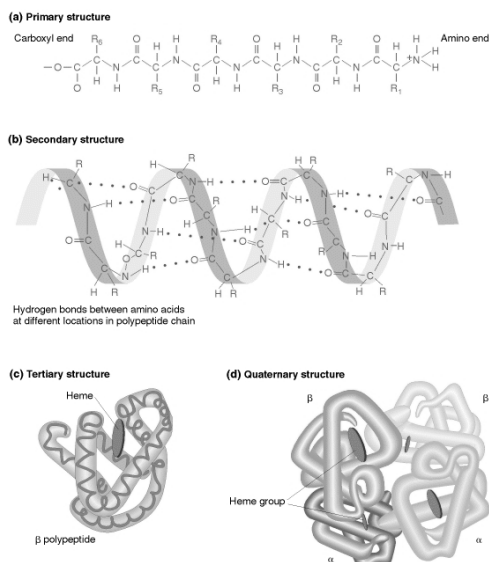
39. FDA, QUALITY CONSIDERATIONS, *supra* note 13, at 9–10 (“Therapeutic protein products can be produced by microbial cells (prokaryotic, eukaryotic), cell lines of human or animal origin (e.g., mammalian, avian, insect), or tissues derived from animals or plants.”).

40. See, e.g., John W. Drake, *A Constant Rate of Spontaneous Mutation in DNA-Based Microbes*, 88 PROC. NAT'L. ACAD. SCI. USA 7160, 7160–64 (1991) (noting the rates of DNA mutation in various microbial organisms).

41. *Small and Large Molecules: Drugs on a Chemical and Biological Basis*, BAYER HEALTHCARE SCIENCE FOR A BETTER LIFE, <http://www.bayerpharma.com/en/research-and-development/technologies/small-and-large-molecules/index.php> (last visited Oct. 2, 2012) (discussing the “classic way” of producing small molecules, the use of “automated synthesis methods” and automated high-throughput screening to comb through a library of two million small molecules).

42. FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 4–5 (“[E]ven minor structural differences . . . can significantly affect a protein's safety, purity, and/or potency . . .”).

43. A.J.F. GRIFFITHS ET AL., MODERN GENETIC ANALYSIS (1999), *image available at* <http://www.ncbi.nlm.nih.gov/books/NBK21385> (hemoglobin protein structure).



Secondary structures refer to localized protein folding and structures, tertiary to the interactions between the secondary structures, and quaternary to interactions between the tertiary structures of two or more individual protein chains.

A number of factors help to define how a produced protein is folded, such as enzymatic interactions and the chemistry present in the producing cell.⁴⁴ The subsequent purification, processing, and storage of such a protein by a drug manufacturer can further affect its structure.⁴⁵ Some structural changes will not alter the function of a protein, but others may significantly affect the safety and efficacy of a drug.⁴⁶

Even where the bioactivity of a biopharmaceutical is identical to the natural protein it mimics, undetectable differences can result in dangerous side effects. One particular danger that may result from such differences is the possibility of increased immunogenicity. Unlike small molecule drugs, protein-based drugs are often large enough to be detected by antibodies, making biological drugs especially vulnerable to immunogenicity issues. Immunogenicity occurs when patients develop antibodies against the biologics with which they have been treated, sometimes leading to an immune system response.⁴⁷

44. Christopher M. Dobson, *Protein Folding and Misfolding*, 426 NATURE 884, 884–89 (2003).

45. FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 5 (“Protein modifications and higher order structure can be affected by environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems, and delivery device materials.”).

46. FDA, QUALITY CONSIDERATIONS, *supra* note 13, at 9 (noting that “minor modifications, such as N or C terminal truncation” may not affect the safety, purity, or potency of some protein-based drugs).

47. Trevor Woodage, *Blinded by (a Lack of) Science: Limitations in Determining Therapeutic*

A good illustration of the danger of biopharmaceutical immunogenicity is the drug Eprex.⁴⁸ Eprex is an erythropoietin drug sold primarily in Europe. The production methodology for Eprex was very similar to that of Epogen.⁴⁹ Both drugs had identical amino acid sequences and were produced in Chinese Hamster Ovary cells, a popular mammalian cell line.⁵⁰ Eprex and Epogen were originally formulated, stored, and shipped in human serum albumin.⁵¹ However, in 1998, Eprex replaced the human serum albumin with polysorbate 80 and glycine in order to avoid the possible risk of transmitting Creutzfeldt-Jakob disease, the human form of what is commonly referred to as mad cow disease, through the human material.⁵² It is not clear how these minor changes affected the protein drugs, but patients subcutaneously injected with Eprex experienced an unexpectedly rapid immune response to the drug.⁵³ The antibodies produced in response to Eprex injection were, in some cases, cross-reactive with patients' natural erythropoietin, essentially triggering an auto-immune response. In other words, the antibodies produced in response to administration of the biologic began to attack the patient's own erythropoietin.⁵⁴ Because auto-immune reactions like this are not generally reversible, these patients experienced a potentially permanent impairment of their own erythropoietin activity, exacerbating their existing anemia.⁵⁵ Some of the affected patients were, however, able to regain some natural erythropoietin activity by undergoing immunosuppressive therapy or a renal allograft.⁵⁶ A renal allograft is a procedure during which a portion of a donor's kidney is

Equivalence of Follow-On Biologics and Barriers to Their Approval and Commercialization, 9 STAN. TECH. L. REV. 1, 6 (2012).

48. Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, B.C. INTELL. PROP. & TECH. F., 2009, at 3.

49. Songpon Deechongkit et al., *Biophysical Comparability of the Same Protein from Different Manufacturers: A Case Study Using Epoetin Alfa from Epogen® and Eprex®*, 95 J. PHARM. SCI. 1931, 1932 (2006).

50. *Id.*

51. Charles L. Bennett et al., *Long-Term Outcome of Individuals with Pure Red Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Epoetin: A Follow-Up Report from the Research on Adverse Drug Events and Reports (RADAR) Project*, 106 BLOOD 3343, 3343-44 (2012).

52. *Id.*

53. See Sahr, *supra* note 48, at 3 (citing Denis Cournoyer et al., *Anti-Erythropoietin Antibody-Mediated Pure Red Cell Aplasia After Treatment with Recombinant Erythropoietin Products: Recommendations for Minimization of Risk*, 15 J. AM. SOC. NEPHROL. 2728, 2728-29 (2004)); see also Deechongkit et al., *supra* note 49, at 1939-40 (noting that Eprex is less likely to re-fold when exposed to extreme conditions than Epogen and suggesting some potential structural differences).

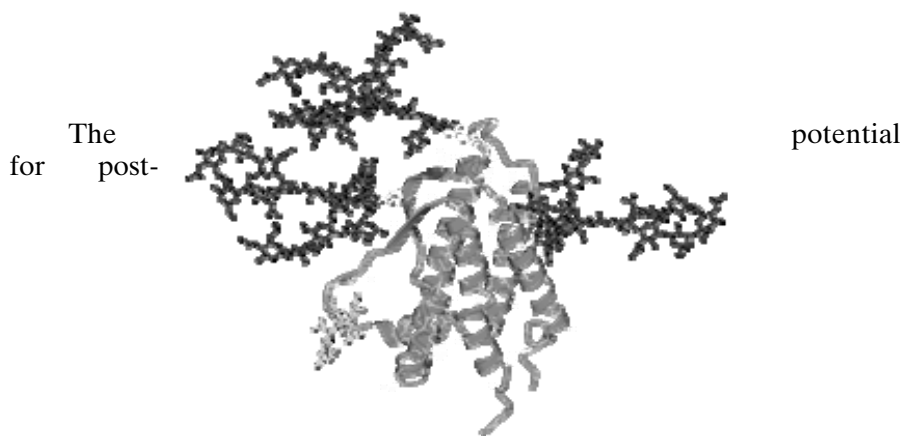
54. Sahr, *supra* note 48, at 3.

55. *Id.*

56. See Nicole Casadevall et al., *Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin*, 346 NEW ENG. J. MED. 469, 470 (2002).

grafted onto the kidney of a recipient in the hopes of restoring kidney function of the recipient.

FIGURE 4⁵⁷



translational modification of a protein is another concern with biosimilars. Post-translational modification occurs when enzymes present in a cell add various non-protein molecules to the protein structure of the drug.⁵⁸ The addition of these non-protein molecules includes, for example, sugars (glycosylation) and phosphate groups (phosphorylation).⁵⁹ Like structural changes, post-translational modification can affect the function, stability, bioavailability, and immunogenicity of a protein.⁶⁰ For example, improper glycosylation of

57. Image courtesy of Mark Wormald, Pauline Rudd, and Raymond, Dwek Glycobiology Institute, Department of Biochemistry, University of Oxford, UK.

58. Sahr, *supra* note 48, at 3.

59. FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 9–10.

60. FDA, QUALITY CONSIDERATIONS, *supra* note 13, at 12 (“[B]ioavailability can be dramatically altered by subtle differences in glycoform distribution or other post-translation modifications.”); Nigel

human erythropoietin (pictured in glycosylated form in Figure 4) can greatly reduce the drug's intended effect.⁶¹ Variations of erythropoietin missing even a single glycosylation site have been shown to have up to 80% less biological activity.⁶² Additionally, differences between producing cell lines may cause variation in post-translational modification, and a given cell may modify proteins differently based on different conditions or stimuli.⁶³

Given that these issues are unique to biopharmaceutical drugs, the preclinical development costs per biological drug candidate are higher than those of small molecule cousins.⁶⁴ Studies have estimated the preclinical costs for biological drugs to be 46% higher than those of small molecule drugs.⁶⁵ In light of these difficulties, and given the Hatch-Waxman Act's success in creating effective generic incentives, an approach similar to Hatch-Waxman's should, in theory, help to mitigate these greater costs and establish similar incentives for both the biosimilar and generic markets. The greater safety and efficacy risks of biological drugs do suggest that the process will always be more cumbersome for follow-on biological drugs than for generics. Nevertheless, the Hatch-Waxman framework provides a reasonable model.

