Note

Biosimilar Regulation: Bringing the United States Up To Speed with Other Markets

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ABSTRACT

In light of the expected end of patent terms for many large molecule drugs called biologics, there has been a rise in the development of biosimilars—non-branded, copycat versions of biologics. Unlike generic drugs, which are non-branded versions of small molecule chemical drugs, biosimilars are not identical to the biologic they reference, since biologics are derived from living organisms and are often injected into the patient, which makes them impossible to replicate perfectly. Despite their complexities, biologics exist to treat important diseases such as AIDS, Alzheimer's, and cancer. In 2010, the Biologics Price Competition and Innovation Act (Biosimilars Act) was added to the Public Health Service Act (PHS Act), outlining the approval process and regulatory plan for biosimilars. The Food and Drug Administration (FDA) subsequently released six Draft Guidance Documents (Guidance Documents) to clarify some of the provisions in the Biosimilars Act and to define ambiguous terms and phrases. Although biosimilars have been an important treatment option in many countries for over twenty years, none have been approved in the United States.

On March 15, 2015, the FDA approved Sandoz's Zarxio after the FDA's Oncological Drugs Advisory Committee recommended approval by the agency. However, on May 5, 2015, the Appeals Court for the Federal Circuit granted an injunction preventing Sandoz from selling Zarxio until further arguments are heard. The FDA may be progressing toward a more lenient view on biosimilar approvals; however, the court's injunction

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indicates that the United States lags in its exploitation of biosimilars, and revisions to the current law will allow for a robust biosimilars market. Previous scholarship has outlined the barriers to biosimilar acceptance in the United States and acknowledged the potential benefit of higher approval rates. This Note analyzes the Biosimilars Act and the Guidance Documents, and proposes revisions to these documents and to the current structure of the insurance and health care systems in relation to biosimilars. These adaptations will allow the United States to improve access to key medical treatments across the country and catch up with other biosimilar markets.

I. INTRODUCTION: BIOLOGICS AND THE EMERGENCE OF BIOSIMILARS

Amgen, a leading U.S. multinational biopharmaceutical company,[1] stated in 2014 that several "leading biologic medicines, worth an estimated $81 billion in global annual sales, will lose their patents by 2020."[2] Biologics are a relatively new genre of medicine, rising in popularity only since the 1970s.[3] They are significantly larger than earlier-developed drugs such as Tylenol and Prozac, which have simple chemical compositions and are referred to as "chemical drugs."[4] Unlike chemical drugs, biologic drugs are derived from living organisms. Common biologics include "vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins,"[5] and they often

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1. Amgen is the largest independent biotechnology firm in the world. Reuters, *Amgen Posts Lower-than-Expected Earnings*, N.Y. TIMES, Apr. 23, 2014, at B2.

2. AMGEN, BIOLOGICS AND BIOSIMILARS: AN OVERVIEW 12 (2014) [hereinafter AMGEN OVERVIEW], *available at* http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf.

3. *Id.* at 4.

4. *Id.* at 4–5. Tylenol (generically referred to as acetaminophen) is a small molecule drug with the chemical formula $C_8H_9NO_2$ and a molecular mass of 151.163 g/mol. *Acetaminophen*, PUBCHEM, http://pubchem.ncbi.nlm.nih.gov/compound/acetaminophen (last visited Apr. 4, 2015). Prozac has a chemical formula of $C_{17}H_{18}F_3NO$ and weighs 309.326 g/mol. *Fluoxetine*, PUBCHEM, http://pubchem.ncbi.nlm.nih.gov/compound/fluoxetine (last visited Apr. 4, 2015).

5. *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm (last updated Apr. 14, 2009). Allergenic products are biologically derived and "administered to man for the

need to be injected into the patient.[6] Comparing the biologic Epogen with the small molecule drug aspirin provides a helpful illustration of the distinction between chemical drugs and biologics.[7] Epogen, made by Amgen, mimics the function of erythropoietin by producing red blood cells to treat anemia.[8] One Epogen molecule is composed of 165 amino acids[9] and weighs approximately 168 times more than a molecule of aspirin.[10]

As the patent terms[11] for many large molecule drugs come to an end in the next five years,[12] several manufacturers are in

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diagnosis, prevention or treatment of allergies." 21 C.F.R. § 680.1(a) (2011). They include Allergenic Extracts and Allergen Patch Tests and may be extracted from sources such as "pollen, insects, . . . mold, food, chemicals, and animals." U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY ON THE CONTENT AND FORMAT OF CHEMISTRY, MANUFACTURING AND CONTROLS INFORMATION AND ESTABLISHMENT DESCRIPTION INFORMATION FOR AN ALLERGENIC EXTRACT OR ALLERGEN PATCH TEST 1 (1999), *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Allergenics/ucm078638.pdf. A somatic cell is any cell within the body of an organism; it does not include germ-line cells such as ova and sperm. MICHAEL ROBERTS ET AL., ADVANCED BIOLOGY 633 (2000). "Gene therapy is an experimental technique that uses genes to treat or prevent disease." *What Is Gene Therapy*, GENETICS HOME REFERENCE (Mar. 30, 2015), http://ghr.nlm.nih.gov/handbook/therapy/genetherapy.

6. AMGEN OVERVIEW, *supra* note 2, at 5.

7. Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars,* 64 HASTINGS L.J. 57, 63–64 (2012). Epogen (also referred to as Epoetin alfa) has a molecular formula of $C_{815}H_{1317}N_{233}O_{241}S_5$ and weighs 18,396.1 g/mol. *Active Ingredient: Epoetin Alfa - Chemistry and Biological Activity*, DRUGLIB.COM, http://www.druglib.com/activeingredient/epoetin_alfa/chembio/ (last visited Apr. 4, 2015) [hereinafter *Active Ingredient*]. Aspirin only weighs 180.157 g/mol and has the chemical formula $C_9H_8O_4$. *Aspirin*, PUBCHEM (Sept. 16, 2004), http://pubchem.ncbi.nlm.nih.gov/compound/2244.

8. Kanter & Feldman, *supra* note 7, at 63.

9. Amino acids are compounds that contain an amino group, –NH2, a carboxylic acid group, –COOH and a unique side chain that distinguishes each amino acid. Amino acids are the major building blocks of protein in the human body. HANS-DIETER JAKUBKE & NORBERT SEWALD, PEPTIDES FROM A TO Z: A CONCISE ENCYCLOPEDIA 20–21 (2008).

10. Kanter & Feldman, *supra* note 7, at 64. Aspirin has many functions including preventing transmission of a pain signal to the brain, preventing blood clotting, and reducing inflammation. Aspirin does not contain any amino acids. *Aspirin*, *supra* note 7.

11. Patent terms typically last twenty years from the time of filing. 35 U.S.C § 154(a)(2) (2012).

12. *See* John Carroll, *Biosimilars Set to Boom as New Patent Cliff on Biologic Superstars Looms*, FIERCEBIOTECH (July 22, 2014), http://www.fiercebiotech.com/story/biosimilars-set-boom-new-patent-cliff-bio

the process of copying these biologics to produce similar drugs, referred to as "biosimilars."[13] In the meantime, Congress and the U.S. Food and Drug Administration (FDA)[14] have started establishing an effective approval pathway and regulation scheme for these copied biologics.[15] A biosimilar is akin to a "generic" version of a small molecule chemical drug;[16] however, the inability to replicate the biological drugs identically means that a biosimilar manufacturer can at best produce a similar molecule, not one identical to the original biologic.[17]

Although there are risks associated with biosimilars, there are invaluable benefits to be gained from their development and the approval process essentially acts as a cost-benefit analysis for each drug that comes before it.[18] In the long run, the utility of biologics will greatly outweigh the risks, and today more than 400 biologic medicines are being studied worldwide for their applicability in treating illnesses such as HIV/AIDS, Alzheimer's disease, cancer, anemia, cystic fibrosis, growth deficiency, diabetes, hemophilia, hepatitis, genital

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logic-superstars-looms/2014-07-22 ("AMR [Allied Marketing Research] counted 10 biologics with a collective $60 billion in revenue that will come off patent in the next four years.").

13. AMGEN OVERVIEW, *supra* note 2, at 10–11.

14. The FDA is a federal agency of the United States Department of Health and Human Services responsible for protecting public health through regulation of food, pharmaceutical drugs (medications), vaccines, and other biologic medicines. P'SHIP FOR PUB. SERV., THE STATE OF THE FDA WORKFORCE 1 (2012), *available at* http://www.washingtonpost.com/r/2010-2019/WashingtonPost/2012/11/19/National-Politics/Graphics/PEW_FDA_Public_19112012.pdf.

15. Carroll, *supra* note 12 ("$1.3 billion [biosimilar market] base is expected to swell to $35 billion by 2020 as new products penetrate the market in North America, Europe and Asia."); *see* AMGEN OVERVIEW, *supra* note 2, at 12, 14. *See generally* Kanter & Feldman, *supra* note 7, at 59–60.

16. The Hatch-Waxman Act's Abbreviated New Drug Application (ANDA) provisions allow small molecule generic drugs to gain approval through a simpler process if they demonstrate bioequivalency with the branded drug. The Biosimilars Act aims to provide a similar, abbreviated pathway for imitation versions of large molecule drugs or biologics. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, 21 U.S.C. § 355(j) (2012); Katherine N. Addison, *The Impact of the Biosimilars Provisions of the Health Care Reform Bill on Innovation Investments*, 10 J. MARSHALL REV. INTELL. PROP. L. 553, 560–62 (2011).

17. Kanter & Feldman, *supra* note 7, at 59.

18. *Economic Impact Analyses of FDA Regulations*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/ (last updated Feb. 17, 2015).

warts, transplant rejection, autoimmune disorders, and many others.[19] Biosimilars are expected to be up to thirty percent cheaper than their branded or innovator biologic counterparts.[20] In addition, the competition will drive prices down further, leading to an expected forty percent price reduction in the long run.[21] Although these reductions will not compare to those seen with generics,[22] they will still increase access to important, life-saving biologics.[23] The increased incentives and security for biosimilar manufacturers will raise the amount of research and development in the area, leading to more knowledge in the field.[24] Finally, the increased access to biologics will allow for more post-market safety and efficacy studies that will lead to safer drugs over time.[25]

This Note argues that biosimilars are a valuable area of drug development, but they are not sufficiently incentivized due to the arduous regulations and uncertainty in current U.S. laws and proposes several novel recommendations to address

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19. Thomas Morrow & Linda Hull Felcone, *Defining the Difference: What Makes Biologics Unique*, 1 BIOTECHNOLOGY HEALTHCARE 24, 24–26, 28–29 (2004); *see* AMGEN OVERVIEW, *supra* note 2, at 8. For a description of these and related genetic disorders, see generally *Genetic Disorders—Common Genetically Inherited Diseases—Alzheimer's Disease, Cancer, Cystic Fibrosis, Diabetes, Huntington's Disease*, LIBR. INDEX, http://www.libraryindex.com/pages/270/Genetic-Disorders.html (last visited Apr. 4, 2015).

