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Biosimilar Naming: A Call for Uniformity in a Complex Field

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BIOSIMILAR NAMING: A CALL FOR UNIFORMITY IN A COMPLEX FIELD

INTRODUCTION

The birth of recombinant technology[1] has opened a pathway for a means of producing a variety of therapeutic proteins and generating the growth of the biopharmaceutical industry.[2] Biopharmaceuticals, or biologics, have become an important therapeutic option in recent years.[3] Biologics represent "therapeutic proteins, DNA vaccines, monoclonal antibodies, and fusion proteins" that are used to treat autoimmune disorders and cancers.[4] These pharmaceuticals are structurally complex and are made in living organisms to provide proteins to treat various diseases, often by genetically engineering living cells.[5] Because of their complexity, biologics can be heat sensitive and susceptible to microbial contamination.[6] Thus, they must be maintained in stable storage environments and administered in a manner that preserves their efficacy in the human body.[7] These inherent characteristics of biologic drugs make immunogenicity[8] a crucial aspect to the success of biologic products.[9]

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1. Recombinant technology, also known as Recombinant DNA, is the process of taking a gene from one organism and inserting the gene into the DNA of another. This process has revolutionized the pharmaceutical industry. *See* Anthony J. Griffiths, *Recombinant DNA Technology,* ENCYCLOPEDIA BRITANNICA, http://www.britannica.com/EBchecked/topic/493667/recombinant-DNA-technology (last updated Mar. 20, 2014).

2. H. Mellstedt et al., *The Challenge of Biosimilars*, 19 ANNALS ONCOLOGY 411 (2008).

3. *See generally id*.

4. Kristina M. Lybecker, *When Patents Aren't Enough: Why Biologics Necessitate Data Exclusivity Protection,* 40 WM. MITCHELL L. REV. 1427, 1433 (2014) (quoting Amgen).

5. *Id.*

6. Jeanne Yang, *A Pathways to Follow-on Biologics*, 3 HASTINGS SCI. & TECH. L.J. 217, 222 (2011) (quoting *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm (last updated Aug. 5, 2015)).

7. *Id.*

8. *Immunogenicity* is defined as "the propensity of therapeutic proteins to generate immune responses to itself and to related adverse clinical events." Food & Drug Admin., U.S. Dep't Health and Human Servs., *Guidance for*

In comparison to the complex nature of biologic drugs, small-molecule chemical drugs are structurally straightforward and well known.[10] Small-molecule chemical drugs are commonly associated with most prescription medicines.[11] While the Food and Drug Administration's (FDA) approval for these types of small-molecule chemical drugs, both generic and brand, is costly, there is a certain ease associated with small-molecule approval that does not exist for biologic and generic biologic approval.[12] Due to the rather simple structure and well-known synthesis of small-molecule chemicals, generic producers can easily reproduce these small-molecule drugs.[13]

In order for the FDA to approve a generic drug, like amoxicillin and simvastatin, which are among the most popular FDA approved small-molecule generic drugs,[14] the drug applicant must establish that the original drug, commonly referred to as the reference product,[15] and the generic are bioequivalent.[16] As

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Industry: Immunogenicity Assessment for Therapeutic Protein Products 1 (2014), http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf.

9. *See* Yang, *supra* note 6, at 236 (noting that upon submission for FDA approval, biologic applicants must establish the comparability of their drug's immunogenicity to that of existing market products).

10. Donna M. Gitter, *Informed By The European Union Experience: What the United States Can Anticipate And Learn From the European Union's Regulatory Approach to Biosimilars*, 41 SETON HALL L. REV. 559, 560 (2011).

11. Stacey L. Worthy & John F. Kozak, *Follow-on Biologics: Protecting Consumers Through State Pharmacy Law in Light of Recent FDA Actions*, 17 QUINNIPIAC HEALTH L.J. 207, 207 (2014).

12. Gitter, *supra* note 10, at 562.

13. Mellstedt et al., *supra* note 2, at 412.

14. It is estimated that over the past decade generic drugs have saved the U.S. healthcare system approximately $734 billion. Anthony D. So & Samuel L. Katz, Opinion, *Biologics Boondoggle,* N.Y TIMES, Mar. 8, 2010, at A23. On average, biologic brand-name drugs cost twenty-two times as much as small-molecule chemical drugs. *Id.* Herceptin, a breast cancer drug, costs patients $37,000 a year, and Humira, a drug for treating rheumatoid arthritis and Chron's disease, costs $50,000 a year. *Id.*; *see also* Michael Bartholow, *Top 200 Drugs of 2012,* PHARMACY TIMES (July 17, 2013), http://www.pharmacytimes.com/publications/issue/2013/july2013/top-200-drugs-of-2012. Thus, the need for cheaper biologic drugs is dire.

15. A reference product may also be called an innovator drug. The term is used in cases of both traditional chemical drugs and biologic drugs to define the original invented drug upon which the generic version aims to "piggyback." *See* Yang, *supra* note 6, at 233.

a comparison between the reference product and the generic, bioequivalence is defined as the absence of a significant difference between the rate and extent to which the active ingredient becomes available at the site of drug action.[17] Essentially, bioequivalence analyzes whether the two drugs have identical active ingredients and produce the same effect in the body.[18] One can establish bioequivalence by demonstrating that the pharmacokinetic properties of the generic and the reference product are similar.[19] Given the makeup of small-molecule chemical drugs, it is not difficult to prove bioequivalence by demonstrating identical chemical composition and similar pharmacokinetics.[20] The inherent properties of small-molecule drugs allow the production of generic drugs to be straightforward, safe, and efficient.[21] Given the complexity of biologic drugs, however, minute changes in the manufacturing process can result in drastic differences in quality, safety, and efficacy between reference product and potential biosimilars.[22] This makes demonstrating bioequivalence for potential biosimilars difficult.[23]

With the patent expirations of a number of biologics in the coming years,[24] there has been an increased interest in the development of generic biologics,[25] also known as biosimilars, and a widespread push for biosimilar FDA approval in the United States.[26] While the pressure for the expansion of biosimilar ap-

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16. *See generally* Food & Drug Admin., U.S. Dep't Health & Human Servs., Guidance For Industry: Bioavailability & Bioequivalence Studies for Orally Administered Drug Products – General Considerations (2003) [hereinafter Bioavailability & Bioequivalence Studies], http://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf.

17. *Id.*

18. *Id.*

19. *See id.*

20. Worthy & Kozak, *supra* note 11, at 217.

21. Mellstedt et al., *supra* note 2, at 412.

22. Gitter, *supra* note 10, at 561.

23. Worthy & Kozak, *supra* note 11, at 221.

24. *See* GOODWIN PROCTER, BIOSIMILARS: A GUIDANCE TO REGULATORY AND INTELLECTUAL PROPERTY ISSUES 10 (2014).

25. Before the Patient and Affordable Care act was passed in 2010, there was public pressure to create an abbreviated approval pathway for biosimilar drugs. Many hoped the development of these biosimilar drugs would substantially reduce the cost of many life-saving biopharmaceutical therapies. *See generally* So & Katz, *supra* note 14.

26. Mellstedt et al., *supra* note 2, at 411.

proval is warranted, the FDA must be cautious when implementing regulatory guidelines. Since biologics differ greatly from small-molecule drugs, biologics have a distinct approval process.[27] Assuming that a biosimilar will be just as safe and effective as its reference product is not a decision that can be taken lightly.[28]

Key players in the pharmaceutical industry have weighed in on this issue and have expressed concern about biosimilar approval,[29] warning that "seemingly small changes to a biologics structure . . . may have unintended clinical consequences."[30] In the late 1990s, such a concern manifested itself in a real life tragedy. A U.S. manufacturer of the drug erythropoietin[31] licensed their rights to another manufacturer to produce the same product in the European Union.[32] The EU manufacturer

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27. Gitter, *supra* note 10, at 561.

28. Pamela Jones Harbour, Commissioner, Federal Trade Commission, Remarks before the American Bar Association Sections of Antitrust and Intellectual Property Law's Conference: Intellectual Property Antitrust – Strategic Choices, Evolving Standards, and Practical Solutions (June 14, 2007) [hereinafter Harbour ABA Remarks], (transcript available at https://www.ftc.gov/sites/default/files/documents/public_statements/competitive-implications-generic-biologics/070614genbio_0.pdf).

29. Companies, such as brand-name biologic producer Sanofi, have expressed concern about the biosimilar approval process. Critics may argue that companies, like Sanofi, only have an interest in preserving their monopoly on the biologics market; however their concerns are not unfounded. In fact, the Pharmaceutical Research and Manufacturers of America (PhRMA) released a set of overarching principles on biosimilar approval. *Approval Pathway for Biosimilar and Interchangeable Biological Products: FDA Public Hearing*, (Nov. 2–3, 2010) (statement of Marie A. Vodicka, PhRMA Associate Vice President of Scientific and Regulatory Affairs), http://www.phrma.org/sites/default/files/pdf/110210_phrma_biosimilars_public_hearing_testimony_final.pdf. PhRMA takes a conservative stance on biosimilar approval and stresses the importance of patient safety above all. *Id.*

30. Robert J. Mattaliano, Group VP Biologics Department, Genzyme Corporation, Remarks before FDA Advisory Committee on Pharmaceutical Science and Clinical Pharmacology, *A PhRMA Member View on Biosimilars: Analytical and Quality Considerations*, at 12 (Aug. 8, 2012), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf.