III. LACK OF CLARITY IN THE REQUIREMENTS FOR PROVING BIOSIMILARITY UNDER THE BIOSIMILARS ACT AND DRAFT GUIDANCES

The Biosimilars Act was enacted as part of the recent Patient Protection and Affordable Care Act.⁶⁶ Similar in spirit to the Hatch-Waxman Act, the Biosimilars Act creates an abbreviated approval pathway for biological products that can be shown to be sufficiently similar to a previously approved biological drug.⁶⁷ While the framework set forth by the Biosimilars Act and the FDA's recent draft guidances is certainly better than no framework at all, the incentives provided for biosimilar development are less robust than incentives for generic

Jenkins et al., *Post-Translational Modifications of Recombinant Proteins: Significance for Biopharmaceuticals*, 39 MOLECULAR BIOTECH. 113, 113-18 (2008).

61. Evelyne Delorme et al., *Role of Glycosylation on the Secretion and Biological Activity of Erythropoietin*, 31 BIOCHEMISTRY 9871, 9871-76 (1992); Syamalima Dubé et al., *Glycosylation at Specific Sites of Erythropoietin Is Essential for Biosynthesis, Secretion, and Biological Function*, 253 BIOCHEMISTRY 17516, 17516-21 (1988).

62. Delorme et al., *supra* note 61, at 9871; Dubé et al., *supra* note 61, at 17516.

63. Gary Walsh & Roy Jefferis, *Post-Translational Modifications in the Context of Therapeutic Proteins*, 24 NATURE BIOTECH. 1241, 1241-52 (2006).

64. DiMasi & Grabowski, *supra* note 4, at 472-77.

65. *Id.* at 475.

66. 42 U.S.C. § 262 (2006).

67. *Id.*

production under the Hatch-Waxman Act, and are unlikely to be sufficient to attract much activity in the biosimilars market.

Under § 351(k) of the Biosimilars Act (“351(k) application”), a biosimilar manufacturer must demonstrate that its product is biosimilar to a prior approved reference product.⁶⁸ In order to meet this standard, the statute requires that an applicant must show that the two products are “highly similar” and have “no clinically meaningful differences” in their safety or efficacy.⁶⁹ The statute does not define what constitutes a clinically meaningful difference, nor does it say what is required for two products to be highly similar. Given the lack of clarity in both of these dimensions, biosimilar manufacturers cannot anticipate whether they will be required to undergo only simple studies regarding protein structure, pharmacodynamics,⁷⁰ and pharmacokinetics,⁷¹ or whether they will have to invest in potentially cost-prohibitive clinical trials.

In its guidances on the Biosimilars Act the FDA provides a stepwise approach for demonstrating biosimilarity.⁷² The goal of this approach is to front-load the costs of demonstrating biosimilarity and to reduce the need for clinical trials.⁷³ The guidances note that the first step in showing biosimilarity is a comprehensive structural analysis of the protein-based drug.⁷⁴ Greater structural characterization will increase the justification for smaller, more targeted tests going forward.⁷⁵ Next, a sponsor must perform functional assays that measure the activity of the biologic drug.⁷⁶ While the resulting data may change the scope of the subsequent tests, the guidances imply that regardless of the outcome of the functional and structural tests, there is a high likelihood that animal or human trials will still be required.⁷⁷ Following the structural and functional analysis, the guidances suggest that a sponsor design and perform animal studies to test

68. *Id.* § 262(k).

69. *Id.* § 262(i)(2).

70. Pharmacodynamic data describe the physiological effect of an administered pharmacological agent. Generally, these data are used to determine the appropriate dose for a drug. *See Pharmacodynamics Definition*, MERRIAM-WEBSTER.COM, <http://www.merriam-webster.com/dictionary/pharmacodynamics> (last visited Oct. 2, 2012).

71. Pharmacokinetic data describe the levels of drug that remain in the body over time. *See Pharmacokinetics Definition*, MERRIAM-WEBSTER.COM, <http://www.merriam-webster.com/dictionary/pharmacokinetics> (last visited Oct. 2, 2012).

72. *See* FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 7–8.

73. *Id.*

74. *Id.* at 8–10.