20. Peyton Howell, *How Much Cheaper Will Biosimilars Be?*, FIERCEPHARMA (Mar. 2, 2012), http://www.fiercepharma.com/story/how-much-cheaper-will-biosimilars-be/2012-03-02.

21. *Id.*

22. *Generic Versus Branded Medicines*, HEALTHSMART, http://www.healthsmart.com/WellnessResourceCenter/GenericVsBrandDrugs.aspx (last visited Apr. 4, 2015). The availability of generic drugs currently saves the U.S. healthcare system over $200 billion each year. GENERIC PHARM. ASS'N, GENERIC DRUG SAVINGS IN THE U.S. 1 (6th ed. 2014), *available at* http://www.gphaonline.org/media/cms/GPhA_Savings_Report.9.10.14_FINAL.pdf.

23. *Biosimilars Can Help Lower Costs and Increase Access*, SANDOZ, http://www.sandoz-biosimilars.com/biosimilars2/importance.shtml (last visited Apr. 4, 2015). A 2012 study by the IGES Institute Berlin analyzed the cost savings from biosimilars in the European Union, and found that it saved Germany €551 million. The study also gathered data on savings for eight other European countries and found that the cumulative savings for the eight countries is expected to be as high as €33 billion by 2020. *Id.*

24. *See id.*

25. *See* AMGEN OVERVIEW, *supra* note 2, at 21.

the issue.[26] Part I (preceding) has provided background on the history and importance of biosimilars. Part II addresses the two issues hindering biosimilar development in the United States: first, the difficulties associated with regulating biosimilars, and second, the shortcomings of the current law. Part III analyzes the current approval process for biosimilars through an examination of the Biosimilars Act and the FDA Draft Guidance Documents, and compares it to the approval process for innovator biologics. Part IV discusses different solutions to the current system in six subparts. First, this Note argues that innovator biologics should be given less exclusivity. Second, this Note advocates requiring fewer studies from biosimilar applicants. Third, measures should be taken to ensure biosimilar safety at the earlier stages of development as opposed to the later, clinical stages. Next, the health care industry should be involved in the dialogue and highlights some elements that must be a part of any approval process regardless of how it is implemented. The fifth subsection discusses two alternative approaches to addressing the question of interchangeability and substitution, for pharmacies and insurance companies. Finally, the last subsection briefly describes the importance of insurance substitution in terms of biosimilars coverage.

This Note argues that to give biosimilars a brighter future in the United States, Congress and the FDA must make several

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26. *See* Kanter & Feldman, *supra* note 7, at 60–61 ("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."); *see also* Addison, *supra* note 16, at 580–82. Addison argues that the FDA has taken an especially stringent view of the Biosimilars Act and that the Act itself is open to a more lenient interpretation. *Id*. This is difficult to predict since the FDA has not yet approved a biosimilar under the new process, and there will be more information once there are a few examples to look to. However, a careful reading of the FDA Guidance Documents and the Biosimilars Act suggests that the FDA will want to see more rigorous clinical studies (i.e., efficiency and safety studies) than the Biosimilars Act indicates. *See* Public Health Service Act, 42 U.S.C. § 262 (2012) (regulation of biological products); *see also* U.S. 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 QUESTIONS AND ANSWERS], *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf. On the other hand, the Biosimilars Act may be more stringent in other areas such as the requirements for proving interchangeability of a biosimilar. *See* § 262; *see also* FDA QUESTIONS AND ANSWERS, *supra*.

revisions to the approval pathway.[27] Promoting the development of biosimilars would be best achieved through a change in the Biosimilars Act and the FDA Guidance Documents, in accordance with some of the approval processes implemented in other countries that have already developed a pathway.[28] An effective biosimilar approval pathway would necessarily need to strike a balance between ensuring safety and providing affordable access to biologic medicines.

II. BARRIERS TO MANUFACTURING AND REGULATING BIOSIMILARS

A. THE COMPLEXITIES OF BIOSIMILARS CREATE A SEVERE CHALLENGE FOR THEIR DEVELOPMENT AND REGULATION

The complex nature of innovative biologics and biosimilars[29] makes them difficult to manufacture and small variations in the manufacturing process have the potential to cause different biological effects in the patient.[30] Also, the patient-specific reactions and side effects to biologics vary widely compared to small molecule drugs.[31]

Given the variables in the biologics manufacturing process—including different genetics of the living components, and environmental factors such as "light, temperature, moisture, packaging materials, container closure systems, and delivery device materials"[32]—that affect the final product, it is

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27. *See* Addison, *supra* note 16, at 563–65 (presenting the FDA approval process for biosimilars); Kanter & Feldman, *supra* note 7, at 60–61 (discussing the need for changes to the approval pathway).

28. *See, e.g.*, Addison, *supra* note 16, at 559 ("Europe appears to be more receptive to approving biosimilars . . . . The year 2007 marked the beginning of the biosimilars era in Europe.").

29. *See infra* text accompanying note 33.

30. Addison, *supra* note 16, at 562–64 ("[B]ecause of the complex nature of biologics compared to traditional chemically synthesized drugs, the new legislation is quite rigorous . . . . In order to implement the new legislation, the FDA created the Biosimilar Implementation Committee."); Joanne Barker, *Biologics for RA: Understanding Risks and Benefits*, WEBMD (June 22, 2011), http://www.webmd.com/rheumatoid-arthritis/features/risks-benefits (discussing the risks and benefits of using biologics to treat rheumatoid arthritis).

31. *See, e.g.*, Barker, *supra* note 30.

32. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 5 (2013) [hereinafter FDA SCIENTIFIC CONSIDERATIONS], *available*

well accepted that the prospect of creating an identical biologic is non-existent sometimes even for the same manufacturer that made the reference product.[33] Several impurities can arise at various stages of the biologic's development. First, vaccines and other biologics are developed on cell substrates,[34] and standardized cell substrates are needed to make consistent biologics.[35] Furthermore, many vaccines are not used continuously and must be stored for long durations.[36] This requires them to either be safely stockpiled[37] or able to be manufactured consistently in batches.[38] Additionally, the cell bank[39] for a particular vaccine may deplete, requiring the creation of a new cell bank, which may behave differently than the previous one.[40] Hence, while generic drugs are practically identical to their branded counterparts, biosimilars can only be similar to their biologic counterparts due to their complex and organic nature.[41]

Two researchers, Glenn Begley and Lee Ellis found that scientists at Amgen were only able to replicate six out of fifty-three (eleven percent) of their pre-clinical research on cancer therapies.[42] The Amgen scientists attempted to replicate a

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at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf; *see* AMGEN OVERVIEW, *supra* note 2, at 34.

33. A company tried to set up two identical laboratories in different locations and used the same process, materials, and machinery in both laboratories, but was unable to replicate the original biologic exactly. Interview with Ralph Hall, Professor of Food & Drug Law, Univ. of Minn. Law Sch. (Nov. 23, 2014), in Minneapolis, Minn.

34. A cell substrate is a group of cells, such as yeast or animal cells, used to produce a certain biological product. *Cell Substrates*, WORLD HEALTH ORG., http://www.who.int/biologicals/vaccines/cell_substrates/en/ (last updated Dec. 15, 2014).

35. *Id.*

36. Anurag S. Rathore et al., *Key Considerations for Development and Production of Vaccine Products*, BIOPHARM (Mar. 2, 2012), http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=763581.

37. *Cell Substrates*, supra note 34.

38. Rathore et al., *supra* note 36.

39. A cell bank is storage of cells with a specific genome for future use in a medical product. Joseph Patrick Nkolola & Thomas Hanke, *Engineering Virus Vectors for Subunit Vaccines*, *in* NOVEL VACCINATION STRATEGIES 283 (Stefan H. E. Kaufmann ed., 2004).

40. Rathore et al., *supra* note 36.

41. *See* AMGEN OVERVIEW, *supra* note 2, at 10.

42. C. Glenn Begley & Lee M. Ellis, *Drug Development: Raise Standards for Preclinical Cancer Research*, 483 NATURE 531, 531–33 (2012).

sample of innovative studies in hopes of basing future developments off of the previous formulas, but were largely unsuccessful in replicating the analytical studies.[43] Although this study concerned only cancer therapies, similar shortcomings may be found in other therapies, suggesting that significant safety concerns arise at the pre-clinical stage of drug development. If this is the case, efforts to improve replicability would be better spent at the earlier stages of development as opposed to the clinical stages, as is proposed by the extensive biosimilar approval requirements.

The FDA defines a biosimilar as a "'biological product [that] is highly similar to the reference product notwithstanding minor differences in clinically inactive components' and 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."[44] Unsurprisingly, the definition uses ambiguous terms and phrases, specifically, "minor differences" and "clinically meaningful differences." Regardless of their precise definitions, however, these minor differences between the original biologic and the biosimilar could pose health risks,[45]

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43. *See id.*

44. FDA QUESTIONS AND ANSWERS, *supra* note 26, at 3 (citing 42 U.S.C. § 351(i) (2006)). Several of these terms, including "minor differences," "clinically inactive," and "potency" have been discussed in the Draft Guidance, but are still not entirely clear. The World Health Organization defines biosimilars as "[a] biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product," where "similarity" is the "[a]bsence of a relevant difference in the parameter of interest." WORLD HEALTH ORG., GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPS) 6 (2009), *available at* http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.