31. *Erythropoeitin* is a hormone and biologic drug that promotes red-blood-cell growth. Wolfgang Jelkman, *Regulation of Erythropoietin Production*, 589 J. PHYSIOLOGY. 1251, 1251 (2011).

32. Worthy & Kozak, *supra* note 11, at 242.

used the same methodology to produce the drug, making only incidental changes.[33] However, EU patients who used the drug developed pure red cell aplasia, "a life threatening condition" wherein the bone marrow stops producing red blood cells.[34] As a result, multiple patients died while others became permanently dependent upon blood transfusions.[35]

It is clear that biosimilars are not just generic versions of biologic drugs.[36] The true complexity of a biosimilar's structure makes it much more difficult to create biosimilar regulatory pathways that can ensure the safety of consumers.[37] The process for approving a biosimilar requires greater analysis and consideration than traditional generic drug approval.[38] Due to the lack of experience in regulating these drugs, authorities have moved cautiously, heavily scrutinizing the first wave of biosimilar applications.[39]

The United States is certainly not the first to provide a pathway for biosimilar approval.[40] The EU, India, Japan, and South Korea have already adopted a regulatory framework for biosimilar approval.[41] The EU began developing their framework in 2005, Japan and South Korea in 2009, and India in 2012.[42] The framework varies slightly from country to country.[43] However, they generally employ the same approach to ensure that pharmacokinetic studies establish the substantial similarity between the reference product and the biosimilar.[44] With the development and implementation of multiple regulatory frameworks, international organizations, such as the World Health

33. *Id.*

34. *Id.* at 209. Pure red cell aplasia resulted from an allergic reaction to biologics. *Id.*

35. *Id.*

36. *See* GOODWIN PROCTER, *supra* note 24, at 1.

37. *See* Harbour ABA Remarks, *supra* note 28. *See generally* GOODWIN PROCTER, *supra* note 24.

38. *Id.* at 1.

39. *Id.*

40. FENWICK & WEST LLP, A COMPARISON OF US AND EU BIOSIMILARS REGIME 3 (2012), https://www.fenwick.com/FenwickDocuments/01-06-12_Comparison_US_EU_Biosimilars_Regimes.pdf.

41. *See* GOODWIN PROCTER, *supra* note 24, at 48.

42. *Id.*

43. *Id.*

44. *Id.*

Organization (WHO), will be tasked with ensuring there are cohesive guidelines for any residual concerns that develop.[45]

With the increase in the number of biosimilars available, the process of naming biosimilars has become an important regulatory concern; causing countries to develop various methods of naming approved biosimilars.[46] Some regulatory bodies use the international nonproprietary name (INN) of the reference product, others such as regulatory bodies in Australia and Japan, attach a short and separate qualifier.[47] In the United States, brand companies have proposed that the biosimilars should receive a unique INN.[48] However, a lack of uniformity in nomenclature would result in the same biological medicine having different meanings in different areas of the world.[49] In attempts to avoid the promulgation of separate and distinct national qualifier systems, several regulatory authorities have requested that the WHO's INN Programme develop a universal nomenclature system applicable to biosimilars.[50]

This Note will analyze the current U.S. and EU approach for defining the necessary measures in demonstrating biosimilarity to a reference product. Part I will lay the foundation for biosimilar regulatory approval by examining the regulatory process and legislative history of the FDA's small-molecule generic drug approval process. Additionally, Part I will discuss the legislative history of approving biopharmaceutical drugs and the FDA's recent biosimilar approval guidelines. This analysis will demonstrate the importance of recent legislation and its effects on the biopharmaceutical market.

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45. *See* World Health Organization [WHO], *Biological Qualifier: An INN Proposal,* at 2–3, INN Working Doc. 14.342 (July 2014) [hereinafter *Biological Qualifier Proposal*], http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf.

46. *Id.* (proposing a short and separate qualifier, referred to as a "BQ," which would complement the INN for a biological substance).

47. *Id.*

48. *Id.*

49. For example, an epoetin registered in Europe by the EMEA using the INN, *epoetin alfa,* was subsequently registered by Australia with an INN-similar nonproprietary name *epoetin lambda. See Biological Qualifier Proposal*, *supra* note 45, at 3.

50. INN experts and the INN Secretariat met in April 2013 and 2015. *Id.* Additionally, an INN Expert Group convened in October 2014 and April 2014 to discuss whether the WHO should devise such a program. *Id.*

Part II will provide an analysis of the EU's approach to biosimilar approval. This analysis will also evaluate both the historical evolution and success of the EU program since its inception. Part III will examine the concerns with biosimilar naming. This part will analyze the current naming framework provided by the EU, United States, and the WHO, and how each framework will affect the success of the biologics market. Finally, Part IV proposes a framework for future biosimilar naming in the United States. Ultimately, this Note suggests that in order to successfully promote the growth of the biosimilars market and facilitate the true intent of global legislation creating abbreviated approval pathways for biosimilars, the WHO, together with the EU and the United States, should ensure biosimilars are afforded INNs that are identical to their existing biologic counterpart.

I. THE U.S. APPROACH TO BIOLOGIC AND BIOSIMILAR APPROVAL

This section will discuss the history of the United States' abbreviated approval pathway for generic small-molecule drugs and the approval pathway for biologic drugs. Further, this section will examine the development of the United States' abbreviated approval pathway for biosimilar drugs through the Biologics Price Competition and Innovation Act (BPCIA).

A. The Predecessor: Drug Price Competition and Patent Term Restoration Act

The United States regulates the manufacture and distribution of drugs through the FDA pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA).[51] The approval process for traditional chemical drugs occurs in multiple steps.[52] First, applicants for a new traditional chemical drug submit an Investigational New Drug application ("IND").[53] This application includes a preclinical phase of developing the chemical drug and continues with discovery and research.[54] After evaluating the

51. DONALD O. BEERS & KURT R. KARST, GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS 3 (8th ed. 2013).

52. *See generally* Yang, *supra* note 6, at 227–28.

53. *Id.*

54. During preclinical trials, drug applicants compile data on efficacy, toxicity, and pharmacokinetics by testing a drug on animals. When presented to the FDA, this data gives a broader picture of the drug, which helps determine

application, the FDA decides whether to grant permission to conduct clinical trials on humans, which take place in three phases.[55] Phase I tests the drug on a small group of twenty to one hundred healthy volunteers to determine whether the drug is safe and effective.[56] Phase II is tested on a larger pool of patients[57] and is used to confirm that the drug has the intended effect.[58] Phase III, the most costly, involves several thousand patients and evaluates the safety and effectiveness of the drug.[59] During Phase III clinical trials, the drug manufacturer submits what is known as a New Drug Application ("NDA").[60] The FDCA was established to provide a pathway for brand name drug applicants only. It was not until the 1980s that an abbreviated approval, or generic, process was formed.[61]

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, colloquially known as the Hatch-Waxman Act, which amended the FDCA.[62] The Hatch-Waxman Act sought to stimulate generic competition in the traditional chemical drug market.[63] The act did so by providing an abbreviated pathway[64] that enabled generic drugs to obtain FDA ap-

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whether to approve a drug application and allow clinical testing on human subjects to begin. *Id.* at 228.

55. *Id.*

56. *Id.*

57. In Phase II of the clinical trial process, the drug is administered to people who suffer from the disease the drug seeks to treat. This pool of people is different than Phase I, which is administered to healthy people. *Id.*

58. Yang, *supra* note 6, at 228.

59. *Id.*

60. *Id.* Currently, only 64 percent of the drugs that make it through preclinical trials and Phases I, II, and III are submitted as NDAs. *Id.*

61. Drug Price Competition and Patent Term Restoration Act (DPCTRA), Pub. L. No. 98–417, 98 Stat. 1585 (codified as amended in scattered sections of U.S.C. (1984)).

62. *Id.*

63. Yang, *supra* note 6, at 228.

63. Myers Squibb Co. v. Royce Labs., Inc., 69 F.3d 1130, 1133–34 (Fed. Cir. 1995) (noting that the Hatch-Waxman Act represented Congress' attempt to "strike a careful balance between the policies of fostering the availability of generic drugs and of providing sufficient incentives for research on breakthrough drugs").

