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# Barriers to Biosimilar Approval: Creating Clarity Through the Publication of Product-Class Specific Guidances

MARTIN MCENRUE\*

## INTRODUCTION

The European Union is far ahead the United States in creating a biosimilar market for its citizens. The Patient Protection and Affordable Care Act (PPACA)<sup>1</sup>, colloquially known as Obamacare, was enacted in 2010 and set out to create a health care plan for the uninsured in an attempt “to rein in rising costs of health care.”<sup>2</sup> Within the PPACA is a section titled the Biologics Price Competition and Innovation Act (BPCIA), which gave guidance for biosimilar approval.<sup>3</sup> Specifically, the Act had the intention of enumerating the requirements for biosimilar approval to create an easier process for the manufacturers.<sup>4</sup> Since the approval of the BPCIA, the United States and the Food and Drug Administration (FDA) have had difficulty in approving a biosimilar product. As of December 2016, the FDA has only approved

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1. 42 U.S.C. §18001 (2010).
2. Michael Levy, *Patient Protection and Affordable Care Act (PPACA)*, ENCYCLOPEDIA BRITANNICA, <http://www.britannica.com/topic/Patient-Protection-and-Affordable-Care-Act>.
3. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, 80 Fed. Reg. 24259, 24260 (Apr. 30, 2015).
4. Joanna M. Shepherd, *Biologic Drugs, Biosimilars, and Barriers to Entry*, 25 HEALTH MATRIX 139, 146 (2015) (stating that the “BPCIA provides an expedited biosimilar approval pathway”).

four biosimilars, Zarxio,<sup>5</sup> Inflectra,<sup>6</sup> Erelzi,<sup>7</sup> and Amjevita.<sup>8</sup> This is falling short to the European Medicines Agency (EMA), the European Union's equivalent to the FDA, which has had much greater success in approving biosimilars. The EMA has approved 25 biosimilars, including Zarzio, since 2006.<sup>9</sup> The FDA should follow the approach of the EMA by creating product-specific guidelines to create a biosimilar market in the United States.

In this Comment, Part IA will define and provide the regulatory history of biosimilars in both the United States and European Union. Part IB will outline the current FDA approval process of biosimilars and Part IC will outline the approval process of the EMA. Part II of this Comment will discuss and analyze the major differences between the EMA's and FDA's methods of biosimilar approval. Part III will discuss how the FDA can adopt EMA methods to facilitate biosimilar approval and create a larger market.

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5. FDA News Release, U.S. Food and Drug Admin., FDA Approves First Biosimilar Product Zarxio, (Mar. 6, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm>. The approval of Zarxio was met with a lawsuit from the manufacturer of Neupogen, Amgen Inc., which claimed that Sandoz, Inc. violated California state law for unfair competition, conversion, and patent infringement. The Federal Circuit Court ruled that Sandoz, Inc did not violate the BPCIA by failing to disclose its application and manufacturing information to Amgen, Inc. and did not violate California's unfair competition or conversion statutes. *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015). This case was granted certiorari by the Supreme Court on January 13, 2017. *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015), cert. granted, 84 USLW 3455, U.S., Jan. 13, 2017.

6. On April 5, 2016, the FDA approved a second biosimilar named Inflectra with the reference product Remicade. U.S. Food & Drug Administration, *FDA approves Inflectra, a biosimilar to Remicade*, U.S. FOOD AND DRUG ADMINISTRATION: PROTECTING AND PROMOTING YOUR HEALTH (Apr. 5, 2016), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm>.

7. On August 30, 2016 FDA approved its third biosimilar, Erelzi, (etanercept-szss) for multiple inflammatory diseases, which is a biosimilar to Enbrel (etanercept). See U.S. Food & Drug Administration, *FDA approves Erelzi, a biosimilar to Enbrel*, U.S. FOOD AND DRUG ADMINISTRATION: PROTECTING AND PROMOTING YOUR HEALTH (Aug. 30, 2016), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518639.htm>.

8. On September 23, 2016, FDA approved its fourth biosimilar, "Amjevita (adalimumab-atto) as a biosimilar to Humira (adalimumab) for multiple inflammatory diseases." See U.S. Food & Drug Administration, *FDA approves Amjevita, a biosimilar to Humira*, U.S. Food & Drug Administration: Protecting and Promoting Your Health (Sep. 23, 2016), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm522243.htm>.

9. Generics and Biosimilars Initiative, *Biosimilars approved in Europe*, GABI ONLINE (Jan. 13, 2017), <http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe>; see also David Kroll, *FDA Approves First US Biosimilar; Hold Your Breath on Cost Savings*, FORBES (Mar. 6, 2015), <http://www.forbes.com/sites/davidkroll/2015/03/06/fda-approves-first-us-biosimilar-zarxio-by-sandoz/#4ef2845c76c9>.