45. *See* World Health Org. [WHO], *Good Manufacturing Practices for Biological Products*, at 21, WHO Doc. TRC/822 (1992), *available at* http://www.who.int/biologicals/publications/trs/areas/vaccines/gmp/WHO_TRS_822_A1.pdf (addressing the variability inherent in manufacturing biologics). The concerns also apply to biosimilars since the same inconsistencies arise in innovator drugs as in copycat versions. *Id.* Between January 1995 and June 2008, "U.S. and European regulators approved 174 biological drugs . . . . But nearly a quarter of the biological drugs—41 out of 174—together had 82 safety regulatory actions" after approval. Miranda Hitti, *Drugs Not Without Risks: Study Charts Safety Issues Reported After Approval of Various Biological Drugs*, WEBMD (Oct. 21, 2008), http://www.webmd.com/news/20081021/biologic-drugs-not-without-risks.

meriting a need for specific regulations for biosimilars at all stages of its development, testing, and marketing.

B. CURRENT BIOSIMILAR LAW HAS ROOM TO GROW

While the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act)[46] set a relatively simple approval pathway for generic drugs, which are identical to their branded counterparts,[47] a parallel regulation pathway for biosimilars would necessarily be unique and more detailed to protect against the environmental variations that could be consequential to the immunogenicity[48] of the biosimilar.[49] Hence, in 2010, the Biologics Price Competition and Innovation Act (Biosimilars Act) was enacted as part of the Affordable Care Act to set a standard for an abbreviated approval process for biosimilars.[50] The Biosimilars Act outlined the approval pathway and timeline for biosimilars[51] and designated the task of implementation to the FDA.[52] The FDA subsequently released six Guidance Documents to clarify some of the ambiguous provisions of the Biosimilars Act, add new restrictions, and tighten the standards for some restrictions.[53]

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46. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, 21 U.S.C. § 355(j) (2012).

47. See *supra* Part II.A. for a comparison of generics and biosimilar drugs.

48. Immunogenicity is the ability of a product to elicit an immune response in the patient's body. This is an important function in vaccines, but the challenge is to have a balanced immune response. *See* Geert Leroux-Roels et al., *Vaccine Development*, 1 PERSP. VACCINOLOGY 115 (2011).

49. *See* Addison, *supra* note 16, at 564–65 ("FDA spokesperson Karen Mahoney has not . . . provided any insight as to when generic biologics may be approved. In fact, she has stated, 'There are so many factors that will impact when biosimilar products will enter the market, [t]herefore, it is not reasonable to speculate.'" (citation omitted)).

50. *See* FDA QUESTIONS AND ANSWERS, *supra* note 26, at 1–2.

51. *See* Public Health Service Act, 42 U.S.C. § 262(k)(1)–(2) (2012) ("Any person may submit an application for licensure of a biological product under this subsection . . . . An application . . . shall include information demonstrating that . . . the biological product is biosimilar to a reference product . . . .").

52. *Id.* § 262(k)(5)(B) ("An application submitted under this subsection shall be reviewed by the division within the Food and Drug Administration that is responsible for the review and approval of the application under which the reference product is licensed.").

53. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CLINICAL PHARMACOLOGY DATA TO SUPPORT A DEMONSTRATION OF BIOSIMILARITY TO A REFERENCE PRODUCT (2014) [hereinafter CLINICAL PHARMACOLOGY DATA], *available at* http://www.fda.gov/downloads/drugs/guidancec

Despite these attempts, both the Biosimilars Act and the FDA Guidance Documents remain unclear on several fronts.[54]

For example, each time the FDA provides some direction on how the Biosimilars Act will be interpreted,[55] the clarification disclaims that the final decision will be "made by the FDA during its review of the 351(k) application."[56] Hence, the FDA maintains full discretion in granting or rejecting the application for any reason it might deem appropriate, which means many key provisions of the Biosimilars Act and the FDA's interpretation remain mysterious to potential biosimilar developers.[57]

The uncertainty, along with the rigorous application requirements, is frustrating the U.S. biosimilars market; no biosimilars are currently in the U.S. market, while several have been developed and approved around the world.[58] On

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ompliance regulatoryinformation/guidances/ucm397017.pdf; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: REFERENCE PRODUCT EXCLUSIVITY FOR BIOLOGICAL PRODUCTS FILED UNDER SECTION 351(A) OF THE PHS ACT (2014), *available at* http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm407844.pdf; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: FORMAL MEETINGS BETWEEN THE FDA AND BIOSIMILAR BIOLOGICAL PRODUCT SPONSORS OR APPLICANTS (2013) [hereinafter BIOSIMILAR BIOLOGICAL PRODUCT FDA MEETINGS], *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/UCM345649.pdf; FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PROTEIN PRODUCT (2012), *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf; FDA QUESTIONS AND ANSWERS, *supra* note 26.

54. *Cf.* Kanter & Feldman, *supra* note 7, at 60–61 (making recommendations to the current FDA policies regarding incentivizing and implementing biosimilars).

55. FDA QUESTIONS AND ANSWERS, *supra* note 26.

56. *See, e.g.*, *id.* at 8. "This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations." *Id.* at 1.

57. Kanter & Feldman, *supra* note 7, at 60 (stating that the FDA and Biosimilars Act need to offer more assurance and incentives to potential manufacturers before they invest in the development of a biosimilar).

58. *Biosimilars Approved in Europe*, GENERICS & BIOSIMILARS INITIATIVE, http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe (last updated Jan. 30, 2015); *see also* Addison, *supra* note 16, at 558–59 (describing the biosimilar approval process in Europe).

March 6, 2015, the FDA approved Sandoz's Zarxio, a biosimilar referencing Amgen's Neupogen, an expensive cancer drug, but on May 5, 2015, the Appeals Court for the Federal Circuit granted an injunction against Sandoz's continued selling of Zarxio until further notice.[59] In addition, two other biosimilars—Celltrion's Remsima and Sandoz's EP2006—have applied for approval, and the Federal Circuit's decision on Zarxio may influence the FDA's stance on future biosimilar applications.[60] These decisions will determine how soon the U.S. will benefit from a robust biosimilars market.

In 2003, the European Medicines Agency (EMA) was designated as the sole authority responsible for the oversight of biosimilars in Europe and the approval process was effectively centralized across all of Europe.[61] The EMA released guidance on the approval process in 2005 and the first biosimilar was approved in 2006.[62] To date, twenty-two biosimilars have been approved in Europe; however, two approvals have been cancelled, leaving twenty biosimilars on the current market.[63]

It is important to consider the reasoning behind the two biosimilars having their approvals withdrawn in Europe. Valtropin, made by BioPartners with the active ingredient somatropin, was approved in April 2006 but withdrawn in May 2012 by the manufacturer itself.[64] The EMA withdrew approval

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59. Patience Haggin, *Appeals Court Hits Pause on First US Biosimilar*, RECORDER (May 5, 2015), http://www.therecorder.com/id=1202725593394/Federal-Circuit-Agrees-to-Block-First-US-Biosimilar?mcode=1202619176004&curindex=3; Steven Ross Johnson, *FDA Panel Recommends First Biosimilar Approval*, MODERN HEALTHCARE (Jan. 7, 2015), http://www.modernhealthcare.com/article/20150107/NEWS/301079947.

60. *See id.*

61. *See Biosimilars Approved in Europe*, *supra* note 58.

62. *Id. But see* Addison, *supra* note 16, at 559 ("The year 2007 marked the beginning of the biosimilars era in Europe."). Hence, there is some disagreement regarding whether 2006 or 2007 was the year that the first biosimilar was approved in Europe.

63.For background and details on the European approval process, see Francis Megerlin et al., *Biosimilars and the European Experience: Implications for the United States*, 32 HEALTH AFF., 1803, 1804–05 (2013). For updated numbers and a list of all approved biosimilars see *European Public Assessment Reports*, EUR. MEDICINES AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp (follow "browse by type" tab; then follow "biosimilars") (last visited Apr. 4, 2015).

64. *Public Statement on Valtropin (Somatropin)*, EUR. MEDICINES AGENCY (May 30, 2012), http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2012/08/WC500130939.pdf (outlining the timeline

upon BioPartners' request and there is very little information available regarding the reasons for the manufacturer's cessation in selling and manufacturing the drug; however, nothing in the records indicates that it was due to safety concerns.[65] The second withdrawn biosimilar was Filgrastim made by Ratiopharm with the active ingredient ratiopharm, which was approved in September 2008 but withdrawn in April 2011, also at the request of the marketing authorization holder, Ratiopharm.[66] Based on the research conducted for this Note, no indication could be found that suggested that the biosimilar was withdrawn because it was unsafe or that the safety concerns arose from not being able to create a biosimilar that sufficiently mimicked the function of the original biologic.

In contrast to the centralized European system, biosimilar approval in Latin America is nationally controlled and each country is at a different stage of the process of developing a regulatory system.[67] The degree of regulation varies from no regulation,[68] to comprehensive and vague regulations.[69] Many Latin American countries saw the emergence of biosimilars even before a regulatory process was developed, and several biosimilars were simply approved under the country's approval

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of the Valtropin approval and withdrawal processes and stating only that the withdrawal was upon the request of the manufacturer following the manufacturer's voluntary removal of the drug from the market).

65. *See id.*

66. *Filgrastim Ratiopharm*, EUR. MEDICINES AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000824/human_med_000792.jsp&mid=WC0b01ac058001d124 (last visited Mar. 22, 2015).

67. *Compare* Brian J. Malkin, *Challenges to the Development of a Biosimilars Industry in the United States*, *in* RECENT DEVELOPMENTS IN FOOD AND DRUG LAW 83, 83 (2013 ed. 2012) (illustrating how the western United States and European approval processes have been centralized), *with* Zachary Brennan, *Uptake of Biosimilars Across Latin America Surges as Regulations Vary*, BIOPHARMA REP. (Oct. 8, 2014), http://www.biopharma-reporter.com/Markets-Regulations/Uptake-of-biosimilars-across-Latin-America-surges-as-regulations-vary (illustrating how the Latin American process varies among nations, with some countries boasting an established approval system and others still reviewing biosimilars under the generic drug model).

68. Venezuela and Chile both have biosimilars on the market but have yet to develop a regulatory pathway specific to biosimilars. Brennan, *supra* note 67. Venezuela also imports biosimilars from other countries due to its lack of production capacity, and there is little information regarding the regulations in place for the drugs that are imported. *Id.*

69. For example, Mexico has a complex but vague set of regulations to allow for case-by-case examination. *Id.*

pathway for generic drugs.[70] Brazil, one the first South American countries to distinguish biosimilars from generics, delegated the task of regulation to the National Health Surveillance Agency (in Portuguese, Agência Nacional de Vigilância Sanitária, ANVISA), the regulatory body for the approval for all drugs.[71] Although an estimated 187 biosimilars are on the market in Brazil, ANVISA has not approved all of them under the new biosimilar approval pathway and there are no readily available records to show how many of these drugs were approved under the generic-drug pathway.[72] One possible way for the FDA to gain information would be to study the countries that have approved biosimilars under less restrictive pathways, to determine whether there were inadequate levels of similarity between the biosimilar and the original biologic.