64. Additionally, otherwise infringing actions are exempt from patent infringement when the actions are related to submissions for FDA approval. 35 U.S.C. § 271(e)(1). This is known as the "Bolar Exemption." In *Roche Products, Inc. v. Bolar Pharmaceutical Co.,* the court decided that "manufacture, use, or sale of a patented invention during the term of the patent constituted

proval.[65] The Hatch-Waxman Act created the regulatory framework to support an abbreviated new drug application ("ANDA"),[66] which is found under § 505(j) of the FDCA.[67] Under § 505(j), an applicant must prove that its drug is safe and effective by establishing that it has (1) the same active ingredients, (2) the same route of administration, (3) the same dosage form, and (4) the same strength as the reference product.[68] If these four requirements are met, ANDA applicants may rely on the reference product's safety and effectiveness to be deemed therapeutically equivalent to the reference product.[69] Importantly, this provision of § 505(j) allows small-molecule generic drug applicants under the Hatch-Waxman Act to forego the clinical testing of drugs since the reference drug has already been proven to be both safe and effective.[70]

B. The Public Health Service Act's § 351(a) Pathway

While the FDA approves traditional small-molecule chemical drugs under the FDCA, biologics receive FDA approval under § 351 of the Public Health Services Act (PHSA).[71] This process entails the submission of a biologics license application ("BLA") under § 351(a).[72] In order to receive approval, the applicant must establish that the biologic drug and the manufacturing product are "safe, pure, and potent."[73] There are no quantified

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an act of infringement, even if it was for the sole purpose of conducting tests and developing information necessary to apply for regulatory approval." 733 F.2d 858, 861 (Fed. Cir. 1984); *see also* Erwin Blackstone et al., *The Future of Competition in the Biologics Market*, 31 TEMP. J. SCI. TECH. & ENVTL. L. 1, 16 (2012).

65. Yang, *supra* note 6, at 228.

65. *Id.*

66. Worthy & Kozak, *supra* note 11, at 216.

67. *See generally* DPCTRA, Pub. L. No. 98–417, 98 Stat. 1585 (codified as amended in scattered sections of U.S.C. (1984)).

68. *Id.*

69. Worthy & Korzak, *supra* note 11, at 217.

70. Yang, *supra* note 6, at 229.

71. 42 U.S.C. § 262; *see also* Shawn P. Gorman et al., *The Biosimilars Act: The United States' Entry into Regulating Biosimilars and Its Implications*, 12 J. MARSHALL REV. INTELL. PROP. L. 332, 325 (2013).

72. *See* 21 C.F.R. § 601.2 (2011); *see also* Gorman et al., *supra* note 71, at 325.

73. In comparison to the FDCA, the PHSA gives the FDA a greater amount of regulatory control over manufacturing processes. Given how critical the manufacturing process is to the safety and efficacy of biologic drugs,

or measurable standards for "safe, pure, and potent."[74] Instead, the FDA analyzes each drug application on a case-by-case basis.[75]

Not surprisingly, the FDA approval process under the § 351(a) pathway is both timely and expensive.[76] However, pharmaceutical companies invest the time and money to apply under § 351(a) because of the exclusivity they receive.[77] Prior to 2010, applicants under § 351(a) knew that because there was no abbreviated approval pathway available for biologics, they would have limited or no competition.[78] The barrier for entry was too high as companies had to invest too much money to receive approval under § 351(a).[79] For those biologics that were available, the high approval cost made them costly for patients.[80] A pathway, similar to the one for generic drugs under the Hatch-Waxman Act, was necessary in order to facilitate the growth of the biosimilar market and the development of cheaper biologics.[81] The approval process for biosimilars must strike a balance between the safety and efficacy of the drugs, and the cost to, and resources of, the generic biologic producers.[82]

C. The Abbreviated Pathway for Biologic Drugs Established by the BPCIA

On March 23, 2010, President Barack Obama signed into law the Patient Protection and Affordable Care Act.[83] Title VII,

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the FDA's regulatory control over manufacturing is not surprising. Worthy & Kozak, *supra* note 11, at 222; *see also* 42 U.S.C. § 262(a)(2)(C)(i).

74. *Id.*.

75. Worthy & Kozak, *supra* note 11, at 222.

76. JOHN R. THOMAS, CONG. RESEARCH SERV., R42890, THE ROLE OF PATENTS AND REGULATORY EXCLUSIVITIES IN PHARMACEUTICAL INNOVATIONS 15 (2013).

77. Worthy & Kozak, *supra* note 11, at 215.

78. So & Katz, *supra* note 14.

79. *Id.*

80. *Id.* It is important to note that this op-ed, which was written before the BCPIA was enacted, relays the landscape of the biologics market before an abbreviated pathway was available.

81. *Implementation of the Biologics Price Competition and Innovation Act of 2009*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm (last updated Mar. 10, 2011).

82. Yang, *supra* note 6, at 218.

83. Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119 (2010) (codified in scattered sections of 42 U.S.C.).

Subtitle A of the Act detailed the BPCIA.[84] The BPCIA created an "abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA licenses reference product."[85] The BPCIA sought to amend the PHSA to provide a regulatory framework for the development of cheaper biologics to enter the market.[86]

Under the BPCIA, biosimilar applicants are able to file a BLA under § 351(k) of the PHSA.[87] The new pathway, by comparing the biosimilar against a reference product already licensed under the full approval process, permits the FDA to approve a biosimilar based on less clinical data than required by § 351(a).[88] Essentially, the BPCIA creates a shorter pathway for biosimilar approval, which in turn allows for cheaper alternatives to many life-saving biologic medicines.

In order to receive approval under the § 351(k) abbreviated pathway, the biosimilar applicant must demonstrate that the biosimilar drug: (1) has the same mechanism of action as the reference (if known), (2) demonstrates the conditions of use previously approved for the reference product, (3) utilizes the same route of administration, dosage form, and strength, and (4) ensures that the proposed product is manufactured,[89] pro-

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84. Steven Kozlowski, Presentation to the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, Biosimilars – An Update Focused on Quality Considerations (Aug. 8, 2012), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf; *see also* Patient Protection and Affordable Care Act § 7002.

85. Kozlowski, *supra* note 84.

86. John Alan Little, Jr., *Taking From Trailblazers: Learning From Those Who Have Gone Before When Approving Biosimilars*, 44 GA. L. REV. 1097, 1101 (2010).

87. Gorman et al., *supra* note 71, at 328; *see also* Harbour Remarks to ABA, *supra* note 28; Suzanne White Junod, *Celebrating a Milestone: FDA's Approval of a First Genetically Engineered Product,* U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm081964.htm (last updated Apr. 10, 2009). However, not every biologic product is subject to the BPCIA. For example, human growth hormones and insulin were approved through a NDA under the FDCA and Hatch-Waxman Act. *Id.*

88. *See generally* Gorman et al., *supra* note 71.

89. *Id.* at 328; *see also* Mellstedt et al., *supra* note 2, at 412 (highlighting the importance of the manufacturing process of biopharmaceuticals, which in

cessed, packed, or held in a facility that meets standards for the maintenance of safety, purity, and potency.[90] The BPCIA defines a biologic as being highly similar to the reference product, therefore notwithstanding minor differences in clinically inactive components; "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."[91]

The FDA released industry guidelines that outline its approach for defining "similarity."[92] The assessment employs a spectrum ranging from "highly similar with fingerprint-like similarity" to "not similar."[93] A biosimilar is given a degree of similarity based upon the analytical data provided.[94] The applicant must submit analytical studies that demonstrate the highly similar features as compared to the reference product, animal studies, including an assessment of toxicity, and one or more clinical studies that are sufficient to demonstrate safety, purity, and potency.[95] The clinical studies must demonstrate that the proposed biosimilar has neither decreased nor increased activity as compared to the reference product.[96] Increased activity of a biologic product may mean more adverse side effects, while decreased activity would preclude the product from being biosimilar to the reference product.[97] Due to the lack of biosimilar applications in the United States, it is difficult to get a clear picture on the exact thresholds for these tests.

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turn explains the stringency of production and distribution facility standards).

90. Since the enactment of BPCIA in 2010, the FDA has released four sets of guidelines that create a rough blueprint of the biosimilar approval pathway. While some of these guidelines are vague, the FDA has thoroughly defined the safety, purity, and potency standards that biosimilar applicants must meet. *See* 21 C.F.R. § 600.3(p)–(s) (2015); 42 U.S.C. § 262(k)(2)(A)(i)(II)–(V) (2010).

91. *Id.*

92. FOOD & DRUG ADMIN., U.S. DEP'T HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: CLINICAL PHARMACOLOGY DATA TO SUPPORT A DEMONSTRATION OF BIOSIMILARITY TO A REFERENCE PRODUCT 5 (2014) [hereinafter CLINICAL PHARMACOLOGY DATA] (defining the four possible assessments of biosimilar applications).

93. *Id.*

94. *Id.*

95. Gorman et al., *supra* note 71, at 329.

96. *Id.* at 331.