## I. BIOSIMILAR APPROVAL

A. *Background and Definitions*

Biological products are a difficult treatment class to define.<sup>10</sup> The FDA chose to define biologics by listing the general categories which the treatments can be included under, providing that the treatment products are “a virus, therapeutic serum, toxin, antitoxin, vaccine, [etc.]”<sup>11</sup> . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”<sup>12</sup> Others use the differences between chemically created drugs and biologics to define the treatment class.<sup>13</sup> The two commonalities that most definitions share are that biologics are created from living organisms and that they are large, complex molecules.<sup>14</sup> The influenza (flu) vaccine is an example of a biologic that is commonly used in the United States; it uses a safe version of the virus to treat and prevent the disease associated with the flu.<sup>15</sup> Any product defined as a biologic and previously approved by FDA can be used as a reference product to a biosimilar product.<sup>16</sup> The FDA defines biosimilarity to mean “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.”<sup>17</sup> There cannot be any “clinically meaningful differences between the biological product and the reference product

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10. Thomas Morrow & Linda Hull Felcone, *Defining the Difference: What Makes Biologics Unique*, BIOTECHNOLOGY & HEALTHCARE, Sept. 2004, at 24.

11. The definition also includes blood, blood component or derivative, allergenic product or analogous, or arsphenamine or derivative of arsphenamine. U.S. FOOD & DRUG ADMIN., INVESTIGATIONS OPERATIONS MANUAL 290 (2016), <http://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf>.

12. *Id.*

13. Morrow & Felcone, *supra* note 10, at 24. This article uses the “two critical traits that distinguish their physical makeup from chemically derived drugs: only living systems can produce them, and biologics are relatively large molecules, with an inherently heterogeneous structure that can contain hundreds of amino acids” as an example of a definition. *Id.*

14. *Id.*

15. *Influenza (Flu): How Influenza (Flue) Vaccines Are Made*, CTRS. FOR DISEASE CONTROL & PREVENTION (Jan. 6, 2015), <http://www.cdc.gov/flu/protect/vaccine/how-fluvaccine-made.htm>

16. *Information on Biosimilars*, U.S. FOOD & DRUG ADMIN. (Feb. 22, 2016), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>. The biologic product must be approved by the FDA. *Id.*

17. Leah Christl, *FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the U.S.*, U.S. FOOD AND DRUG ADMIN., at 6, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM428732.pdf>.

in terms of the safety, purity, and potency of the product.”<sup>18</sup> For instance, Zarxio, the first approved biosimilar in the United States, uses the biologic Neuopogen as its reference.<sup>19</sup> Both of these products use filgrastim, a protein used to increase the number of white blood cells in cancer patients, as the active ingredient for treatment.<sup>20</sup>

Under the current biosimilar framework, there are also requirements for an “interchangeable product,” which are much more specific than that of biosimilars in their similarity to the reference product. For a product to be interchangeable, it must be “biosimilar to the reference product; it can be expected to produce the same clinical result as the reference product in any given patient.”<sup>21</sup> The FDA also includes that “[t]he interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”<sup>22</sup> There are currently no approved interchangeable products in the United States or Europe.

There are many similarities between biosimilar products and generic drugs, most specifically their purpose and relation to the reference product. However, their differences are more significant. The Hatch Waxman Amendments of 1984 (Hatch Waxman)<sup>23</sup> created the modern generic drug market.<sup>24</sup> Although generic drugs were able to be approved before these amendments, they had to go through the same approval process as the listed drug they referenced.<sup>25</sup> Hatch Waxman created the Abbreviated New Drug Application (ANDA), a new approval process specifically for generic drug manufacturers.<sup>26</sup> This application significantly shortens the length of time and lessens the cost

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18. *Id.*

19. FDA News Release, *supra* note 5.

20. *Id.*; *Filgrastim*, CHEMOCARE.COM, <http://chemocare.com/chemotherapy/drug-info/filgrastim.aspx>.

21. Christl, *supra* note 17, at 8.

22. *Id.*

23. The “Hatch-Waxman Amendments” refer to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984). Statement of Daniel E. Troy, U.S. Food & Drug Admin., Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments), Aug. 1, 2003, <http://www.fda.gov/newsevents/testimony/ucm115033.htm>.