Although no country has developed a perfect process for the approval of biosimilars, there are some lessons the United States can learn from the laws and approval processes developed around the world to arrive at an appropriate approval pathway.[73] An effective biosimilar approval pathway would necessarily need to strike a balance between ensuring safety and providing affordable access to biologic medicines.

III. CURRENT APPROVAL PROCESS FOR BIOSIMILARS

A. CURRENT APPROVAL PROCESS FOR INNOVATOR BIOLOGICS

The Center for Biologics Evaluation and Research (CBER) oversees the approval of original biologics.[74] A biologic

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70. *The Future of Biosimilar Use and Regulation in Latin America*, GENERICS & BIOSIMILARS INITIATIVE (Aug. 29, 2014), http://www.gabionline.net/layout/set/print/Biosimilars/Research/The-future-of-biosimilar-use-and-regulation-in-Latin-America.

71. PHARM. PROD. DEV., DEVELOPING BIOSIMILARS IN EMERGING MARKETS: REGULATORY AND CLINICAL CONSIDERATION 9–10 (2013), *available at* http://www.healthtrustpg.com/biosimilars/pdf/ppd.pdf.

72. Lisa Mueller & Gustavo de Freitas Morais, *Understanding Biologics and Biosimilars in Brazil*, BRIC WALL BLOG (Sept. 4, 2013), http://bricwallblog.wordpress.com/2013/09/04/understanding-biologics-and-biosimilars-in-brazil/ (outlining the biosimilar approval process in Brazil).

73. *See, e.g.*, *supra* note 71 and accompanying text.

74. The CBER gains its authority to regulate biologics from the Public Health Service Act § 351 and specific sections of the Federal Food, Drug and Cosmetic Act. *Vaccine Product Approval Process*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicslicenseapplicationsblaprocess/ucm133096.htm (last updated June 18, 2009).

manufacturer seeking approval for a biologic must first submit an Investigational New Drug application (IND) to the FDA, describing how it was manufactured, results of tests that were conducted for quality, the biologic's safety and immunogenicity[75] in animal testing, and an outline of the proposed clinical studies the company plans to conduct if the IND is approved.[76]

If permitted to proceed, the biologic undergoes at least three phases of clinical trials.[77] Phase 1 involves immunogenicity studies performed on a small group of closely watched individuals, while Phase 2 studies enroll hundreds of subjects, on varying doses of the drug.[78] Finally, Phase 3 trials, for effectiveness and safety, involve thousands of subjects.[79] If clinical trials are successful, the manufacturer may file a Biologics License Application (BLA).[80] Thereafter, the FDA reviews all submitted information, conducts a physical inspection of the manufacturing lab during operation, and makes a recommendation for rejection or approval of the drug.[81] However, until a biologic is on the market for some time, it is difficult to anticipate all possible side effects.[82] Thus, Phase 4 clinical trials may be necessary to evaluate long-term effects of a biologic.[83] If any Phase raises concerns about safety

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75. Immunogenicity is the "ability to elicit a protective immune response." *Id.*; *see supra* note 48.

76. *Vaccine Product Approval Process*, *supra* note 74.

77. *Id.*; *see also Clinical Trials*, BILL & MELINDA GATES FOUND., https://docs.gatesfoundation.org/documents/clinical_trials.pdf (last visited Dec. 19, 2014) ("A clinical trial is a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions . . . .").

78. Nandita Rao, *FDA Q&A: The Approval Process for Vaccines and Trumenba with Rachael Conklin: Communications Officer*, PRINCETON PUB. HEALTH REV. (Dec. 2, 2014), https://pphr.princeton.edu/2014/12/02/fda-qa-the-approval-process-for-vaccines-and-trumenba-with-rachael-conklin-communications-officer/.

79. *Vaccine Product Approval Process*, *supra* note 74.

80. *Id.*

81. *Id.*

82. *Id.*

83. Phase 4 clinical trials are the post-marketing surveillance trials that are conducted through soliciting feedback from patients and health care practitioners and facilities. *See* LAWRENCE M. FRIEDMAN ET AL., FUNDAMENTALS OF CLINICAL TRIALS 7–8 (4th ed. 2010). Phase 4 trials are also longitudinal and help with understanding the long-term effects of the drug on the population. *Id.*

or effectiveness, the FDA can require additional studies, or halt the process altogether.[84]

B. THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT

In addition to the biologic approval process, the Biologics Price Competition and Innovation Act was added to the Public Health Service Act (PHS Act) as section 351(k) to create an approval pathway for biosimilars, grant exclusivity periods, and set requirements for interchangeability.[85] The Biosimilars Act requires that a biosimilar establish its similarity to a reference biologic through analytical data regarding its bioequivalence,[86] the results of animal studies, and clinical studies.[87] The Act also adds that the Secretary may waive any of the requirements if it is deemed unnecessary.[88] The Biosimilars Act also establishes a twelve-year exclusivity period for the reference product (the original biologic), during which no biosimilar can be approved,[89] and sets a four-year exclusivity period for the reference product during which no biosimilar can even submit an application.[90]

Under the Biosimilars Act, an applicant may apply for interchangeability status either at the time it files for approval or later.[91] If a biosimilar is "interchangeable," a pharmacist will be allowed to substitute the biosimilar for a prescription of the reference product without a doctor's approval.[92] To apply for interchangeability, the applicant must additionally submit information that the biosimilar would produce the same clinical

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84. *Vaccine Product Approval Process*, *supra* note 74.

85. Public Health Service Act § 351(k), 42 U.S.C. § 262(k) (2012); *see* FDA QUESTIONS AND ANSWERS, *supra* note 26, at 4–15. Interchangeability is the status a biosimilar may gain in addition to being approved as a biosimilar. *See* discussion *infra* Part IV.E.

86. Bioequivalence refers to "the relationship between two preparations of the same drug in the same dosage form that have a similar bioavailability." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (William Alexander Newman Dorland ed., 32d ed. 2011).

87. *See* FDA QUESTIONS AND ANSWERS, *supra* note 26, at 2–3; Kanter & Feldman, *supra* note 7, at 71.

88. § 351(k)(2)(A)(ii).

89. This is in addition to patent protection, so many innovator drugs are protected by both. Some may not choose to be patented, but will still have protection for twelve years under the Biosimilars Act. § 351(k).

90. § 351(k)(7)(A)–(B); Kanter & Feldman, *supra* note 7, at 75.

91. § 351(k).

92. Kanter & Feldman, *supra* note 7, at 73.

effects as the reference product, and that if a patient switched back and forth between using the biosimilar and the reference biologic, the safety and efficacy would not change.[93] The first biosimilar with interchangeability gains one year of exclusivity over other biosimilars.[94]

The Biosimilars Act also provides that the "subsection (k) applicant" must provide the "sponsor" (owner) of the reference product with a copy of the biosimilar application, and any other information regarding the manufacturing process for the biosimilar.[95] The reference product sponsor must keep the information confidential but use it to give the sponsor of the biosimilar application a list of all the ways (if any) the applicant may be infringing on the reference product's patents, and identify which patents it would be willing license to the developer of the biosimilar.[96]

Then, the applicant has a chance to respond to the reference product sponsor by either agreeing with the accusations of infringement, claiming that the patents asserted by the reference product sponsor are invalid or not infringed by the biosimilar, or providing a clarification that the biosimilar is not going to be marketed before the expiration of the asserted patents[97] (biosimilar manufacturers may not be liable for infringing a patent by making the product[98]). At this point, the reference product sponsor has a chance to respond to the biosimilar applicant, explaining why the patent(s) will be infringed or why they are valid.[99] Finally, the Biosimilars Act provides a procedure for resolving patent disputes between

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93. § 351(k)(4).

94. *Id.* § 351(k)(6)(A); Kanter & Feldman, *supra* note 7, at 73.

95. Public Health Service Act § 351(*l*)(2)(A), 42 U.S.C. 2(*l*)(2)(A) (2012).

96. *Id.* § 351(*l*)(1)(B)(iii), (3)(A)(i)–(ii).

97. *Id.* § 351(*l*)(3)(B)(i)–(ii).

98. Although a patent usually confers to its owner the right to exclude others from making, using, or selling the patented invention, there is an exception to this rule called the "research exception," which states that one will not be liable for patent infringement for performing research and tests in preparing a product (most likely a drug) for regulatory approval, for instance by the FDA, before the end of its patent term. Hence, developers of generic drugs may practice the patented elements of the branded drug before the expiration of the patent term. Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187 (1999).

99. *Id.* § 351(*l*)(3)(C).

biosimilar manufacturers and the innovator biologic manufacturer.[100]

The biosimilar manufacturer is disadvantaged in the litigation process because it might be forced to disclose trade secrets to the reference product sponsor by sharing its application.[101] On the other hand, all elements of the reference product may not be fully disclosed if they are not patented.[102] Hence, the biosimilar manufacturer is much more exposed than the innovator.

Although long and detailed, the Act leaves several questions unanswered and the FDA Draft Guidance Documents have attempted to fill in the gaps to offer clarification and certainty.[103]

C. THE FDA DRAFT GUIDANCE DOCUMENTS FOR BIOSIMILARS

Since the enactment of the Biosimilars Act, the FDA has released six Draft Guidance Documents to clarify some of the uncertainties found in the Biosimilars Act.[104] These documents are non-binding but provide some suggestions and recommendations for courts and the industry.[105] Unlike the EMA, the FDA has refused to set a specific guide for each type of biosimilar and has said it is going to take a case-by-case approach instead, deciding the level of preclinical and clinical studies required individually for each biosimilar.[106] Despite its

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100. *Id.* § 351(*l*)(4)–(6); *see* FDA QUESTIONS AND ANSWERS, *supra* note 26, at 329.

101. Kanter & Feldman, *supra* note 7, at 77.

102. *See* Addison, *supra* note 16, at 578.

103. FDA QUESTIONS AND ANSWERS, *supra* note 26; Kanter & Feldman, *supra* note 7, at 71.

104. *See supra* note 53 (listing all six FDA Draft Guidance Documents).