97. *Id.*

"Interchangeable" is an additional designation given by the FDA to a biosimilar applicant.[98] A product is labeled "interchangeable" when the biological product is both biosimilar to the reference product and produces identical clinical results as the reference product in any given patient.[99] Therefore, when the biosimilar is administered more than once to a single individual, the risk in terms of safety or diminished efficacy of switching between the reference product and the biosimilar is not greater than the risk of using the reference product alone.[100] A biosimilar that meets the high burden of being interchangeable "may be substituted for the reference product without the intervention of the health care provider that prescribed the reference product."[101]

D. Incentives to Invest in Biologic Drug Applications

Various federal regulations allow the biologic market to flourish.[102] Arguably, the most important regulations are those that afford exclusivities.[103] Exclusivities can be broken down into two forms: data exclusivity and market exclusivity.[104] Data exclusivity gives the reference product a set amount of time of data protection.[105] Companies looking to produce a biosimilar of the reference product may not have the ability to produce their own data packaging and need the reference product data for the development process.[106] Thus, data exclusivity can postpone biosimilar development until the reference product has had a certain number of years of exclusivity.[107] The second form,

98. 42 U.S § 262(k)(4)(A)(i)–(ii) (2010).
99. *Id.*; *see also* Gorman et al., *supra* note 71, at 332.
100. 42 U.S § 262(k)(4)(B).
101. 42 U.S § 262(i)(3).
102. Prior to the passing of the BCPIA, exclusivities and incentives were not incredibly important because biologic drug manufacturers had no potential competition with a generic version. *See generally* Erwin A. Blackstone et al., *The Economics of Biosimilars,* 6 AM. HEALTH & DRUG BENEFITS 469 (2013) [hereinafter *Economics of Biosimilars*].
103. Serge Lapointe & Julie-Anne Archambault, *Importance of Non-Patent Exclusivities in the Life Cycle of Management of Pharmaceuticals*, 27 CAN. INTELL. PROP. REV. 115, 115 (2011).
104. *See generally* Gorman et al., *supra* note 71, at 337.
105. THOMAS, *supra* note 76, at 4.
106. *Id.* at 4–5.
107. *Id.*

market exclusivity, ensures that the reference product has a certain number of years on the market without competition.[108]

The BPCIA established two separate sections of exclusivity for biologic applicants,[109] or the reference product, that undergo the full licensing application through § 351(a).[110] First, no other applicant can submit an application under § 351(k) until four years after the reference product was first licensed under § 351(a).[111] This period mirrors market exclusivity and prevents any biosimilar applicant from applying for FDA approval until after those four years have ended.[112]

Second, the FDA cannot approve a biosimilar application under § 351(k) until twelve years after the reference product was first licensed under § 351(a).[113] The BPCIA failed to expressly define whether this twelve-year regulatory exclusivity period referred to data or marketing exclusivity.[114] Members of Congress drafted letters to the FDA explaining that the twelve-year period acted as data exclusivity.[115] These letters explained that it was intended that the regulatory exclusivity period "protects the FDA from allowing another manufacturer to rely on the data of an innovator to support another product . . . it does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of competitive product."[116] Therefore, during the twelve years of data exclusivity, companies seeking to produce a biosimilar may not use any data from the reference product to assist in their biosimilar de-

108. *Id.*

109. The two separate sections of exclusivity run concurrently with a start date of the day the reference product was first licensed. U.S. DEP'T HEALTH & HUMAN SERVS., BIOSIMILARS: ADDITIONAL QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 (2015) [hereinafter BIOSIMILARS Q&A].

110. *Id.*

111. *Id.*

112. *Id.*

113. THOMAS, *supra* note 76, at 8–9.

114. *Id.* at 9.

115. Letter from Kay Hagan, Senator of N.C., et al., to Dr. Margaret Hamburg, Comm'r, Food & Drug Admin. (Jan. 7, 2011), http://www.ip-watch.org/weblog/wp-content/uploads/2011/01/H-E-H-Letter-1-7-11-Senate-Biologics-letter-to-FDA.pdf.

116. Letter from Anna G. Eshoo, Representative Cal., et al. to Food & Drug Admin., Division of Dockets Management (Dec. 21, 2010), http://www.hpm.com/pdf/EIB%20Ltr%20FDA%20DEC%202010.pdf.

velopment.[117] This period of time is relatively long, and in an effort to ensure there is no evergreening,[118] the law states that an additional twelve years will not be given for reference products for supplemental or subsequent applications that make minor changes.[119] While the first approved biosimilar drug does not retain any right to exclusivity, another biosimilar designation, known as interchangeable, is granted between twelve and forty-two months of exclusivity.[120]

E. The First Filing of a Biosimilar Application Under the § 351(k) Abbreviated Pathway

While the BPCIA established a pathway for biosimilar approval back in 2010, the FDA did not receive its first application until 2014.[121] On July 24, 2014, Sandoz Inc.[122] announced that the FDA had accepted their filing for its biosimilar.[123] Sandoz Inc.'s application was for a proposed filgrastim[124] and is comparable to Amgen's Neupogen,[125] since then the FDA has received several INDs for biosimilars.[126] However, Sandoz Inc.'s

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117. 42 U.S.C. § 262 (k)(7)(B) (2010).

118. "Evergreening" is an extension of a drug's exclusivity period. Worthy & Kozak, *supra* note 11, at 223.

119. *Id*.

120. *See* 42 U.S.C. § 262(k)(6) (2010).

121. *See* Press Release, *FDA Accepts Sandoz Application for Biosimilar Filgrastim*, SANDOZ (July 24, 2014), http://www.sandoz-biosimilars.com/en/mediacenter/press_releases/140724_FDA_accepts_Sandoz_application_for_biosimilar_filgrastim.shtml.

122. Sandoz is the generic pharmaceutical division of Novartis and is a global leader in the generic pharmaceutical sector. *See* SANDOZ INC., http://www.sandoz.com (last visited Jan. 25, 2015).

123. *See generally* Alexander Gaffney, *Sandoz First Company to File for Biosimilar Approval in U.S. Under New Pathway*, REG. AFF. PROF. SOC'Y: NEWS (July 24, 2014), http://www.raps.org/Regulatory-Focus/News/2014/07/24/19818/Sandoz-First-Company-to-File-for-Biosimilar-Approval-in-US-Under-New-Pathway/.

124. Filgrastim is a granulocyte-colony stimulating factor that is produced by recombinant DNA technology. *See* Sandoz, FDA Oncologic Drugs Advisory Committee Meeting: Zarxio 9 (Jan. 7, 2015), *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428782.pdf.

125. Neupogen is an FDA-approved treatment used to decrease the rate of infection in patients with nonmeyloid malignancies who are already receiving chemotherapy. *Id.*

126. *See generally* Gaffney, *supra* note 123.

application is the first to be submitted for full market approval under the § 351(k) abbreviated pathway, created in the BPCI Act, instead of the traditional § 351(a) pathway.[127]

On January 7, 2015, an independent panel unanimously advised the FDA to approve Sandoz Inc.'s biosimilar, referred to as EP2006.[128] The advisory committee stated that the comparative analytical data demonstrated EP2006 was highly similar to Neupogen, "notwithstanding minor difference in clinically inactive components."[129] The briefing report from the independent panel closely mirrors the guidance provided by the FDA in its May 2014 guideline.[130] This guidance document sets out the four-part spectrum for biosimilarity that ranges from not similar all the way to highly similar with fingerprint-like similarity.[131] Additionally, the guidance document provides direction for the development of clinical pharmacology data that would support the showing of an application as biosimilar.[132] It appears that the panel closely used the FDA's guidance document to make their decision on EP2006. This insight will help future applicants navigate what they will have to present to the FDA.

Not only did the panel determine EP2006 was highly similar to Neupogen, they determined that EP2006 should be approved for all five of its indications.[133] In their application, Sandoz Inc. requested to be approved for labeling for the following five indications: "1. Cancer patients receiving myelosuppressive chemotherapy, 2. Patients with acute myeloid leukemia receiving in-

127. *Id.*

128. Lisa L. Mueller, *Inching Closer to the First Biosimilar Approval in the United States*, NAT'L L. REV. (Jan. 12, 2015), http://www.natlawreview.com/article/inching-closer-to-first-biosimilar-approval-us.

129. *See* Sandoz, *supra* note 124.

130. *See* FOOD & DRUG ADMIN., FDA Briefing Document: Oncologic Drugs Advisory Committee Meeting (2015) [hereinafter ODAC Brief], http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428780.pdf. *See generally* CLINICAL PHARMACOLOGY DATA, *supra* note 92, at 5.

131. Kozlowski, *supr*a note 84.

132. ODAC Brief, *supra* note 130.

133. Sanya Sukduang et al., *Zarxio's Approval: Some Insights and Unanswered Questions Regarding the Future of U.S. Biosimilars,* FINNEGAN (Mar. 24, 2015), http://www.finnegan.com/resources/articles/articlesdetail.aspx?news=f3514819-0f2a-4db0-b166-a8efb4ca6ef9.

duction or consolidation chemotherapy, 3. Cancer patients receiving bone marrow transplant, 4. Patients undergoing peripheral blood progenitor cell collection, and 5. Patients with severe chronic neutropenia."[134]

The panel approved all the requested indications through a method[135] called "extrapolation."[136] Essentially, extrapolation is where Sandoz Inc. provides evidence that the most sensitive indication, in this case number one above, is highly similar to the reference product.[137] Then, using the "totality of the evidence,"[138] the panel may approve EP2006 for the remaining four indications.[139] With the panel's unanimous approval,[140] the pharmaceutical industry, as well as American patients and physicians, awaited the final word from the FDA. On March 6, 2015, the FDA took the panel's advice and approved Sandoz's biosimilar Zarxio.[141]

II. THE EU APPROACH TO BIOLOGIC AND BIOSIMILAR APPROVAL

In 2003, the EU passed a distinct regulatory process to approve biosimilars.[142] This legislation empowered the European Medicines Agency ("EMEA") to release guidelines for approval of biologic products.[143] Since then, the EMEA's Committee for

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134. *Id.*

135. While extrapolation involves approval of a drug for indications for which it has not been clinically tested, this method still requires applicants to make a showing that, given the comparability to the reference product, it is reasonable to extend the approval to other specified indications. *See* Gitter, *supra* note 10, at 589.