75. *Id.*

76. *Id.* at 10. Functional assays are useful for showing the mechanism of action for a drug. Evidence that the mechanism of action is identical between two drugs helps to narrow the scope of future tests to demonstrate biosimilarity. *Id.*

77. *Id.* at 11, 12.

the toxicity, pharmacokinetics, pharmacodynamics, and immunogenicity of the sponsored drug.⁷⁸

Next, the guidances discuss the need for human clinical trials, noting that a sponsor must demonstrate that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”⁷⁹ In order to accomplish this, the guidances recommend conducting human studies on immunogenicity, pharmacokinetics, and pharmacodynamics.⁸⁰ Unfortunately, the lack of current tools to adequately characterize complex biopharmaceuticals almost guarantees the need for at least some clinical testing. In a 2007 statement before the House Committee on Oversight and Government Reform, Dr. Janet Woodcock, the Deputy Commissioner and Chief Medical Officer of the FDA, noted that the “ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited.”⁸¹ Because of this limitation, Dr. Woodcock concluded that “some degree of clinical assessment of a new product’s immunogenic potential will ordinarily be needed.”⁸²

Finally, the guidances provide that if there are “residual uncertainties” about the biosimilarity of a drug, clinical studies for safety and efficacy should be performed.⁸³ These are the most expensive and time-consuming categories of clinical trials because they require the measurement of clinical endpoint results which for some drugs may take a long period of time, depending on its mechanism of action and associated risks.⁸⁴ The guidances do not provide the extent of the required clinical trials, and instead provide factors that “may influence the type and extent of the comparative clinical safety and effectiveness data needed.”⁸⁵ These factors include, for example, the complexity of the reference product, the extent to which differences between the brand and biosimilar predict differences in clinical outcomes, the extent to which human pharmacokinetics and pharmacodynamics predict clinical

78. *Id.*

79. *Id.* at 12 (quoting § 7002(b)(3) of the Affordable Care Act, adding § 351(i)(2) of the Public Health Services Act).

80. *Id.*

81. *Follow-On Protein Products: Hearing Before the H. Comm. on Oversight and Gov’t Reform*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm’r, Chief Medical Officer, Food & Drug Admin.).

82. *Id.*

83. FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 16.

84. *See* PhRMA, *supra* note 1, at 13.

85. FDA, SCIENTIFIC CONSIDERATIONS, *supra* note 6, at 16.

outcomes, the extent of clinical experience with the reference product, and the extent of clinical experience with the proposed product.⁸⁶

If extensive safety and efficacy clinical testing is required, it might be cost-prohibitive for biosimilar manufacturers. At some point, it may simply make more sense to apply for a new drug application, which brings considerably more freedom than a biosimilar designation. Furthermore, the FDA has not clarified what may constitute a residual uncertainty that requires such clinical testing—although it has listed some factors that might go into the consideration—nor has it defined how such a determination will be made.⁸⁷ As a practical matter, from a scientific viewpoint, there will always be some uncertainty as to whether two complex molecules are completely identical, and the FDA has stated that “current analytical methodology may not be able to detect all relevant structural and functional differences between two proteins.”⁸⁸ In effect, this could mean that most or all biosimilar drugs will have to undergo some clinical trials.

Given the expansive testing requirements under the new guidances, the uncertainty over whether efficacy and safety clinical trials will be required, and the vagueness of the “no clinically meaningful differences” standard, it seems likely that biosimilar drugs will take much longer to approve and cost much more money than the average small molecule generic drug. Considering the high cost of clinical trials, even a few such studies might cost tens or hundreds of millions of dollars, compared to the approval of a generic small molecule drug which is a much simpler and less expensive process.⁸⁹ Under the ANDA approval process, a small molecule drug manufacturer need only show that its drug delivers the same active ingredient to the blood at the same rate as the brand drug in twenty-four to thirty-six healthy volunteers.⁹⁰

The FDA could remove some of these uncertainties by establishing clearer guidelines for the approval process and by defining key terms such as “residual uncertainties” and “clinically meaningful differences.” Given today’s scientific tools and understanding, it would be difficult for the FDA to quantitatively define what positive factors will lead to approval of a follow-on biologic. Accordingly, it is understandable that the FDA would want to set forth very broad guidelines so that it maintains the greatest amount of discretion. However, the FDA could

86. *Id.*

87. *Id.* at 12.

88. *Id.* at 5.

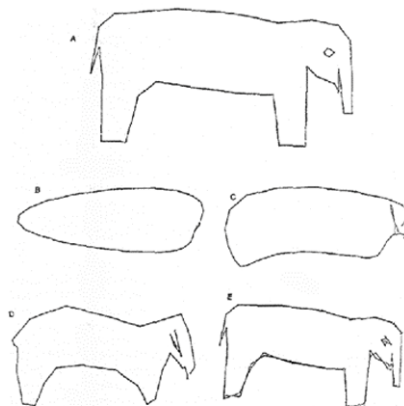
89. See Dimasi et al., *supra* note 1, at 151.

90. *Abbreviated New Drug Application (ANDA): Generics*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics> (last updated Sept. 7, 2012).

maintain its discretionary totality-of-the-evidence approach while still providing biosimilar manufacturers with better approval guidelines. One way that this could be accomplished is by setting forth conditions that would result in the rejection of a biosimilar. For example, the FDA could set limits on the type and frequency of primary-sequence differences in a biosimilar or maximum differences in bioavailability. Any biosimilar with characteristics outside of the tolerated range of differences would very likely be rejected. While this approach is not as useful to a manufacturer as definite approval conditions, it would provide an opportunity for biosimilar manufacturers to gauge the viability of their drug during the evaluation process. Any range or other quantifiable element would allow businesses to better calculate and manage their risk.