105. *E.g.*, FDA QUESTIONS AND ANSWERS, *supra* note 26, at 1 ("This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.").

106. Malkin, *supra* note 67, at 92 ("The FDA's approach, moreover, puts a high burden on would-be biosimilar applicants to develop appropriate analytical techniques to compare their products to the referenced biological as a prerequisite to design preclinical and clinical studies. Unfortunately, the FDA has not specified what those analytical techniques should be. Companies are frustrated because the agency has said it will not offer such guidance for fear of mandating outdated technologies. According to the FDA, it wants to provide an opportunity for biosimilar applicants to develop new analytical methods as appropriate and feasible.").

attempt to clarify some of the requirements, the FDA Guidance Documents are still ambiguous and leave many questions unanswered.[107] In addition, some aspects of the FDA requirements are more stringent than the Biosimilars Act.[108] This leaves biosimilar applicants with little direction in the development of a biosimilar, creating high stakes and low incentives for biosimilar developers in the United States.[109]

The FDA first asks the biosimilar sponsor to demonstrate the biosimilar's comparability to the reference product.[110] A biosimilar applicant that can demonstrate greater similarity to the reference product will be required to conduct fewer studies.[111] The FDA also clarified that the innovator's comparability studies with regards to different batches of the

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107. Kanter & Feldman, *supra* note 7, at 60 ("To combat some of the uncertainties in the Biosimilars Act, the FDA released several draft guidances in February 2012. 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. 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, [and] give only a vague outline for FDA approval requirements . . . ." (footnotes omitted)).

108. Malkin, *supra* note 67, at 89 ("The FDA currently views an interchangeability determination as a two-step process. First, the FDA wants an applicant to obtain approval for biosimilarity. Once the biosimilar has been on the market without untoward safety or efficacy effects, the applicant can submit additional data/information showing that it meets the interchangeability requirements. The Biosimilars Act, however, does not require this two-step process and permits an applicant to file its initial 351(k) application as an interchangeable biosimilar.").

109. Kanter & Feldman, *supra* note 7, at 60 ("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."); Malkin, *supra* note 67.

110. Raymond Kaiser, *Why Comparability Studies Are the Key to a Biosimilar's Success*, CONVANCE (Mar. 6, 2013), http://blog.covance.com/2013/03/key-to-biosimilars-success/ ("In February 2012, the FDA issued formal draft guidance on biosimilars titled 'Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,' in which it states that since a one-size-fits-all pathway is not possible, it will 'consider the totality of evidence' when assessing follow-on products. The cornerstone of this approach is the structural and functional analyses of the proposed molecule demonstrating comparability with the reference drug.").

111. *Id.* ("Sponsors with compelling comparability data observe a reduced regulatory burden.").

innovator biologic might not be proper guidance for comparing the biosimilar to the innovator drug.[112] The FDA additionally requires that the biosimilar needs to be of equal strength as the reference, and suggests that an applicant is unlikely to obtain both biosimilarity and interchangeability through an original 351(k) application.[113] The FDA also iterates its hesitance in allowing comparability studies from other countries, but does not give a reason for this exclusion.[114]

Following a showing of analytical and physical comparability,[115] the FDA approval pathway starts with the applicant conducting *in vitro* studies to show similarity of the physiological properties of the drug, followed by animal testing for toxicity.[116] The final stage is *in vivo* clinical studies.[117] According to the Biosimilars Act, the Secretary has the discretion to waive any stage of the testing requirements.[118] One of the most important questions for biosimilar developers will be how likely the FDA will be to require clinical studies—the most costly and time-consuming stage of the approval pathway.[119] Another key question will be the requirements and process of gaining interchangeability of biosimilars.

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112. Malkin, *supra* note 67, at 96 ("The FDA has said that while an innovator's comparability studies may be useful as goalposts for biosimilars, they may not apply to or be practical when developing a biosimilar product.").

113. FDA QUESTIONS AND ANSWERS, *supra* note 26, at 10 ("Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the 'strength' of the proposed biosimilar product is the same as that of the reference product.").

114. *See id.* at 7–8.

115. Comparability needs to show that the primary, secondary, tertiary, and quaternary structures are the same as the innovator product, that the biological activity is sufficiently similar, and that there are negligible product and process impurities. This analysis is done through various advanced technologies including mass spectrometry, NMR, and other measures. Kaiser, *supra* note 110.

116. Malkin, *supra* note 67, at 96 ("For example, at the beginning of the product development process, the first tests are *in vitro*, followed by some animal testing to prove that the drug is not toxic.").

117. *Id.* ("Next, smaller clinical studies are conducted *in vivo* to determine whether the drug has some beneficial effect, followed by a study to determine the optimal dosing strategy.").

118. *See* Public Health Service Act, 42 U.S.C. § 262(k)(2)(A)(ii) (2012).

119. CLINICAL TRIALS OF DRUGS AND BIOPHARMACEUTICALS 1–2 (Chi-Jen Lee et al. eds., 2005) (discussing the factors that determine whether clinical studies are required for biopharmaceuticals).

One helpful guide provided by the FDA is its attempt to clarify the ways in which a biosimilar applicant can demonstrate similarity to the reference product. The FDA encourages the applicant to submit information about how the biosimilar compares to the reference product with regards to "structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness."[120] The guidance lists some of the specific impurities and inconsistencies may appear in the biosimilar manufacturing process as well as how these impurities appear.[121] The Guidance Document proceeds to list technologies and methods that may, and should, be employed to detect these inconsistencies between products.[122] In essence, however, the FDA Guidance Document says little more than what is already in the Biosimilars Act.[123] In fact, it re-affirms that the default expectation is that a biosimilar application will contain analytical studies, animal studies, and clinical studies, unless otherwise specified by an FDA official.[124] The general impression given by the Guidance Documents is that at least one clinical study will be required.[125] For example, the guidance clearly states, "Animal PK and PD assessment will

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120. FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 2. PK refers to the body's absorption, distribution, metabolism, and elimination of a drug. *Id.* at 13 n.25. PD refers to the biochemical and physiologic effects the drug has on the body. *Id.*

121. *Id.* at 5 ("In general, proteins can differ in at least three ways: (1) primary amino acid sequence; (2) modification to amino acids, such as sugar moieties (glycosylation) or other side chains; and (3) higher order structure (protein folding and protein-protein interactions).").

122. *Id.*

123. *See* Kanter & Feldman, *supra* note 7, at 71–73.

124. FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 4 ("An application submitted under section 351(k) of the PHS Act must contain, among other things, information demonstrating that 'the biological product is biosimilar to a reference product' based upon data derived from: Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; Animal studies (including the assessment of toxicity); and A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product." (citation omitted)).

125. *See generally id.*

not negate the need for human PK and PD studies."[126] This does little more than to reiterate the provisions of the Biosimilars Act. Hence, the uncertainty of Biosimilars Act remains, and it places a disproportionate amount of discretion in the FDA approval process.[127]

Another way the FDA attempts to resolve the uncertainty is by stating that it will have up to five formal meetings with each prospective biosimilar applicant throughout the development and testing process to provide the applicant with feedback.[128] The first meeting involves the applicant providing "preliminary comparative analytical similarity data" so the FDA may assess whether the biosimilar approval is feasible.[129] The last of the five meetings assist the applicant in preparing a "section 351(k)" application to file.[130] This process will supposedly give the applicant a better idea of how much investment will be required for the application process before it begins.

The FDA further relaxes the requirements by suggesting that biosimilars do not need to have exactly the same "formulation" or production method as the reference biologic and may be enclosed in a different container or delivery device.[131] Also, biosimilars may obtain approval for only some of the elements embodied in the reference product.[132] For example, the applicant may only want to obtain biosimilarity status for the strength or container of the reference product.[133] The FDA also notes that biosimilar applicants could use comparative studies from the non-U.S.-licensed product to

126. *Id.* at 13.

127. *See id.* at 4, 13.

128. BIOSIMILAR BIOLOGICAL PRODUCT FDA MEETINGS, *supra* note 53, at 3.

129. *Id.*

130. *Id.* at 4.

131. FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 8 ("A sponsor may be able to demonstrate biosimilarity even though there are formulation or minor structural differences, provided that the sponsor provides sufficient data and information demonstrating that the differences are not clinically meaningful and the proposed product otherwise meets the statutory criteria for biosimilarity.").

132. *Id.* at 5 ("Thus, as set forth in the PHS Act, data derived from analytical studies, animal studies, and a clinical study or studies are required to demonstrate biosimilarity unless FDA determines an element unnecessary.").

133. *See* FDA QUESTIONS AND ANSWERS, *supra* note 26, at 5–6.

demonstrate a biosimilar's equivalency to a reference biologic, specifically for animal and clinical studies.[134] However, the original reference product needs to have been approved in the United States and the FDA has a long list of eligibility requirements before an applicant may reference a foreign-licensed product.[135] In addition, clinical comparisons with a non-U.S.-licensed product would likely not support a finding of interchangeability, even if approval were granted.[136] Also, an applicant may extrapolate clinical data of biosimilarity from one condition to another condition for which the reference product is licensed.[137]

Despite these attempts to clarify the process, many uncertainties in the approval pathway remain. The FDA Guidance Documents are nonbinding and have only been implemented in the approval of one biosimilar so far. Furthermore, most sections of the FDA Draft Guidance Documents disclaim that the ultimate decision will be left to the official at the time of approval.[138]

IV. PROPOSED REVISIONS AND RECOMMENDATIONS TO THE BIOSIMILAR DEVELOPMENT AND APPROVAL PROCESS

The primary challenge with developing an effective approval process for biosimilars is finding a happy balance between ensuring safety and efficacy while improving access and incentivizing research, development, and fair

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134. FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 6 ("However, under certain circumstances, a sponsor may seek to use data derived from animal or clinical studies comparing a proposed product with a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act. In such a case, the sponsor should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product." (citation omitted)). See argument, *infra* Part IV., for a discussion regarding using other countries' data on biosimilarity and suggestions for extrapolating that data for use in U.S. approval systems.

135. FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 6 (citing FDA QUESTIONS AND ANSWERS, *supra* note 26, at 7–8).

136. *Id.*

137. *Id.* at 19–20.