136. Sandoz, *supra* note 124.

137. *Id.*

138. The FDA has established that they intend to use a "totality of the evidence" approach. Such an approach would permit some sponsors prove biosimilarity despite formulation or minor structural differences, so long as no clinically meaningful differences exist. FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS. GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 8 (2014) [hereinafter DEMONSTRATING BIOSIMILARITY].

139. Sandoz, *supra* note 124.

140. *See* Mueller, *supra* note 128.

141. Sabrina Tavernise & Andrew Pollack, *F.D.A. Clear "Biosimilar" Mediation, Its First Ever,* N.Y. TIMES, Mar. 7, 2015, at B1.

142. Yang, *supra* note 6, at 231.

143. Ingrid Kaldre, *The Future of Generic Biologics: Should the United States "Follow-On" the European Pathway?*, DUKE L. & TECH. REV., no. 9, 2008, ¶ 20, *available at*

Medicinal Products for Human Use ("CHMP") has been the main force behind these regulatory guidelines.[144] The CHMP's guidelines are effective throughout the twenty-seven EU-member states.[145] The EMEA approved its first biosimilar in 2006 and since then has approved a total of twenty biosimilars.[146]

A. Europe's Success Approving Biosimilar Applications Through an Abbreviated Pathway

The EMEA approves biosimilars through the abbreviated pathway on a case-by-case basis.[147] The EMEA has produced various general guidelines for such biosimilar applications. The three essential requirements are as follows: (1) the provisions of the requisite preclinical and clinical data, (2) a comparability exercise to show biosimilarity in quality, efficacy, and safety, and, (3) product specific pharmacovigiliance and risk-management plans to monitor potential immunogenicity.[148]

The abbreviated pathway mandates a showing of clinical trial data to ensure that the biosimilar is both safe and effective.[149] Therefore, the success of an abbreviated approval for a biosimilar is heavily dependent upon the ability to characterize the biosimilar and demonstrate the similar nature between the reference product and the biosimilar.[150] However, the EMEA does retain the discretion to request a "full array of preclinical

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http://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=1184&context=dltr.

144. FENWICK & WEST LLP, *supra* note 40, at 3; *see also* Huub Schellekens, *Biosimilar Therapeutics – What Do We Need To Consider?*, NEPHROLOGY DIALYSIS PLUS, at i31 (2009).

145. Gitter, *supra* note 10, at 569.

146. *See* GOODWIN PROCTER, *supra* note 24, at 46.

147. FENWICK & WEST LLP, *supra* note 40, at 2.

148. Risk-management plans are used to monitor the effects of the biosimilar on patients in the marketplace. It is undisputed by both the FDA and the EMEA that monitoring immunogenicity and establishing risk-management plans are crucial to the success of biosimilars in the market. Gitter, *supra* note 10, at 570–71, & 571 n.65.

149. FENWICK & WEST LLP, *supra* note 40, at 2.

150. Gitter, *supra* note 10, at 569.

and clinical data if the biologic's structure is too complex to establish equivalence adequately."[151]

The EMEA and the FDA provide comparable definitions of biosimilarity.[152] The EMEA states that a biosimilar contains a version of the active substance of an already authorized reference product, and is similar to the reference product in terms of quality, safety, or efficacy.[153] In their most recent guideline[154] the EMEA explains that

> if the biosimilar comparability exercise indicates that there are relevant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will be established, a stand alone development[155] . . . should be considered.[156]

The EMEA indicates that previously published information, alone, will not be sufficient for approval.[157] Therefore, extensive comparability will be required in order to show the similarities between the biosimilar and the reference product.[158] Compara-

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151. Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 535, 548 (2010).

152. The FDA defines a biosimilar in further detail than the EMEA. In an expansion on the EMEA's definition, the FDA distinguishes that "a biosimilar is a biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components." *See* CLINICAL PHARMACOLOGY DATA, *supra* note 92, at 5.

153. Eur. Medicines Agency, *Guideline on Similar Biologic Medicinal Products*, EMEA/CHMP/437/04 Rev 1, at 4 (Oct. 23, 2014) [hereinafter *Guideline on Similar Biologic Medicinal Products*], http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf.

154. The EMEA released a draft update of their guideline in May 2013. This version is intended to update the EMEA's October 2005 guideline on biosimilarity. *See* Eur. Medicines Agency, *Guideline on Similar Biologic Medicinal Products*, EMEA/CHMP/437/04, at 6 (May 22, 2013), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf.

155. A stand-alone development means that the company should attempt to obtain approval for the biologic drug on its own, and not as a biosimilar of an already established reference product. For example, in the United States, a stand-alone development would be applying for approval through the § 351(a) pathway instead of the § 351(k) pathway. *Id.*

156. *Id.*

157. *Id.*

158. *Id.*

bility tests are typically stepwise procedures that start with pharmacokinetic and pharmacodynamic studies.[159] While the EMEA does not expect the biosimilar and the reference product to have identical attributes, the EMEA suggests that applicants use pharmacokinetic studies to explore the difference in the drugs and compare the products in a population where possible clinical difference may be best observed.[160]

The final consideration by the EMEA is postmarket monitoring.[161] As previously explained, immunogenicity is unpredictable and incredibly important for consumer welfare.[162] In the EU, postmarketing monitoring is required to assess the potential immunogenicity of the biologic drug.[163] Often, postmarketing monitoring is referred to as pharmacovigilance.[164] This describes the "detection, assessment, understanding, and retention of adverse effects after the launch of a product onto the market."[165] Many factors, such as presence of impurities, structural modifications resulting from manufacturing or storage, administration techniques, and patient characteristics can affect the immunogenic potential and therefore makes it impossible to predict the immunogenicity in a patient.[166] Because of the abbreviated approval pathway, there tends to be limited clinical data about the safety risks of biosimilars, which makes pharmacovigilance crucial.[167]

The pharmacovigilance program established by the EU is slightly different than the program anticipated by the United States. The program was established for all pharmaceuticals, both chemical and biologic, and contains several components.[168] The first component allows healthcare professionals to report suspected adverse reactions through the EudraVigilance network.[169] Second, the EMEA requires drug manufacturers, during their approval process, to develop and implement their own

159. *See* Gorman et al., *supra* note 71, at 329.
160. *Guideline on Similar Biologic Medicinal Products*, *supra* note 153, at 6.
161. Schellekens, *supra* note 144, at 32.
162. *Id.*
163. Gitter, *supra* note 10, at 573.
164. Schellekens, *supra* note 144, at 32.
165. *Id.*
166. Gitter, *supra* note 10, at 573.
167. *See* Mellstedt et al., *supra* note 2, at 415–16.
168. Gitter, *supra* note 10, at 574.
169. *See* Mellstedt et al., *supra* note 2, at 416.

pharmacovigilance plans.[170] Applicants for market authorization must provide the EMEA with a risk-management plan.[171] Each risk-management plan must establish a proactive approach that market authorization applicants will undertake to identify and manage potential safety risks.[172]

B. Incentives to Invest in Biologic Drug Applications

The EU has exclusivity incentives very similar to those found in the United States.[173] For a reference drug, the EU awards a total of ten years of exclusivity.[174] The first eight of those years are data exclusivity, and the last two are market exclusivity.[175] Comparatively, the EU provides reference products with more data protection than the United States.[176] The EMEA does not have the authority to designate interchangeability.[177] In fact, the Executive Director of the EMEA, Thomas Lonngren, has taken the position that "[i]t is not possible [the EMEA] would guarantee a biosimilar is interchangeable (with its originator)."[178] The EU leaves the regulation of substitution for each individual member nation.[179] In 2007 the EMEA declared that "[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient" with either a reference product or a biosimilar should be reserved for healthcare professionals.[180]

As of 2011, France and Spain had enacted legislation that banned automatic substitution of a biosimilar for the reference products without the express consent of the prescribing

170. *Id.*
171. *Id.*
172. *Id.*
173. Gorman et al., *supra* note 71, at 340.
174. *Id.*
175. *Id.*
176. THOMAS, *supra* note 76, at 4.
177. Phani Kishore Thimmaraju et al., *Legislations on Biosimilar Interchangeability in the US and EU – Developments Far From Visibility,* GABI ONLINE (June 1, 2015), http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility; *see also* Gitter*, supra* note 10, at 582.
178. Nick Smith, *EMEA "Will Not Guarantee" that Biosimilars are Interchangeable with Originator,* APM HEALTH EUR. (July 21, 2006, 4:00 PM), http://www.apmhealtheurope.com/print_story.php?numero=3250.
179. Gitter*, supra* note 10, at 581.
180. *Id.*

healthcare provider.[181] However, in 2014, France introduced legislation that would allow the substitution of a biosimilar for a reference product as long as the prescribing healthcare provider did not explicitly mark the prescription as non-substitutable.[182]

Since the beginning of the EMEA's approval of biosimilars, there have been many success stories. For example, Sandoz Inc.'s EP2006, the drug approved unanimously by the FDA panel was first approved in Europe in 2009 as Zarzio.[183] Additionally, the EMEA has approved Sandoz's Omnitrope, a biosimilar version of the reference product Genotropin, for indications in which clinical trials have not been evaluated.[184] The EMEA, similar to the FDA panel, has used extrapolation of clinical data to find the biosimilar may be used for multiple indications.[185] In 2009, it was estimated that biosimilars saved $1.4 billion in the EU.[186]

III. THE SUCCESS OF THE BIOSIMILAR MARKET DEPENDS ON THE NAMING OF BIOSIMILAR PRODUCTS

The name of a biological drug carries serious implications for the FDA's faith in its success. The name conveys to clinicians whether or not the biologic has met certain regulatory criteria and is considered to be biosimilar. If the name does not convey such similarity it is likely to limit access to these low-cost, safe, and effective drugs.