24. Statement of Daniel E. Troy, *supra* note 23.

25. *Id.* The full approval process is costly and time consuming. Generic drugs having to complete the full process most likely increased the expense of the final generic drug once it entered the market and delayed the drug entering the market. *Id.*

26. *Id.* In an ANDA, the generic drug manufacturer only has to show bioequivalence to the previously approved NDA and “relies on the Agency’s finding of safety and effectiveness of the listed drug product.” *Id.*

to develop a generic drug.<sup>27</sup> This allows manufacturers to charge less for the drug and makes the drug accessible to more people.

After Hatch Waxman, there was a great increase in the number of generic drugs on the market,<sup>28</sup> as it was relatively easier to recreate a listed reference drug that was chemically manufactured in a lab.<sup>29</sup> Being chemically created, the entire drug serves a purpose in the treatment it is listed for.<sup>30</sup> Biologics are different because they come from a live product that is not originally manufactured in a lab.<sup>31</sup> Live biologic products are much more complex than other pharmaceuticals.<sup>32</sup> The active ingredient for treatment may be just one of many components found in the biologic.<sup>33</sup> A biosimilar product must only replicate the active ingredient(s) in the reference product, as long as the other components are inactive.<sup>34</sup> The major difference between drugs and biologics is the complexity of biologics, which biosimilar manufacturers must overcome in creating their product.

### B. Biosimilars in the United States

The approval process for biosimilar products is enumerated in the BPCIA, passed by Congress with the PPACA.<sup>35</sup> The BPCIA amended 42 U.S.C. § 262 by adding sections related to biosimilars and patents for biologic products.<sup>36</sup> It also included information biosimilar manufacturers are required to provide to the FDA for approval, the Secretary's process of determining whether the product should be approved, and the exclusivity of the reference product.<sup>37</sup> Also included within the

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27. *Id.*

28. *Id.* A generic drug is defined as “[a] drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route, administration, quality and performance characteristics, and intended use.” Ted Sherwood, *Generic Drugs*, U.S. FOOD & DRUG ADMIN., at 7, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Small-BusinessAssistance/ucm127615.pdf>.

29. *How Drugs Are Developed and Approved*, U.S. FOOD & DRUG ADMIN. (Aug. 18, 2015), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved>.

30. *See, e.g., id.*

31. Shepherd, *supra* note 4, at 142.

32. *Id.*

33. Barbara Mounho et al., *Global Regulatory Standards for the Approval of Biosimilars*, 65 FOOD & DRUG L.J. 819, 825 (2010).

34. Christl, *supra* note 17, at 6.

35. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119.

36. U.S. FOOD & DRUG ADMIN., SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY 1 (2015).

37. *Id.*

Act is a crucial section on future guidance documents related to biosimilars.<sup>38</sup> This section shows the intent of the FDA to develop rules and regulations related to biosimilars over time.<sup>39</sup>

The FDA's scientific requirements for approval of biosimilars were first enumerated in the BPCIA and then further developed through draft guidances. The FDA uses a stepwise approach to generate data with evaluation of residual uncertainty while evaluating the research compiled by the manufacturer of the biosimilarity to the reference product.<sup>40</sup> The administration uses a totality-of-the-circumstances approach in evaluating applications.<sup>41</sup> This approach is justified by the FDA in stating there is "no 'one size fits all' assessment."<sup>42</sup> The FDA claims this benefits the sponsor of the biosimilar, allowing the administration's scientists to evaluate the "various types of information to provide an overall assessment that a biological product is biosimilar to [the] reference product."<sup>43</sup> It is then left to the discretion of these scientists to approve the product if the data received provides that the sponsor's product is similar enough to the reference product to be approved.<sup>44</sup>

The data that the FDA considers is developed by the manufacturer using analytical studies, animal studies, and clinical studies.<sup>45</sup> The Guidance, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* created the process that biosimilar manufacturers should follow.<sup>46</sup> The analytical data is collected using two studies, the structural analyses and functional assays.<sup>47</sup> In the structural analysis, the FDA requires that the expression of the biosimilar product encodes the same primary protein structure as the reference product.<sup>48</sup> This ensures the structure of the active protein in the biosimilar has the same structure as the active protein in the reference product.<sup>49</sup> The functional

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38. 42 U.S.C. § 262(k)(8) (2012); see e.g., U.S. Food and Drug Administration, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, Guidance for Industry (Dec. 2016), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf>.

39. *Id.*

40. Christl, *supra* note 17, at 19.

41. *Id.*

42. *Id.* at 20.

43. *Id.* The reference product must be licensed in the United States. *Id.*

44. *Id.*

45. 42 U.S.C. § 262(k)(2)(A)(i)(I).

46. U.S. FOOD & DRUG ADMIN., *supra* note 36, at 1.

47. *Id.* at 9–10.

48. *Id.* at 9.