138. *See* FDA QUESTIONS AND ANSWERS, *supra* note 26, at 2–3.

competition.[139] At the moment, however, the scale tips strongly against biosimilars.[140] The reasons for this are not necessarily safety and efficacy concerns, but rather political lobbying and interests of current industry players.[141] Innovator biologics and their beneficiaries are pushing for more stringent requirements for biosimilar approval in order to protect their own market interests and limit competition.[142] On the other hand, many scientists, lawyers, and governmental agencies have expressed the view that the current approval process is unnecessarily rigorous for biosimilar applicants and is discouraging research and limiting access to important large molecule pharmaceuticals.[143] This view has gained several supporters in the last few years, especially in light of the fact that not a single biosimilar has entered the market in the United States since the enactment of the Biosimilars Act in 2010, while several biosimilars have been safely introduced into foreign markets.[144]

Although several companies have filed biosimilar applications, including Celltrion's outstanding application for a

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139. *See Economic Impact Analyses of FDA Regulations*, *supra* note 18 (discussing the FDA's cost-benefit analysis in approving and regulating drugs).

140. Kanter & Feldman, *supra* note 7, at 69 ("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 production under the Hatch-Waxman Act, and are unlikely to be sufficient to attract much activity in the biosimilars market.").

141. *See* Timothy J. Shea, Jr., Director, Sterne, Kessler, Goldstein & Fox P.L.L.C., Presentation at the BIO International Conference, The New Biosimilars Act: Overview of the Legislation and IP Implications (Mar. 4, 2011), *available at* http://www.skgf.com/themes/default/public/media/pnc/9/media.1299.pdf (discussing the political climate in the industry on pages 3–5).

142. Groups such as the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Organization fought fiercely to increase the number of years of exclusivity for innovator biologics. *See e.g.*, Donna Young, *Obama Reignites 7-Year Biosimilar Exclusion and Inflames "Innovators"*, PHARMASHARE (Apr. 10, 2011), http://www.pharma-share.com/obama-reignites-7-year-biosimilar-exclusion-inflames-innovators.

143. *See id.*

144. *See* Kanter & Feldman, *supra* note 7, at 78; Haggin, *supra* note 59; Lisa Mueller, *A Review of the Status of Biosimilars in the U.S.*, BRIC WALL BLOG (Oct. 27, 2014), http://bricwallblog.wordpress.com/2014/10/27/a-review-of-the-status-of-biosimilars-in-the-u-s/.

biosimilar version of infliximab,[145] several revisions will need to be made not only to the Biosimilars Act, but also to the FDA's implementation of the Act, and to the overall understanding of biosimilars among health care professionals and the general public if we are to truly realize the benefits of biosimilars.[146]

One approach to changing the state of the biosimilar laws in the United States is to look to the approval pathways of other countries such as those in Europe, Asia, and Latin America to see which strategies have worked in those countries. Other approaches involve engaging with domestic health care practitioners, policy makers, and the general public to understand the unique needs of the U.S. pharmaceutical market.

A. INNOVATOR BIOLOGICS SHOULD BE GRANTED LESS EXCLUSIVITY

One of the main deterrents for the development of biosimilars is the twelve-year exclusivity period for innovator biologics, which has repeatedly been characterized as excessive by bodies such as the Generic Pharmaceutical Association (GPhA), the Federal Trade Commission, and President Obama.[147] Those holding this belief assert that the requirement should be around five to seven years as for small molecule chemical drugs.[148] Estimates from the White House contend that this measure could save as much as $2.34 billion in health

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145. Mueller, *supra* note 144. Remicade is the commercial name for infliximab in many countries. *Id.*

146. *Id.*

147. Kanter & Feldman, *supra* note 7, at 75, 80. The FTC stated that the twelve-year exclusivity period is "unnecessary to promote innovation by brand biologic drug manufacturers and can potentially harm consumers by directing scarce research and development funding toward developing low-risk clinical data for drug products with proven mechanisms of action rather than toward new products to address unmet medical needs." OFFICE OF MGMT. & BUDGET, EXEC. OFFICE OF THE PRESIDENT, TERMINATIONS, REDUCTIONS, AND SAVINGS: BUDGET OF THE U.S. GOVERNMENT, FISCAL YEAR 2012, at 119 (2011) (footnote omitted), *available at* http://www.whitehouse.gov/sites/default/files/omb/budget/fy2012/assets/trs.pdf.

148. Malkin, *supra* note 67, at 88 ("Biological innovators want more time, while biosimilar applicants, many legislators, and even President Barack Obama, want this exclusivity period to be closer to the five-year new-chemical-entity exclusivity period for small molecules."); Young, *supra* note 142 ("In his $3.73 trillion fiscal year 2012 budget announced 14 February is a proposal that seeks to reduce from 12 to seven the years of data exclusivity protection for "innovator" biologics against follow-on biologics.").

care costs over ten years.[149] In addition, innovative biologic developers would still recover the costs of developing a novel drug under the reduced exclusivity period and patents, allowing for double protection, would also cover many drugs.[150] Arriving at an effective exclusivity term involves balancing the desire to provide incentives for innovators while encouraging the creation of copycat drugs that lower the cost of necessary treatment for Americans.

One country that follows an extreme version of this proposal is Brazil. Brazil's recently enacted biosimilar law does not grant any period of exclusivity to the original biologic developer.[151] Therefore, there is no data exclusivity period for new biological products and a generic or biosimilar could be registered any time after a new small molecule drug or biologic has been approved.[152]

Alternatively, Congress could enact a separate, shorter patent term only for biologics, or a provision that states that the only exclusivity available to innovator biologics would be the twelve years afforded by the Biosimilars Act and FDA Guidance Documents.[153] In Europe, although the patent term is also twenty years, many biologic patents are expected to expire much earlier than in the United States and more biosimilars have been developed.[154] For example, Ovaleap, a follitropin alfa biosimilar made by Teva Pharmaceutical Industries was approved in the European Union in September 2013.[155] The

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149. Young, *supra* note 142 (stating that this is "an argument the President had made during the formulation of the health reform law last year, but which had been rejected").

150. *See id.*

151. Mueller & de Freitas Morais, *supra* note 72 ("Brazilian law does not provide any regulatory/data exclusivity periods for new pharmaceuticals (small molecules) or new biological products (biologics) for human use.").

152. *Id.* ("Thus, in practice, ANVISA will register any generic drug (such as a branded or non-branded small molecule) or biological product (biosimilar) for human use any time after the registration of a new drug or new biological product (biologic).").

153. *See supra* note 89 and accompanying text.

154. *See* Leigh Anderson, *Biosimilars in 2015 – What Can We Expect?*, DRUGS.COM (Jan. 2015), http://www.drugs.com/news/biosimilars-2015-can-we-expect-55159.html.

155. *EMA Approves Biosimilar Follitropin Alfa and Somatropin*, GENERICS & BIOSIMILARS INITIATIVE (Sept. 20, 2013), http://www.gabionline.net/Biosimilars/News/EMA-approves-biosimilar-follitropin-alfa-and-somatropin ("[O]n 9 September 2013, the [European Medicines Agency] announced the approval of

European patents for the original follitropin alfa, Gonal-F, expired in 2009, whereas the U.S. patents expire in 2015.[156] A shorter duration in patent term will counter the delay in follow-on biologics (including biosimilars and biobetters[157]) entering the market, and expedite the availability of the drug to the population in the same way that limiting the Biosimilars Act exclusivity would. Patent terms are longer than twelve years, which will mean drugs protected only by the Biosimilars Act will be able to be copied much earlier.

However, patents are uncertain and require a showing of several other elements such as novelty and non-obviousness, which means that biosimilarity exclusivity is more likely to be granted than patent protection.[158] This will provide more certainty for biologics, but also limit the exclusivity of a drug if only one provision is providing it with exclusivity instead of two. In addition, patents require that the product information be publicly disclosed for all the elements of the product, which assists biosimilar developers in making comparable products.[159] This is a great benefit for the follow-on biologic and limiting it will affect developers' ability to make comparable biosimilars, which is a primary factor in their approval decision.[160] One way to resolve this issue would be to require that the original biologic manufacturer disclose the elements of their product at the end of the twelve-year exclusivity period. Under this structure, the exclusivity will provide a full twelve years before any biosimilar can be approved, during which time

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a new somatropin biosimilar. The follitropin alfa biosimilar (Ovaleap) is produced by generics giant Teva Pharmaceutical Industries.").

156. *Biosimilars Applications Under Review by EMA – 2013 Q4*, GENERICS & BIOSIMILARS INITIATIVE (Jan. 17, 2014), http://gabionline.net/Biosimilars/General/Biosimilars-applications-under-review-by-EMA-2013-Q4.

157. Unlike biosimilars, biobetters are "improved" versions of the original biologic, although they are in the same family as the biologic. Biobetters may qualify for their own patent and the FDA twelve-year protection. Fiona Barry, *Generation of Biobetters Could Push Out Biosimilar Development, Says Expert*, BIOPHARMA (Apr. 23, 2014), http://www.biopharma-reporter.com/Bio-Developments/Generation-of-biobetters-could-push-out-biosimilar-development-says-expert.

158. *See* America Invents Act, 35 U.S.C. §§ 102–103 (2012).

159. *Id.* § 102.

160. *Biosimilars*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm (last updated Mar. 6, 2015).

biosimilar manufacturers will be free to reverse-engineer the original product, as is the case currently. After the twelve-year period, however, the information will be disclosed to help future biosimilar developers to make the product a more accurate copy of the original.

B. APPROVAL SHOULD REQUIRE FEWER STUDIES

Another way to incentivize biosimilars is by limiting the number of tests and studies for the application process, and finding other ways for the biosimilar applicant to demonstrate biosimilarity, safety, and efficacy. This can be done in several ways, especially given the numerous technological advances that allow for accurate characterization of proteins and chemical molecules. Deciding on an optimum number of studies required to ensure safety and efficacy while maintaining incentives for drug developers poses a careful balancing act for the FDA.

First, the FDA could require fewer studies if the biosimilar has been approved in different countries. For example, if the biosimilar manufacturer has been approved to produce the same biosimilar in a foreign country, the FDA could allow—to a greater degree than is presently accepted—the results of analytical studies, animal studies and clinical studies from that approval process to be used in the application in the United States. Currently, the FDA has said that foreign animal and clinical studies may be accepted, but must show a sufficient connection to the biologic reference product approved in the United States through bridging studies between the biosimilar and the U.S.-licensed reference product.[161] In an FDA guidance document regarding the acceptability of foreign clinical data used for small molecule drugs, the FDA cites to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[162] for an idea of how bridge studies may be conducted.[163] Some of the factors the FDA considers in

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161. FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 6.