Typically, drugs have two names: a nonproprietary name and a brand name. A common example is the pain medicine Advil™, which also has a nonproprietary name ibuprofen.[187] On

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181. *Id.*

182. *France to Allow Biosimilars Substitution,* GABI ONLINE (Feb. 21, 2014), http://gabionline.net/Policies-Legislation/France-to-allow-biosimilars-substitution.

183. Sabrina Tavernise, *For First Time, F.D.A. Panel Approves Generic Copy of Costly Biologic Drug*, N.Y. TIMES, Jan. 7, 2015, at B3.

184. Guillermina Forno & Eduardo Orti, *Biosimilars: Current Situation and Future Expectations*, 3 EUR. J. RISK & REG. 213, 214 (2012).

185. *Id.*

186. *Id.*

187. FDA Approved Drug Products Containing Ibuprofen, U.S. FOOD & DRUG ADMIN., http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.SearchAction&SearchType=BasicSearch&SearchTerm=IBUPROFEN

pharmacy shelves there are many generic versions of Advil that have different brand names, however each product shares the same nonproprietary name—ibuprofen.[188] The nonproprietary names establish a language amongst clinicians and pharmacists that identify the expected "active ingredient" of a product.[189] Of course, Advil is a traditional small drug, and therefore does not produce the same complexities as various biologic products.[190] However, the importance of naming does not change from traditional small drugs to biologics. Whether the product is a traditional small-molecule drug or biologic product, clinicians, pharmacists, and even patients rely on product naming when choosing, dispensing, and taking medications.

A. The WHO's Attempt to Unify a Biosimilar Naming Scheme

The WHO oversees the global INN system. INNs identify the active ingredients in pharmaceutical substances.[191] Since its establishment in 1953, the INN has established approximately seven thousand names.[192] The INN system seeks to provide healthcare providers with a universally available designated name to identify each pharmaceutical.[193] A universal INN is crucial to clear identification, safe prescription, and dispensing of medicines to patients.[194]

(listing various brand-name drugs contain ibuprofen as its active ingredients).

188. *Id.*

189. The right column of the chart on the FDA's website is denoted "active ingredient." *Id.*

190. The FDA Application number for 200 milligram Advil Tablets is NDA #018989. *See* History and Information Related to 200 Milligram Oral Tablets of Advil, U.S. FOOD & DRUG ADMIN., http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=ADVIL. This indicates that Advil was approved as a traditional small molecule drug, not a biologic, which would have a BLA number.

191. Gitter, *supra* note 10, at 586.

192. Programme on Int'l Nonproprietary Names, World Health Org., GUIDELINES ON THE USE OF INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES 1, Doc No. WHO/PHARMS/NOM/1570 (1997) [hereinafter INN Guideline], http://apps.who.int/medicinedocs/pdf/h1806e/h1806e.pdf.

193. *Id.*

194. *Id.*

Additionally, INN helps facilitate clear communication and the exchange of information amongst healthcare providers and scientists worldwide.[195] Pharmaceuticals that come from the same therapeutic or chemical class are usually given names with the same stem.[196] This assists healthcare providers and pharmacists with recognition of the substance.[197] The use of the INN designation is elected by each nation that chooses to use it, and its use is widespread.[198] With the growth of biologic drugs and the development of abbreviated pathways for biosimilars, regulatory bodies such as the FDA and EMEA have developed new regulatory methods to establish a universal biosimilar market.[199] However, one issue has not been entirely settled and in fact has garnered much attention as of late.[200] The next big issue with the development of the biosimilar market is whether biosimilars should be given the same INN as the brand-name biologic.

In July 2014, the WHO released a draft of their proposed stance on biologic naming,[201] and invited comments and suggestions on the proposal.[202] The intended purpose of this proposal was to receive feedback from interested parties.[203] The proposal suggested that applicants request a Biological Qualifier to complement the INN from the INN Secretariat.[204] A Bio-

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195. *Id.*

196. INN GUIDELINE, *supra* note 192, at 1.

197. *Id.*

198. INN GUIDELINE, *supra* note 192, at 33. For example, national names such as the British Approved Names (BAN), the Denominations Communes Francasises (DCF), the Japanese Adopted Names (JAN), and the United States Accepted Names (USAN) are identical to the INN.

199. Ed Silverman, *What's in a name? WHO Issues Proposal for Biosimilar Names*, WALL ST. J., (Aug. 1, 2014, 10:25 AM), http://blogs.wsj.com/pharmalot/2014/08/01/whats-in-a-name-who-issues-proposal-for-biosimilar-names/.

200. *Id.*

201. Biological Qualifier Proposal, *supra* note 45, at 1.

202. *Id.*

203. *Id*.

204. *Id.*; at 2. In October 2015, the WHO released a final proposal for Biosimilar naming. This final proposal defined the Biological Qualifier as a "code formed of four random constants in two 2-letter blocks separated by a 2-digit checksum." World Health Organization [WHO], *Biologic Qualifier: An INN Proposal*, at 2, INN Working Doc. 14.342 (October 2015), http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf?ua=1.

logical Qualifier would be an alphabetic code assigned at random to a biological active substance manufactured at a specified site.[205] The scheme would be applicable to all biological active substances to which INN are assigned.[206] The Biological Qualifier would not be part of the INN, but instead would be used to complement the INN and uniquely identify directly, or indirectly, the manufacturer and the manufacturing site of the active substance in a biological product.[207] This proposal emerges from a period of debate amongst regulators across the globe.[208]

B. The United States and Europe: A Naming Conundrum

The BPCIA does not address what nomenclature the FDA should apply to biosimilars; thus sparking debate about what the naming of biosimilars should look like.[209] Back in 2006, the FDA outlined its stance in a statement to the WHO.[210] In this statement, the FDA clearly supported the idea of biosimilars having INNs identical to the reference product.[211] The FDA stated that it would be preferable that "INNs continue to be

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205. Biological Qualifier Proposal, *supra* note 45, at 5.

206. *Id.* at 4.

207. *Id.*

208. *Id.* at 1.

209. Patient Protection and Affordable Care Act, Pub. L. 111–148, §§ 7001–03 129 Stat. 119, 804–821. Notably, the word "name" is not used once in the BPCIA. This distinguishes the BPCIA from the Hatch-Waxman Act, which mandated that ANDAs have labels identical to the reference product. *See* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j)(2)(A) (2015).

210. The FDA has since removed this statement from its website. While there has been no formal press release that the FDA has changed its position on this topic, some have interpreted the statement's removal as a tacit admission of a changed stance. *Biosimilar Naming Debate Intensifies,* GABI ONLINE (Nov. 22, 2013), http://gabionline.net/Biosimilars/General/Biosimilars-naming-debate-intensifies; *see also US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars*, U.S. FOOD & DRUG ADMIN. (Sept. 1, 2006), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandAp-
proved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm375086.htm.