The FDA recently provided a good analogy for looking at failure conditions in biosimilar approval. In February, Dr. Rachel Sherman, Associate Director for Medical Policy at the Center for Drug Evaluation and Research, delivered a presentation explaining the FDA's guidance and stepwise totality of the evidence approach to proving biosimilarity.⁹¹ Her presentation included a sketch of an elephant that represented a brand biopharmaceutical drug (labeled "A" in Figure 5), and several other sketches each representing an analytical or clinical study performed by a biosimilar applicant, coming together to provide a more complete picture of the drug candidate (labeled "B-E").

Figure 5⁹²



91. See generally RACHEL E. SHERMAN, BIOSIMILAR BIOLOGICAL PRODUCTS: BIOSIMILAR GUIDANCE WEBINAR (2012).

92. *Id.* at 8.

Using this analogy, it was noted that the appearance of a beak or fins when the applicant expects to see an elephant might inform an applicant at an early stage that their product will not qualify for approval.⁹³ While humans are well qualified to recognize a beak or fin, determining whether a structural difference in a complex protein constitutes a minor, unimportant change or a major, prohibitive modification is not so simple. If the FDA helps to define what types of changes are not likely to be acceptable, biosimilar manufacturers will be in a better position to evaluate the potential success or failure of their drug and make more informed decisions about whether to continue with their drug candidate or to go back to the drawing board.

IV. INTERCHANGEABILITY UNDER THE BIOSIMILARS ACT AND DRAFT GUIDANCES

Under the Biosimilars Act, an applicant may attempt to show that a biosimilar is “interchangeable” with the original drug.⁹⁴ An interchangeable biological drug, in theory, would enjoy similar benefits to those of generic small molecule drugs.⁹⁵ For example, the Biosimilars Act allows an interchangeable biosimilar to be substituted for its reference product without the approval of a health care provider.⁹⁶ However, proving interchangeability can be very difficult, and the substitution provisions may conflict with some state substitution statutes that are better adapted for small molecule drugs.

A. OBTAINING INTERCHANGEABILITY STATUS IS DIFFICULT.

Interchangeability status is achieved by demonstrating: 1) biosimilarity to the original drug, 2) that the drug is expected to produce the same clinical results as the original brand-name drug, and 3) that repeated administration of the drug will not reduce its efficacy or increase its toxicity or side effects in a way that is beyond what is expected from the brand-name drug.⁹⁷ Essentially, the interchangeable drug must be at least as effective as the brand drug and have no greater side effects with repeated dosage.

While this is a highly sought-after status, the guidances make it clear that interchangeability for biosimilars is a long way off. In one of the guidances, the FDA notes that it is possible for an applicant to obtain a determination of interchangeability in an original 351(k) application, but

93. *See id.*

94. 42 U.S.C. § 262(k) (2006).

95. *See id.* § 262(i).

96. *Id.* § 262(i)(3).

97. *Id.* § 262(k)(4).

that “[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability” in such an application “given the statutory standard for interchangeability and the sequential nature of that assessment.”⁹⁸

Without an easy pathway to substitution, biosimilar drugs may not be able to capture market share as effectively as small-molecule generic drugs can, which could result in higher overall prices or delays in price reduction for the average consumer. Because small differences in biosimilar drugs are likely to exist, however, allowing substitution without a showing of clinical identity could result in unacceptable safety issues. As a result, the stringent requirements for interchangeability status may be necessary to protect patient safety.

B. STATE LAWS MAY INTERFERE WITH THE SUBSTITUTABILITY OF INTERCHANGEABLE BIOPHARMACEUTICALS.

Substitutability is one way that a generic drug can quickly capture a large market share. However, many state laws are not yet adapted for use with biopharmaceuticals, and this can create conflicts with interchangeability benefits under the Biosimilars Act. For example, section 4073 of the California Business and Professions Code permits California pharmacists to exchange generic drugs for the brand name without permission from the prescribing doctor.⁹⁹ However, the statute requires that the substituted drug have the “same active chemical ingredients,” which is more restrictive than the definition of interchangeability.¹⁰⁰ As described above, biosimilars are rarely exact copies of brand-name biological drugs and often contain undetectable differences, which make the notion of “same active chemical ingredients” a poor fit for biologics.

This issue may be a source of short-term uncertainty, as it will likely be resolved in time by each individual state legislature as they update their substitution laws or enact new ones to deal with interchangeable biosimilars. However, in the meantime, prospective biosimilar manufacturers will not be able to predict how states will treat their drug if the manufacturers achieve interchangeability status. This issue could be remedied quickly by a federal law preempting state substitution laws. Congress, however, allowed states to design their own substitutions laws with respect to generics and may choose to adopt the same approach with biosimilars.