162. ICH is an international platform that brings together regulatory pharmaceutical bodies from around the world to discuss drug registration and compliance. ICH, http://www.ich.org/ (last visited Mar. 17, 2014).

163. FDA GUIDANCE FOR INDUSTRY: E5 – ETHNIC FACTORS IN THE ACCEPTABILITY OF FOREIGN CLINICAL DATA 2 (2006), *available at* http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073120.pdf ("[I]f the

assuming a sufficient bridge between the biosimilar and the U.S.-licensed biologic include the design of the overseas clinical study, the manufacturers of the biosimilar and reference product, and the standards that were followed in obtaining approval for the biosimilar overseas.[164]

The more thoroughly a biosimilar applicant addresses these issues, the more likely the foreign studies are to be sufficient. However, the FDA still maintains that the requirements are "not limited to" these criteria, creating uncertainty for the applicant.[165] In addition, although the FDA states factors it will consider, it does not state how these factors will affect the decision and to what extent each factor matters.[166] The FDA also fails to answer important questions such as whether the clinical studies have to be at a certain dose or strength in order to fulfill the requirements.[167] Although there are countless little details that no guidance can cover, it would be helpful for the FDA to give a list of examples of the kinds of clinical and animal studies that would be acceptable. These examples would make up for the lack of history in biosimilar approval.

In addition, if there are already several biosimilar drugs on the market that copy the same reference product, and if the applicant's biosimilar has a structure and function within the range of drugs on the market that have been proven to be effective and safe, the FDA could lower the requirements since previous applicants have already tested similar processes and proven them to be safe. As the number of biosimilars copying a single reference product increases, there will be less uncertainty in the effects of minor changes to its structure, genetic make-up, container, and other variables. Therefore, the second biosimilar application should be viewed less stringently than the first, and the third should be approved more readily

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data developed in one region satisfy the requirements for evidence in a new region, but there is a concern about possible intrinsic or extrinsic ethnic differences between the two regions, then it should be possible to extrapolate the data to the new region with a single bridging study. The bridging study could be a pharmacodynamic study or a full clinical trial, possibly a dose-response study.").

164. FDA QUESTIONS AND ANSWERS, *supra* note 26, at 7–14.

165. *See* FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 10.

166. *Id.* at 16–17.

167. *Id.* at 17–20.

than the second, given that there are only negligible changes in the manufacturing process and final product.

C. TESTING SHOULD INCREASE AT EARLIER STAGES OF DEVELOPMENT

Another way to reduce the burden on biosimilar developers is to rely heavily on technological advances that allow for accurate imaging and characterization of a biosimilar. There are many instruments and scientific methods that make it possible for a researcher to view the amino acid and protein structures, modifications, and minor impurities.[168] Although these methods are not perfect, they can provide a strong sense of a biosimilar's likeness to an innovator biologic.[169] Although some of the instruments are expensive, this method of testing biosimilars is still cheaper than clinical studies, so more time and resources should be invested in conducting careful visual, chemical, and biological analysis to determine the structural biosimilarity of the drug.[170] Both the drug developer and the FDA testing office can perform these tests and many such tests are already in use.[171] When combined with reasonable policies and regulations, these technological measures can reduce the inconsistencies that exist in biologic and biosimilar development.[172]

First, a pharmaceutical company already must comply with the FDA's Current Good Manufacturing Practices (CGMPs).[173] These practices ensure that a manufacturer uses "proper design, monitoring, and control of [the] manufacturing

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168. *See, e.g.*, Yi Qun Xiao, *Meeting the Challenges of Biosimilars*, MPI RES. (June 12, 2014), http://www.mpiresearch.com/meeting-challenges-biosimilars/ (discussing a pharmacokinetics assay and a technique that combines two assay results to overcome the challenges of biosimilar development).

169. *Id.*

170. *See generally* Leili Fatehi et al., *Recommendations for Nanomedicine Human Subjects Research Oversight: An Evolutionary Approach for an Emerging Field*, 40 J.L. MED. & ETHICS 716, 723 (2012) (discussing, generally, the costs of trials on human subjects).

171. *See* CLINICAL PHARMACOLOGY DATA, *supra* note 53, at 4–6; FDA SCIENTIFIC CONSIDERATIONS, *supra* note 32, at 8–10.

172. Rathore et al., *supra* note 36.

173. *Facts About the Current Good Manufacturing Practices (CGMPs)*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm (last updated Jan. 6, 2015).

processes and facilities."[174] Following these practices "assures the identity, strength, quality, and purity of drug products," by requiring "strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories."[175] This is only the first step of many checkpoints that ensure that the final product is safe.[176]

Second, there are many ways to observe and characterize the biological products at the microscopic level, which can provide information about their similarity to the innovator and detect potential inconsistencies. Two of these advanced techniques of characterizing molecules are light scattering[177] and nuclear magnetic resonance (NMR) spectroscopy.[178] Through these techniques, each intermediate product of the process can be closely characterized to create continuous cell lines for consistent same cell substrates, and see the folding patterns and added side chains in the final molecule.[179]

There have been very few (if any) cases of biosimilars being dangerous because they were inaccurately copied from the innovator. In addition, although some branded biologics have been removed from the market, it has seldom been due to the inconsistency between batches.[180] In the past, the FDA has required batch certification for antibiotics, which requires the manufacturer to send samples for batch-specific testing even after the drug was approved.[181] However, as technology and

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174. *Id.*

175. *Id.*

176. *See id.*; Daron I. Freedberg, *Improvement of Biological Product Quality by Application of New Technologies to Characterize of Vaccines and Blood Products: NMR Spectroscopy and Light Scattering*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/biologicsbloodvaccines/scienceresearch/biologicsresearchareas/ucm127270.htm (last updated Feb. 13, 2015).

177. Light scattering identifies molecular weight and size by examining the reflection of light off the molecule. Freedberg, *supra* note 176; *see* CRAIG F. BOHREN & DONALD R. HUFFMAN, ABSORPTION AND SCATTERING OF LIGHT BY SMALL PARTICLES 3–11 (1983).

178. NMR uses magnetic fields and radio waves to form images of organic molecules. L.G. WADE, JR., ORGANIC CHEMISTRY 559–61 (6th ed. 2006).

179. *See Cell Substrates*, *supra* note 34.

180. *See infra* note 182 and accompanying text.

181. *Regulatory Information: FDA Backgrounder on FDAMA*, U.S. FOOD & DRUG ADMIN. (Nov. 21, 1997), http://www.fda.gov/regulatoryinformation/legis

regulation improved, there was less need for the intermittent testing and by 1981, less than one percent of batches were rejected from safety issues arising during the batch tests.[182] Although the batch certification requirement has since been abolished,[183] there are new areas of safety to focus on.

As Glenn Begley and Lee Ellis's findings suggest, at least a significant part of the issue lies at the initial stages of the development process because the *in vitro* analytical data were not able to be replicated easily,[184] suggesting we need to work on increasing the replicability of data from the analytical stages, because that will lead to better *in vivo* results downstream.[185] Another challenge is finding anti-biosimilar antibodies for immunogenicity assays, which are not as readily available as for the biologic.[186] One solution is to use two assays composed of both the innovator and biosimilar as attaching and detecting agents, and then compare the two assays for drug tolerance, sensitivity, and specificity in the enzyme-linked immunosorbent assays.[187] Through adopting these and other measures, the biosimilar manufacturers and FDA testing agency can ensure comparability of the biosimilar at the analytical stage and require fewer clinical and animal studies. In addition to being cost-prohibitive and time-consuming, clinical studies are not as useful as they are often purported to be, since clinical studies are usually performed on healthy

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lation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdama/ucm089179.htm.

182. U.S. GEN. ACCOUNTING OFFICE, FDA SHOULD REDUCE EXPENSIVE ANTIBIOTIC TESTING AND CHARGE FEES WHICH MORE CLOSELY REFLECT COST OF CERTIFICATION 8 (1981), *available at* http://www.gao.gov/assets/140/135632.pdf ("The rejection rates for antibiotic batches has traditionally been low. Since 1948, the annual rejection rate has not exceeded 1.2 percent and has been as low as 0.13 percent.").

183. Richard Rowberg et al., *Food and Drug Administration Modernization Act of 1997 – The Provisions*, *in* THE FOOD AND DRUG ADMINISTRATION (FDA) 63, 79 (Meredith A. Hickmann ed., 2003).

184. *See supra* Part II.A.

185. Their study suggests that the analytical stages of the biologic's development are the most vulnerable to replicability problems. Begley & Ellis, *supra* note 42. *See supra* Part II.A.

186. Enzyme-linked immunosorbent assays require antigens that will bind to the biosimilars. Michele Kessler et al., *Immunogenicity of Biopharmaceuticals*, 21 NEPHROLOGY DIALYSIS TRANSPLANTATION 9, 9–11 (2006).

187. Xiao, *supra* note 168.

subjects who are not representative of the population that will be using the drug.[188]

Furthermore, none of the already-approved biosimilars have been found to have serious negative health effects.[189] This indicates that post-grant recall for safety is not a major concern. Ortwin Renn conceptualizes risk with an integrative approach considering the technical, social, cultural, and economic aspects of the harm, as well as the magnitude of the harm.[190] He also states, "society is not only concerned about risk minimization. People are willing to suffer harm if they feel it is justified or if it serves other goals."[191] Hence, although pharmaceuticals may never be risk free, a logical balance may be struck between the safety, efficacy, cost, and accessibility of biosimilars.

D. PHARMACISTS AND DOCTORS MUST BE IN THE LOOP

Any biosimilars reform necessarily needs to involve health care practitioners, such as doctors, nurses, and pharmacists, not only to be able to control the distribution of biosimilars, but also to spread the word to the public about their risks, benefits, and regulatory schemes. At the moment, few people are aware of the existence of biosimilars, particularly in the United States, and even fewer have a basic understanding of the concepts behind them. If doctors are well informed about the risks and benefits, they will be more or equally likely to prescribe the biosimilar as compared to the innovator biologic, providing manufacturers incentives to develop biosimilars even without interchangeability.

Pharmacists can also be educated to make effective and safe biosimilar substitutions and they may be given more say in the substitution decision.[192] The FDA should plan to educate pharmacists about the available biosimilars and how they are

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188. *See The Utility of Clinical Trials for Biosimilars*, GPHA, http://www.gphaonline.org/gpha-media/gpha-resources/the-utility-of-clinical-trials-for-biosimilars (last visited Mar. 7, 2015).