211. *Id.*

granted based only on molecular characteristics and pharmacological class of the active ingredient(s)."[212]

However, in August 2015, the FDA published industry guidance on the *Nonproprietary Naming of Biological Products*.[213] This FDA guidance explains that the main concern in regards to biosimilar naming is patient safety, and that biological product naming must do all it can to prevent inadvertent substitution of biological products.[214] The FDA states that a failure to employ such a naming convention could lead to unintended switching of biological products that have not been deemed interchangeable.[215] The FDA adopts a scheme similar to the WHO and suggests "the nonproprietary name includes a distinguishing suffix for biological products that have not been determined to be interchangeable."[216] Essentially, the name will be divided into two separate parts, the nonproprietary name, and the suffix. For example, products sharing the INN "replicamab" would be named "replicamab-cznm" or "replicamab-hixf."[217]

The FDA specifically addresses interchangeable products in this naming guidance. It suggests that interchangeable products would either have both an INN and a suffix, like biosimilars, or a suffix that is shared with the reference product.[218] The FDA approves a biosimilar application to be interchangeable if it is found to be biosimilar to the reference product and produce clinical results identical to the reference product in any given patient.[219] Therefore, an interchangeable biosimilar may be substituted for a reference product without any risk to immunogenicity. If the FDA chooses to provide an interchangeable biosimilar product with a different suffix than the reference product, it is removing all incentives for drug companies to research and develop a biosimilar drug that is so advanced it

212. *Id.*
213. U.S. Food & Drug Admin., U.S. Dep't Health & Human Servs., *Nonproprietary Naming of Biological Products: Guidance for Industry* (2015) [hereinafter *Naming Guidance*], http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm459987.pdf.
214. *Id.* at 1.
215. *Id.*
216. *Id.*
217. *Id.* at 8.
218. *Id.* at 9.
219. 42 U.S.C. § 262(k)(4)(B) (2010).

has been proven to have identical clinical results to the reference product. This is just one example of how the FDA's new naming guidance will thwart the expansion of the biosimilar market.

Prior to the FDA's guidance, companies and organizations submitted petitions to the FDA outlining their vision for biosimilar naming.[220] It is not surprising where generic and brand name pharmaceutical companies fall in this debate.[221] Brand-name drug makers and biotechs would like to see biosimilars have a unique name to distinguish the biosimilar from the reference product.[222] The reasoning is that different names would make it easier to track adverse events,[223] and would be less confusing for healthcare providers and pharmacists.[224] Additionally, brand companies argue that assigning the biosimilar and the reference product the same INN will encourage treating all biosimilars as biogeneric equivalents.[225]

However, companies that manufacture generic drugs feel that assigning different INNs or creating a new unique naming system just gives brand name companies the upper hand.[226] They claim that establishing separate INNs for biosimilars will only stunt substitution of the reference product for the biosimilar; arguing that a new naming standard would create confusion for physicians and pharmacists because they will have to figure out "whether the products are really the same as they try verifying dosing and requirements."[227]

The Generic Pharmaceutical Association (GPA) points out that current FDA practices allow a reference product to maintain the same INN even after the manufacturing process or

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220. Letter from Richard Dolinar, Chairman for the All. for Safe Biologic Med., to Dr. Margaret Hamburg, FDA Comm'r (Apr. 16, 2012) [hereinafter Dolinar Letter], http://safebiologics.org/pdf/comments/ASBM-Comments.pdf; *see also* Letter from Ralph G. Neas, President and CEO Generic Pharm. Ass'n to FDA (Sept. 17, 2013) [hereinafter GPA Citizens Petition], *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1153-0001.

221. Silverman, *supra* note 199.

222. *Id.*

223. Tracking adverse events is also known as pharmacovigilance, or post-marketing monitoring. Dolinar Letter, *supra* note 220, at 2.

224. *Id.* at 1.

225. Silverman, *supra* note 199.

226. *Id.*

227. *Id.*

production facility changes.[228] Based on the FDA's reasoning for providing unique INN for biosimilars, any biologic produced in another manufacturing plant or with any manufacturing changes, should also be given a unique INN.[229] Additionally, GPA argues that because all biologics approved under § 351(k) are highly similar they have no clinically meaningful differences, and thus should share the same INN as the reference.[230] In regards to tracking adverse reactions, the GPA believes a more narrowly tailored solution will better fix the problem.[231] The GPA suggests practitioner education and system enhancements would better serve the patients.[232] Further, the GPA stresses that the adoption of unique INNs to identify biosimilars would frustrate the main purpose of the BPCIA, which is to create competition in the biologics marketplace.[233] On October 23, 2013, a group of bipartisan Senators sent a letter to FDA Commissioner Hamburg, which stated that "if biosimilars are unable to share the same active ingredient name as the brand name originator product, we believe the Congressional intent behind the BPCIA would be undermined as would the safety and accessibility of affordable biosimilars."[234] In these letters, the Senators also addressed the complicated issue of substitution; arguing that unique naming runs the risk of interfering with many state-generic substitution laws.[235] Given

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228. GPA Citizens Petition, *supra* note 220.

229. Biopharmaceuticals are sensitive to environmental changes, and therefore manufacturing plays an important role in the development of biopharmaceuticals. As one scholar noted,

> [t]here is a wide variability in the composition and bioactivity of products produced outside of the United States and Europe. In a study comparing 11 epoetin products from four different countries (Korea, Argentina, China, India) the isoform distribution among these product was variable and there were substantial deviations from specification for *in vivo* bioactivity.

Mellstedt et al., *supra* note 2, at 412.

230. GPA Citizens Petition, *supra* note 220, at 1.

231. *Id.* at 3.

232. *Id.*

233. *Id.*

234. Letter from Senator John D. Rockefeller IV et al. to FDA Comm'r Dr. Margaret Hamburg (Oct. 23, 2013), http://amcp.org/WorkArea/DownloadAsset.aspx?id=17326.

235. *Id.*

that generic substitution is a common cost savings tool, it is not something that "we can afford to lose."[236]

The United States is not the only country having this naming debate; the EU has also voiced a strong opinion about how biosimilars should be named.[237] In October 2013, the European Commission Pharmaceutical Committee met and discussed the issues surrounding biosimilar naming.[238] The majority of EU-member states "strongly supported" that biosimilars should have the same INN as their reference product.[239] EU-member states made arguments similar to the GPA, stating that unique INNs could undermine the public perception of biosimilars.[240] Additionally, EU-member states addressed that traceability is not an issue because both the brand name and INN are reported, while the batch number is often reported, making it simple to discover the source for any adverse reactions.[241] A report from the EU in 2013 stated that every medicine would "either have an invented (trade) name, or the name of the active substance together with the company name/trademark," thereby eradicating the need for a unique INN.[242] Clear identification, the report stated, was important for reporting and monitoring adverse drug reactions.[243] In order to ensure the safety of consumers, the EMEA monitors biosimilar products through both postmarketing monitoring and risk-management plans identifying products by manufacturer name and batch number.[244] Ideally, such additional precautions would allow biosimilars to share the same INN as its reference product.

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236. *Id.*

237. *EU Majority Says Same INNs for Biosimilars*, GABI ONLINE (Feb. 28, 2014), http://www.gabionline.net/Biosimilars/General/EU-majority-says-same-INNs-for-biosimilars.

238. *Id.*

239. *Id.*

240. *Id.*

241. *Id.*

242. EUROPEAN COMMISSION, WHAT YOU NEED TO KNOW ABOUT BIOSIMILAR MEDICINAL PRODUCTS 13 (2013), *available at* http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf.

243. *Id.*

244. EuropaBio*, Naming, Pharmacovigilance and Risk Management Plans, in* GUIDE TO BIOLOGICAL MEDICINES – A FOCUS ON BIOSIMILAR MEDICINES 6 (2011), http://www.europabio.org/sites/default/files/report/guide_to_biological_medicines_a_focus_on_biosimilar_medicines.pdf.

In response to the FDA's request for comments, two European Associations commented on the EMEA's approach to biosimilar regulations.[245] The comments stated that in the EU certain biosimilars have an identical INN to the reference product whereas others have a unique INN.[246] The European Associations stressed the need for authorities to take proper measures to track the specific biologic products, either reference product or biosimilar, given to patients.[247] In addition, the comments suggested that the FDA take a simpler approach to ensure patient safety, such as requiring physicians to prescribe biologics by the invented or brand name, instead of the INN.[248]

IV. HOW CAN THE FDA PROMOTE CONFIDENCE IN BIOSIMILAR PRODUCTS THROUGH NAMING?

The naming convention wherein the same nonproprietary name is used has proven safe and effective for both small-molecule and biological drugs in Europe.[249] Therefore, "it should be the standard in the United States."[250] In order for physicians, pharmacists, and consumers to trust the biosimilar market, the FDA must reject their most recent guidance that suggests biosimilars be given a unique suffix to attach to the INN. This approach will not only confuse healthcare professionals, but neglect to build trust in the biosimilar market.

The BPCIA's main goal is to provide affordable biosimilar drugs to terminally ill patients.[251] Therefore, the FDA must not forget this important objective to create a viable abbreviated

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245. EuropaBio*, FDA Request for Comments on "Approval Pathway for Biosimilar and Interchangeable Biological Products"* 8 (2010), http://www.europabio.org/sites/default/files/position/europabio_ebe_joint_submission_to_fda.pdf.

246. *Id.*

247. *Id.*

248. *Id.* at 9.

249. *AMCP is Disappointed in FDA's Draft Guidance and Proposed Rule Calling for Suffix on Nonproprietary Names of Biological Products*, PR NEWSWIRE (Aug. 27, 2015), http://www.prnewswire.com/news-releases/amcp-is-disappointed-in-fdas-draft-guidance-and-proposed-rule-calling-for-suffix-on-nonproprietary-names-of-biological-products-300134442.html.