98. FDA, BIOSIMILARS, *supra* note 13, at 11.

99. CAL. BUS. & PROF. CODE § 4073 (Deering 2012).

100. *Id.* § 4073(a); see MARSHA N. COHEN & SAMI SEDGHANI, PHARMACY LAW FOR CALIFORNIA PHARMACISTS, 188–89 (7th ed. 2012) (discussing California generic substitution laws).

V. EXCLUSIVITY UNDER THE BIOSIMILARS ACT AND DRAFT GUIDANCES

A. THERE ARE SEVERAL FORMS OF EXCLUSIVITY FOR BRAND-NAME MANUFACTURERS.

The Biosimilars Act provides several forms of exclusivity for brand-name biopharmaceutical manufacturers. First, the Act prohibits the filing of biosimilar applications under section 351(k) until four years after the approval of the brand drug.¹⁰¹ This is similar to the five-year exclusivity afforded under the Hatch-Waxman Act.¹⁰² Additionally, the Biosimilars Act prohibits FDA approval of any follow-on application until at least twelve years after the date on which its reference product is first licensed.¹⁰³ Finally, if the FDA requests pediatric studies from an applicant and the applicant completes those studies, it will receive an additional extension of six months exclusivity for both of the above-mentioned periods.¹⁰⁴

In theory, these expansive periods of exclusivity would help a brand-name manufacturer recover the greater costs associated with developing biopharmaceuticals, assuming that the drug's patents expire prior to the end of the exclusivity. However, studies show that overall costs in producing a new brand biological drug are lower than those associated with producing a new small-molecule drug.¹⁰⁵ One potential explanation for this is that biopharmaceutical candidates are usually copies or variations of natural human proteins, and so they are better adapted for their given purpose. Additionally, in the case of biopharmaceuticals that simply copy human proteins, researchers have a blueprint upon which to work and do not need to screen a molecular database, resulting in fewer failed candidates. Given that brand biological drug development costs are lower than those of brand small-molecule drugs, such a long period of exclusivity for brand biological drug manufacturers may be excessive and may serve only to unduly delay biosimilar entry into the market. The Biosimilars Act was added at the last minute to the massive 2010 health care reform bill and lacks the extensive legislative history that would normally accompany legislation of this complexity. As a result, the logic for the twelve-year period is absent, and Congress may want to revisit this issue once it has gained experience with the effects of the legislation.

101. 42 U.S.C. § 262(k)(7)(B).

102. See 21 U.S.C. § 355(j)(5)(E)(ii) (2007).

103. 42 U.S.C. § 262(k)(7)(A).

104. *Id.* § 262(m)(2)–(3).

105. See generally PHRMA, *supra* note 1.

B. THERE IS EXCLUSIVITY FOR BIOSIMILAR MANUFACTURERS IF THEIR FOLLOW-ON BIOLOGIC IS THE FIRST TO BE DEEMED INTERCHANGEABLE WITH A REFERENCE PRODUCT.

The Biosimilars Act also provides exclusivity for the first follow-on biologic that is deemed interchangeable with a reference product.¹⁰⁶ This exclusivity lasts for up to one year, but may be shortened under some circumstances.¹⁰⁷ Unlike the Hatch-Waxman Act's generic exclusivity, which promises exclusivity to the first filing parties, interchangeability exclusivity applies to the first drug that is deemed by the FDA to be interchangeable.¹⁰⁸ While this does solve the common Hatch-Waxman issue of multiple first-to-file manufacturers who each claim exclusivity, it creates a situation where biopharmaceutical manufacturers must invest in creating the drug and pursuing its approval as both biosimilar and interchangeable without knowing whether it will benefit from a period of exclusivity.

One potential solution to this problem is to divide the approval process into two parts, one for biosimilar approval and the next for drugs that have already been deemed biosimilar and wish to apply for interchangeability. Under this approach, the FDA could provide exclusivity to the first party to file for interchangeability status. The variable period of time required to complete the biosimilar approval process would help to space out the manufacturers, preventing the multiple first filer issues seen under Hatch-Waxman. It would also permit manufacturers to foresee whether they would have some form of exclusivity before investing heavily in the clinical trials needed to obtain interchangeability, allowing them to make better risk management decisions.

VI. PATENT LITIGATION UNDER THE BIOSIMILARS ACT AND DRAFT GUIDANCES

The Biosimilars Act, like the Hatch-Waxman Act, makes it an act of artificial patent infringement to submit an application for a biosimilar when its reference product is still under patent coverage.¹⁰⁹ The Biosimilars Act also sets forth a complicated set of requirements for both

^{106.} 42 U.S.C. § 262(k)(6).

^{107.} *Id.* (providing for up to one year of exclusivity, cut short by the earliest of: 18 months after a final court decision (including non-prejudicial dismissal) of an infringement action against one of the applicant's patents, 42 months after the approval of the first applicant's 351(k) application if a patent suit is ongoing, or 18 months after the approval of the applicant's 351(k) application if no patent infringement suit was brought).