189. *See supra* notes 63–66 and accompanying text.

190. Ortwin Renn, *Concepts of Risk: A Classification*, *in* SOCIAL THEORIES OF RISK 53, 77 (Sheldon Krimsky & Dominic Golding eds., 1992).

191. *Id.*

192. Malkin, *supra* note 67, at 90.

different (if material) from the biologic.[193] Congress should enact laws that allow pharmacists to make informed decisions regarding the substitution of a biosimilar.[194] One way to enable pharmacists to make substitutions would be to require that all biosimilars are "labeled with . . . International Nonproprietary Names (INNs), using individual National Drug Codes (NDCs)" so pharmacists can easily identify and distinguish reference biologics and their biosimilars and make educated decisions in substituting them.[195]

E. TWO ALTERNATIVES TO THE INTERCHANGEABILITY PROCEDURE

The other way to make biosimilars a more proximate reality is to reform the law around interchangeability. Presently, to gain interchangeability, the biosimilar manufacturer needs to prove that the biosimilar has the "same clinical result in any given patient as the referenced product. In addition, for biological products that are administered more than once, the biosimilar product would produce the same clinical result when switching from the referenced product to the biosimilar and back again."[196] But switching between the products need not be an integral part of the interchangeability status. With diligent recordkeeping, a patient can be kept on one biologic or biosimilar and not have to switch back and forth.

There are two ways the FDA could alter this standard. First, the FDA could maintain a rigorous approval process for biosimilars but grant interchangeability to all approved biosimilars. The approval requirements for biosimilars would

193. *Id.* (discussing how pharmacists want the FDA's help in such education and how "they want the FDA to opine on when pharmacists can substitute biosimilar products without a physician's consent").

194. *Id.*

195. *Id.* at 67–68. The INNs for biologics are decided by a committee such that the names are standardized and easy to understand around the world. WORLD HEALTH ORG., WHO INFORMAL CONSULTATION ON INTERNATIONAL NONPROPRIETARY NAMES (INN) POLICY FOR BIOSIMILAR PRODUCTS 4–5 (2006), *available at* http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf. While the FDA is hesitant to use this approach for biosimilars as well, the WHO guidelines on naming suggest that the same naming approach be taken for biosimilars as is taken for innovator biologics. *Id.* at 11–12 (providing the recommendations proposed for the biosimilars naming process).

196. Malkin, *supra* note 67, at 89.

need to be more rigid to ensure safe substitution of prescribed biologics. This could be achieved in several ways, including requiring a greater number of studies to show comparability, safety and efficacy. One risk with automatic substitution is not being able to trace the cause in case of an adverse drug reaction.[197] If biosimilars are automatically interchanged, records might be less thorough, especially if a patient switches back and forth between the original biologic and many other biosimilars. However, as mentioned in the previous paragraph, this could be corrected for with extensive recordkeeping and not having patients take different biosimilars that are based on the same biologic. One more concern of easily granted interchangeability "is the possibility that repeated switches between the biosimilar and the reference product may increase immunogenicity with potentially negative effects on the safety and/or efficacy of the products."[198] Automatic substitution has not yet been accepted in the European Union, and "more than 12 countries across Europe have introduced rules to prevent automatic substitution of biological medicines by biosimilars."[199]

Alternatively, the FDA could continue to treat interchangeability as a separate question, requiring a separate application, but lower the standards for obtaining biosimilar status. This way, either the approval pathway for biosimilars is made easier and interchangeability is only granted after a drug has proven itself on the market, or the pathway is similarly maintained in its current burdensome state but the biosimilar is deemed interchangeable as soon as it is approved as a biosimilar. Either way, under this second alternative, the biosimilar approval process would be much less rigorous, reducing the number of studies required. Of course, the glaring concern with this approach is that biosimilars will be interchangeable with less scrutiny, which may lead to unsafe

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197. Martina Weise et al., *Biosimilars: What Clinicians Should Know*, 120 BLOOD J. 5111, 5114 (2012).

198. *Id.*

199. *Efficacy, Extrapolation and Interchangeability of Biosimilars*, GENERICS & BIOSIMILARS INITIATIVE (Apr. 19, 2013), http://www.gabionline.net/Biosimilars/Research/Efficacy-extrapolation-and-interchangeability-of-biosimilars; *see also Frequently Asked Questions About Biosimilar Medicines*, EUR. GENERIC MEDICINES ASS'N, http://www.egagenerics.com/index.php/biosimilar-medicines/faq-on-biosimilars (last visited Apr. 6, 2015).

results. To resolve this issue, the FDA should take several actions.

First, the biosimilar applicant should be required to make public all the information about the product, including the risks, the differences from the innovator biologic, whether it has been approved in other countries, and any potential side effects observed in animal or local studies. With this information readily available, doctors, pharmacists, and patients will be able to make educated decisions about prescribing and using the biosimilar. Such an approach is implemented in the overall health care system in Singapore and could provide useful reference for other countries.[200] The FDA could mandate that the biosimilar applicant release analytical information about the drug, the number of empirical studies conducted, the results of any animal or clinical tests, and names of other similar drugs.[201] In addition, patients could be required to sign a waiver that indicates that they have read the relevant information and understand the risks and benefits. This would shift part of the burden of the decision to the patient, ensuring that patients are taking measures to educate themselves about the risks and benefits, instead of simply buying the cheapest drug and assuming it is equally effective and safe.

Currently, interchangeability is one of the main incentives for biosimilar developers because it greatly increases the profitability of a biosimilar.[202] The FDA presently requires the

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200. WILLIAM A. HASELTINE, AFFORDABLE EXCELLENCE: THE SINGAPORE HEALTHCARE STORY 14–15 (2013) (discussing the practices of one of the world's best medical systems, and the role different groups—including doctors, regulatory officials, and patients play in the system to keep it alive).

201. Karen Feldscher, *Singapore's Health Care System Holds Valuable Lessons for U.S.*, HARV. SCHOOL PUB. HEALTH NEWS (Jan. 28, 2014), http://www.hsph.harvard.edu/news/features/singapores-health-care-system-holds-lessons-for-u-s/ (synthesizing Haseltine's book and the advantages of the Singapore system). Singapore is known to have one of the world's more efficient and fair health care systems. The system has a policy of transparency where all the information regarding a hospital or health care professional is publically available, including the prices and fees associated with their services. This allows patients to compare options and make an educated decision for themselves. Although this policy is applied on a broader basis in Singapore, for the whole health care system, it would be applicable to the biosimilars market in the U.S. as well since there are many considerations and a different choice might be right for each patient. *See generally id.*

202. *See generally* Addison, *supra* note 16, at 577; Kanter & Feldman, *supra* note 7, at 74.

applicant to first gain approval as a biosimilar;[203] then, after being on the market for a while without any indications of safety concerns, the applicant may provide the FDA with additional information such as efficacy and safety clinical data to apply for interchangeability status.[204] This is a departure from the Biosimilars Act's requirements, which allows an applicant to file for interchangeability along with its 351(k) application.[205]

Regardless of which approach is taken, there is bound to be some disagreement among scientists, regulators, and the general public about where the balance between accessibility and precaution lies; therefore, the final policies require "multilateral exchange" between experts, the FDA, and the public.[206] As noted by Sheila Jasanoff, there is a "grey zone between science and policy or facts and values" such that "there is no single right way to iron out the multiple ambiguities in the regulatory record."[207]

F. INSURANCE SUBSTITUTION STATUS

In order to increase the benefits of biosimilars at the state level, it will be important for insurance companies to recognize and reimburse biosimilars in coverage plans.[208] This way, the biosimilars will be interchangeable at the pharmacy and insurance levels. One reason patients and doctors may be less likely to select the biosimilar is if insurance companies do not reimburse for the biosimilar as easily as they do for the

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203. FDA QUESTIONS AND ANSWERS, *supra* note 26, at 2–3. Some argue that this is not required by the Biosimilars Act, but is rather an additional requirement by the FDA. The Biosimilars Act could be interpreted to mean that an application for biosimilarity status is also an application for interchangeability. This is a debate that health care officials, pharmacists, and regulatory officials have been having for a while, where pharmacists are pushing for fewer regulations that tie their hands and give them less flexibility in prescribing drugs independently from the doctor. *See* Malkin, *supra* note 67, at 89–90.

204. Kanter & Feldman, *supra* note 7, at 73–74 (arguing that the level of clinical testing required for interchangeability is so stringent that it will lead to more manufacturers filing for approval under the regular biologic approval pathway—Biological License Application (BLA)).

205. Malkin, *supra* note 67, at 89.

206. *See generally* Sheila Jasanoff, *Procedural Choices in Regulatory Science*, 17 TECH. SOC'Y 279, 290 (1995).

207. *Id.* at 292.

208. Interview with Ralph Hall, *supra* note 33.

innovator biologics.[209] Insurance is more likely to be available for biosimilars if there is a publically available list of biosimilars, that are "therapeutically equivalent" to their innovator counterparts, as is done with small molecule drugs.[210] Without such an automatic substitution system in place, the burden will be on the pharmacy and the patient to contact the insurance provider to confirm acceptability of a biosimilar, which will be onerous and hence seldom done.

CONCLUSION

This Note argues that the current state of biosimilar law is overly burdensome for potential biosimilar developers and that it provides a windfall for innovator biologics manufacturers. This is due to extreme provisions and unclear guidelines provided in the Biosimilars Act and by the FDA Draft Guidance Documents. An effective and less burdensome biosimilars approval pathway would increase accessibility and research for important therapies; therefore, reforming the current system must be a high priority for policy makers and experts. This Note suggests six possible ways to reform the current law and guidance around biosimilars and insists that a balance must be struck between reducing risk and increasing accessibility of biosimilars by engaging medical experts, law makers, and the general public in dialogue as well as looking to the well-established approval processes of other countries.

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209. *See generally* Aslam H. Anis, *Substitution Laws, Insurance Coverage, and Generic Drug Use*, 32 MED. CARE 240 (1994).

210. U.S. DEP'T HEALTH & HUMAN SERVS., EXPANDING THE USE OF GENERIC DRUGS 8–9 (2010), *available at* http://aspe.hhs.gov/sp/reports/2010/genericdrugs/ib.pdf.