250. *Id.*

251. Amanda Potter, *Interpreting the BPCIA – Is the "Patent Dance" Mandatory?*, COLUM. SCI. & TECH. L. REV. BLOG (Mar. 31, 2015), http://stlr.org/2015/03/31/interpreting-the-bpcia-is-the-patent-dance-mandatory/.

approval pathway for biosimilars.[252] This includes a naming system that bolsters the use of these biosimilars by healthcare professionals and patients. In order to maintain the integrity of the BPCIA's founding concern, the FDA should adopt a two-pronged approach to ensure the BPCIA's success. First, the FDA must produce a final guidance that assigns biosimilars, including those found to be interchangeable, the same INN as their reference counterparts. Second, the FDA must develop a final guidance allowing biosimilar products to include detailed and pertinent information through labeling.

A. Step One: A Uniform Naming System

Given the importance of naming, it is crucial that the FDA modify their current approach and adopt a naming scheme that balances consumer safety with the expansion of biosimilar use. The practice of assigning identical INNs to products that are biosimilar to a reference product will not harm consumers and will positively impact the use of biosimilars by healthcare professionals.

Congress enacted the BPCIA to incentivize development of biosimilars.[253] When the FDA finds a product to be biosimilar it has analyzed a multitude of clinical results, efficacy studies, and immunogenicity tests.[254] All of these provide analytical data that the product has no clinically meaningful difference from the reference product.[255] Assigning a unique suffix to a biosimilar conveys that the product has differences from the reference product and suggests that the product should have been approved through a different pathway, such as § 351(a).[256]

Even prior practice dictates that if the FDA finds a product to be biosimilar, then it should have the same INN.[257] Historically, biologic names that included a prefix or suffix signaled that

252. *Id.*

253. Blackstone et al., *supra* note 102, at 469.

254. Gorman et al., *supra* note 71, at 329.

255. *See* 42 U.S.C. § 262(k)(2)(A)(i)(II)–(V) (2010).

256. Sumant Ramachandra, Senior Vice President and Chief Scientific Officer, Hospira, *What's in a Name?* 12–13 (2013), http://www.biologicsblog.com/wp-content/uploads/2015/03/Whats-In-a-Name-Hospira-Policy-Paper.pdf.

257. *Id.* at 12. While Hospira, as a biosimilar producer, may be biased, all assertions from this policy paper referenced herein were fact-checked.

there were *significant differences* between products.[258] For example, interferon, which is a class of proteins, is designated with the suffix alfa or beta.[259] Interferon alfa is used to help patients with hepatitis or melanoma,[260] while interferon beta is used for treating multiple sclerosis.[261] Interferon alfa and interferon beta are actually different at the molecular level and therefore have different clinical effects on patients.[262] In contrast, a biosimilar is deemed to have no clinically meaningful difference when compared to a reference product.[263] Therefore, carrying this practice over to biosimilars will not only confuse healthcare professionals but ultimately prevent them from prescribing biosimilar products.

The FDA argues INN suffixes are necessary in order to track adverse events to a specific manufacturer and facilitate the safe use of the product and protection of patients.[264] However, when a biosimilar has an identical INN to the reference product, it still has its own brand name. For example, Sandoz's product Zarxio shares the INN "filgrastim," with Amgen's Neupogen.[265] In order to prevent confusion a clinician should prescribe the biosimilar by its unique name Zarxio, instead of the INN filgrastim. The use of brand names should prevent inadvertent substitution and will also make postmarketing monitoring easier. Postmarketing monitoring can be conducted by brand name, manufacturer, or specific lot number.[266] Using the brand name to prescribe a biosimilar will help point to a specif-

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258. *Id.*

259. Runkel et al., Differences in Activity Between α and beta ß Type 1 Interferons Explored by Mutational Analysis, 273 J. BIOLOGICAL CHEMISTRY 8003, 8003 (1998).

260. *See generally* Interferon alfa-2b, Recombinant Medication Guide, FDA.GOV (2011), http://www.fda.gov/downloads/Drugs/DrugSafety/ucm111337.pdf.

261. *See generally* Interferon beta-1b Betaseron, FDA.GOV (1993), http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm087676.pdf.

262. Runkel, *supra* note 259 at, 8003.

263. *See* 42 U.S.C. § 262 (k)(2)(A)(i)(II)–(V) (2010).

264. Naming Guidance, *supra* note 213.

265. Sukduang et al., *supra* note 133.

266. Naming Guidance, *supra* note 213.

ic manufacturer, which in turn can identify a specific lot number.

The FDA argues that most passive pharmacovigilance systems do not include brand names or national drug code numbers in any adverse event reports.[267] If that is the case, then the answer is not to adapt a dysfunctional naming system that thwarts the goals of the legislation that spurred this industry in the first place. The solution is to adopt a new pharmacovigilance system, one that uses the brand name, manufacturer, and lot number. This shows both healthcare professionals and patients the reliability of biosimilar drugs and the FDA's ability to achieve comprehensive monitoring. The naming system established by the FDA was designed to avoid inadvertent substitution and to ensure the safe use of the product and protection of patients.[268] However, prescribing biosimilars possessing the brand name, such as Zarxio or Neupogen, can prevent inadvertent substitution.

B. Step Two: A Detailed Approach to Labeling

Similar to the naming debate, the BPCIA is silent regarding labeling requirements. The Hatch-Waxman Act mandates that every ANDA application have labeling that is identical to the reference product.[269] Given the lack of explicit guidance, the FDA has the sole discretion to determine the labeling guidelines.[270] The FDA should evaluate each biosimilar on a product-by-product basis and work with the applicant to propose labeling based on the science in the application.[271] This will give the FDA the option, depending on the product, to either approve the same label, or require a different one. The FDA took simi-

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267. *Id.* at 9.

268. *Id.* at 9.

269. 21 U.S.C. § 355(j)(2)(A) (1984). Despite this requirement's existence, the FDA is authorized to approve ANDAs that omit labeling carried by the reference product when the label is protected by either patent or exclusivity *See* Julie Dohm, *Expanding The Scope of the Hatch-Waxman Act's Patent Carve-out Exception to the Identical Drug Labeling Requirement: Closing the Patent Litigation Loophole*, 156 U. PA. L. REV. 151, 157 (2007).

270. 21 U.S.C. § 321(n) (1976).

271. Letter from Bruce A. Leicher, Senior Vice President and Gen. Counsel, Momenta Pharms., to Food & Drug Admin., Division of Dockets Management, at 9 (Oct. 27, 2015) [hereinafter Leicher Letter], *available at* http://www.biologicsblog.com/wp-content/uploads/2015/11/Comment_from_Momenta_Pharmaceuticals_Inc.pdf.

lar action with regards to Sandoz's Zarxio application.[272] With this application, the FDA carefully reviewed the label and ultimately determined that the label was informative and not misleading.[273] It can also be assumed that extraneous factors affected the FDA's reasoning. For example, concluding Zarxio needed a different label would mislead healthcare professionals into thinking that Zarxio was not an alternative for Neupogen, but instead an entirely different product.

The FDA should avoid instituting a labeling requirement wherein a biosimilar application must have a different label than the reference product. Such labeling requirement would run contrary to intent of the BPCIA.[274] Additionally, such a labeling requirement would provide less incentives to drug manufacturers to invest in the production of biosimilars.[275] From the start, biosimilars would be at disadvantage when compared with the reference product. Even worse, drug manufacturers would have no incentive to create an interchangeable biosimilar.[276] Instead, a product-by-product labeling system is preferable.[277] Through this system, drug manufacturers can choose to convey certain additional information to clinicians about their biosimilar product. For example, a drug manufacturer may want to include that the product is interchangeable and has been approved for automatic substitution on the label.[278]

CONCLUSION

Ultimately, the efforts supporting the production of biosimilars have been international. As seen in the EU, countries have enacted abbreviated pathways with the intention of providing

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272. *See* Sandoz, *supra* note 124.

273. The FDA decided that any additional information could be found in the "Purple Book" available on the FDA's website. Whether the Purple Book is a sufficient alternative for this type of information is hotly debated. Leicher Letter, *supra* note 271, at 9. However, this discussion is beyond the scope of this Note.

274. That express labeling requirements were not included in the BPCIA implies that Congress intended to defer to the FDA's discretion with respect to best-labeling practices. In addition, the BPCIA was enacted to facilitate the use of biosimilars, but mandating different labeling prevents such use. 21 U.S.C. § 321(n).

275. Leicher Letter, *supra* note 271, at 5.

276. *Id.*

277. *Id.* at 9.

278. *Id.* at 9.

cheaper life-saving biologic medicines to patients. Although the implications of biosimilar naming are complex and difficult to navigate, it is important that regulators do not lose sight of the importance of biosimilar substitution. Requiring biosimilars to be given new unique INNs is detrimental to the future production and distribution of biosimilars. There are numerous ways that regulators can ensure the safety of patient health through pharmacovigilance, without each biosimilar receiving a unique INN. Providing new unique INNs to biosimilars will stunt the potential of the biosimilars market, will create confusion in the healthcare system, and effectively undermine the true intent of the BPCIA. Continuing the use of the small-molecule INN naming system for biosimilars will prevent yet another misstep in a market already plagued by confusion, inefficiency, and high costs.

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