^{108.} *Id.*

^{109.} 35 U.S.C. § 271(e)(2) (2006).

the biosimilar and brand manufacturer in a patent suit.¹¹⁰ However, because the statute is relatively young and complex, there are numerous uncertainties in how it will be applied and how it will interact with existing laws. Additionally, the complicated procedures appear to favor the brand manufacturer. This Article illustrates several striking uncertainties regarding the patent litigation dance delineated in the Biosimilars Act, but it will take years of experience with litigation under that act to truly work out all of the dimensions of the interactions. As always, uncertainty brings risk and a corresponding reluctance to enter the field.

A. THE DISCLOSURE REQUIREMENTS FOR A BIOSIMILAR APPLICANT ARE UNCLEAR.

In order to keep brand-name drug manufacturers informed about biosimilar applications that may infringe their patents, the Biosimilars Act places several disclosure requirements on the biosimilar applicant.¹¹¹ For example, shortly after a biosimilar application has been accepted by the FDA, the applicant is required to provide a copy of the application and “such other information that describes the process or processes used to manufacture the biological product that is the subject of such application” to the reference sponsor.¹¹² However, the statute does not further define what constitutes “other information,” and it is not clear how a court will interpret the statute. Conceivably, an applicant might be forced to provide trade secrets or other confidential information. In particular, although pharmaceutical companies are required to disclose trade secrets to the FDA, the FDA maintains confidentiality for many aspects of those secrets and does not reveal them to third parties. With biologics, however, the biosimilar manufacturer would need information about the process used by the original biologic manufacturer in order to sufficiently replicate it, which could require the disclosure of trade secrets.

B. THE BIOSIMILARS LITIGATION PROCESS IS COMPLEX AND APPEARS TO FAVOR BRAND MANUFACTURERS RATHER THAN FOLLOW-ON DEVELOPERS.

Under 42 U.S.C. § 262(l), when the biosimilar manufacturer applies for approval, the parties must engage in a complex pre-suit “Patent Information Exchange” process.¹¹³ This process provides for initial

110. 42 U.S.C. § 262(l).

111. *Id.* § 262(l)(2)(A).

112. *Id.*

113. *Id.* § 262(l).

litigation over essential patents and permits subsequent litigation or court action on the remaining patents only after resolution of that initial suit. The reference product sponsor must first provide a list of patents that it believes it can assert against the biosimilar applicant.¹¹⁴ The parties then negotiate on which essential patents will be subject to the first round of litigation.¹¹⁵ If the parties do not agree on which patents shall be litigated, the applicant may specify a number of patents that the reference sponsor may assert.¹¹⁶ In each case, the reference sponsor must assert at least one patent.¹¹⁷ The statute prohibits declaratory judgments for the un-asserted patents during this first round of litigation, though they are still infringed.¹¹⁸ A party may only move for declaratory judgment on these remaining patents after completion of the first round, or upon a 180-day advance notice that the generic intends to market.¹¹⁹

Even when declaratory judgment becomes available, there is no guarantee that a court will grant it. Accordingly, a brand manufacturer may have un-asserted patents that it can still assert against the biosimilar applicant. A biosimilar manufacturer in such a situation most likely would not want to begin producing and selling its drug, given that actual damages might begin to accrue. In other words, the risk would be too great, and the biosimilar might choose to stay out of the market.

C. A POTENTIAL CONFLICT EXISTS BETWEEN THE PATENT STATUTE AND THE REQUIRED PATENT NEGOTIATION PROCESS UNDER THE BIOSIMILARS ACT.

The complex litigation process provided for by the Biosimilars Act may conflict with modifications that the Biosimilars Act made to the patent statute.¹²⁰ For example, under 35 U.S.C. § 271(e)(2)(C), the infringement of the sponsor's to-be-asserted patents exists as soon as an application for a biosimilar is filed. However, 42 U.S.C. § 262(l) does not seem to prohibit an immediate lawsuit. Instead, it provides a number of situations where a manufacturer "shall bring an action" in response to different outcomes of the negotiation process.¹²¹ As a result, it may be possible for a brand manufacturer to sue the applicant upon providing its list of asserted patents and thus circumvent the rest of the exchange and negotiation process.¹²² It is not clear how a court would handle an

114. *Id.* § 262(l)(3).

115. *Id.* § 262(l)(4).

116. *Id.* § 262(l)(5).

117. *Id.*

118. *Id.* § 262(l)(9)(A).

119. *Id.* § 262(l)(9)(B).

120. *See* 35 U.S.C. § 271(e)(2)(C) (2006).

121. 42 U.S.C. § 262(l)(6).

122. *See* 35 U.S.C. § 271(e); 42 U.S.C. § 262(l).

attempt to sue outside of the litigation framework set forth in 42 U.S.C. § 262(l), or whether the remaining provisions of § 272(l) would remain in effect for such litigation.

VII. HIGHER COSTS DUE TO INHIBITION OF BIOSIMILAR AND INTERCHANGEABLE BIOPHARMACEUTICAL MARKET ENTRY

If biosimilar drugs are inhibited from entering the marketplace, the price of biosimilars will likely remain high due to a lack of competition.¹²³ Studies have shown that the entry of a first generic small molecule drug into the market actually causes the price of the brand drug to go higher.¹²⁴ One reason for this increase in brand cost is that there is a segment of the market that is price insensitive and will almost always choose the brand name.¹²⁵ When a generic enters the market, it captures a great segment of the price sensitive segment, and so the brand drugs capitalize on the remaining price insensitive segment by increasing prices.¹²⁶ Furthermore, the first generic to market, having little or no other generic competition, tends to keep its prices relatively high as well, though somewhat lower than the brand drug.¹²⁷ It is not until multiple generics enter the market that there is sufficient competition to cause the prices to fall dramatically.¹²⁸ If this experience holds true for the biopharmaceutical market, in order for consumers to significantly benefit from the biosimilars licensing process, an application under the Biosimilars Act will need to be sufficiently cost-effective and dependable to entice the development of multiple biosimilar products for each brand biopharmaceutical.

CONCLUSION

The natural complexity, difficulty, and added costs in developing a biosimilar and attempting to mimic a reference brand drug present challenges to biosimilar market entry. While this stems partially from our scientific inability to cheaply and effectively create biosimilars, the FDA can help to alleviate these issues by providing incentives for biosimilar development and by providing a well-defined biosimilar approval pathway.

123. See Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 *MANAGERIAL & DECISION ECON.* 439, 439 (2007).

124. See Richard G. Frank & David S. Salkever, *Generic Entry and the Pricing of Pharmaceuticals*, 6 *J. ECON. MGMT. STRATEGY* 75, 79, 89–90 (1997); see also Joel Lexchin, *The Effect of Generic Competition on the Price of Brand-Name Drugs*, 68 *HEALTH POL'Y* 47, 52–53 (2004).

125. See Frank & Salkever, *supra* note 124, at 76–77.

126. *Id.*

127. Lexchin, *supra* note 124, at 47–48.

128. See *id.*; see also WENDY H. SCHACHT, CONG. RESEARCH SERV., R 41483, *FOLLOW-ON-BIOLOGICS: THE LAW AND INTELLECTUAL PROPERTY ISSUES* 16 (2011); Frank & Salkever, *supra* note 124, at 75–90.

Unfortunately, the Biosimilars Act and its guidances raise a number of uncertainties for biosimilar approval and do not yet provide strong incentives for biosimilars. The approval process may be improved through future guidances that define key terms such as “residual uncertainties” and “no clinically meaningful differences.” Some of the uncertainty can also be alleviated by providing more quantitative guidelines for approval, such as required bioavailability levels. Such guidelines need not guarantee approval and would still be useful to a manufacturer if they help to define situations where a biosimilar application is likely to be denied. While there would still be some uncertainty, manufacturers would be in a better informed position to evaluate their chance of obtaining biosimilarity status.

The requirements for interchangeability status under the Biosimilars Act also present hurdles to biosimilar development. The status, which is required for substitution of the biosimilar for a brand prescription, is difficult to achieve, expensive to prove, and might conflict with existing state laws. While instituting strict requirements for interchangeability is necessary for public safety, the great difficulty in achieving the status increases biosimilar costs. Furthermore, biosimilar manufacturers cannot rely on first interchangeable drug exclusivity until interchangeability status has actually been awarded. This might be remedied by instituting first-to-file interchangeability exclusivity, much like generic exclusivity under the Hatch-Waxman Act, and by separating interchangeability approval into a separate process to be completed only after biosimilarity is achieved.

The expansive exclusivity for brand drugs under the Biosimilars Act is another potential hindrance to biosimilar market entry. Given the relative costs between new small molecule and new biopharmaceutical drugs, a period of exclusivity more in line with that provided to brand small molecule drugs under the Hatch-Waxman Act seems more appropriate. In other words, the twelve-year exclusivity for branded biologics seems relatively long given the greater expense and difficulties that biosimilars will face in order to obtain approval.

Most important, litigation under the Biosimilars Act is complex and appears to favor the brand manufacturer. Adding to the troubles, the litigation statutory procedures have not yet been fully interpreted by the courts. These factors lower the incentives for challenging a brand manufacturer’s patents and thus may slow biosimilar market entry.

In the current atmosphere, many companies considering entering the biosimilars market may decide to forgo the pathway offered by Congress. The alternative for these companies is to create what are known as biodifferents or biobetters. These are variations on the original branded drug that would not be subject to the Biosimilars Act at all.

Such companies would have to do all of the extensive testing required for new drugs under FDA regulations. Although this would increase the costs of production, these companies would benefit from the greater certainty of the process for new drugs over the many uncertainties in the Biologics Act, as well as the better pricing available for a new drug. The loser, of course, is the consumer. It is doubtful that biobetters and biosimilars will have the same price-lowering effects as generics. These drugs will be patented themselves, creating full exclusivity in the market. If so, prices will remain high in the biological drug space. It would be unfortunate if the tremendous energy and creativity invested in designing and implementing the Biosimilars Act were to have very little effect in the long run.