49. *Id.* (stating that the "sponsors should consider all relevant characteristics of the protein product . . . to demonstrate that the proposed product is highly similar to the reference

assays, another step in the analytical collection of data, evaluates the activity of the proteins in the product.<sup>50</sup> These functional assays are used to provide data to show that the “biologic activity and potency of the proposed product are highly similar to those of the reference product.”<sup>51</sup> They are also used to complement the animal and clinical data to assess minor difference in structure between the reference and similar products.<sup>52</sup>

Following the analytical studies, the biosimilar product must be tested in animal studies.<sup>53</sup> The animal studies are required to demonstrate biosimilarity and the results can be used to support the safety evaluation.<sup>54</sup> The animal toxicity study is the first animal study that must be conducted.<sup>55</sup> This study is conducted to address uncertainties in the safety of the product before the clinical trials begin.<sup>56</sup> The manufacturer can use this test to compare the degree of similarity with the reference product.<sup>57</sup> Animal immunogenicity tests are also conducted for the purpose of assisting the interpretation of animal study results.<sup>58</sup> Differences in the animal immunogenicity “may reflect potential structural or functional differences between the two products.”<sup>59</sup> The clinical studies can begin once the animal studies are completed and show biosimilarity to the reference product.

The FDA requires the sponsor of a biosimilar drug to conduct clinical trials to prove there are no meaningful differences between their product and the reference product.<sup>60</sup> First, a human pharmacology and clinical immunogenicity assessment must be conducted before the

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product”).

50. *Id.* at 10 (stating that the functional assays can be either in vivo, in vitro, or both).

51. *Id.* at 11.

52. U.S. FOOD & DRUG ADMIN., *supra* note 36.

53. *Id.*

54. *Id.*

55. *Id.*

56. *Id.* The FDA states this may contribute to the totality of the evidence that supports a demonstration of biosimilarity. *Id.* at 13.

57. *Id.* at 12.

58. *Id.* at 13. These studies, in contrast with their name, typically do not predict potential immune responses. *Id.*

59. U.S. FOOD & DRUG ADMIN., *supra* note 36.

60. *Id.*

clinical trials begin.<sup>61</sup> The human pharmacology assessment uses a justifiable<sup>62</sup> human population to conduct pharmacokinetic<sup>63</sup> and pharmacodynamic<sup>64</sup> profiles.<sup>65</sup> The clinical immunogenicity assessment's purpose is to compare and evaluate the differences in incidence and severity of human immune responses.<sup>66</sup> The sponsor should demonstrate that there are no meaningful differences in immune response with the reference product while conducting their study.<sup>67</sup> The population for this study must be justified and agreed to by the Agency and a follow-up evaluation is required.<sup>68</sup> The study "should consider . . . the immune response . . . , the clinical relevance and severity of consequences . . . , the incidence of immune responses, and the population being studied."<sup>69</sup>

Comparative Clinical Studies are conducted to support a demonstration of biosimilarity to the reference product if there is uncertainty after the prior tests.<sup>70</sup> When a sponsor decides it is necessary to conduct a comparative clinical study, they must provide a scientific justification for the factors they choose to determine what type of clinical study they will conduct.<sup>71</sup> The sample size and duration of the study should be "adequate to allow for the detection of clinically meaningful differences" with the reference product<sup>72</sup> and the study "should be designed to investigate whether there are clinically meaningful differences" with the reference product.<sup>73</sup> The clinical study should establish evidence

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61. *Id.* at 14.

62. Sponsor must provide the FDA with reasoning as to why it chose specific groups (patients vs. healthy subjects) of people to be involved in the clinical trial. *Id.*

63. Pharmacokinetic profiling analyzes "how the body affects the drug." Garth T. Whiteside & Jeffrey D. Kennedy, *Consideration of Pharmacokinetic Pharmacodynamic Relationships in the Discovery of New Pain Drugs*, in *TRANSLATIONAL PAIN RESEARCH: FROM MOUSE TO MAN* (L. Kruger & A.R. Light eds., 2010).

64. Pharmacodynamic profiling analyzes "how the drug affects the body." *Id.*

65. *Id.* In selection of the human population, the sponsor must consider the relevance and sensitivity of such population and parameters. *Id.*

66. U.S. FOOD & DRUG ADMIN., *supra* note 36, at 16. It is recommended for the sponsor to collect immunogenicity data in all clinical studies. *Id.*

67. *Id.* at 13

68. *Id.* at 17. The follow-up period is recommended to be one year. *Id.*

69. *Id.* at 16.

70. *Id.* at 18. A sponsor must justify the reason for not conducting comparative clinical studies. *Id.*

71. *Id.* at 19.

72. U.S. FOOD & DRUG ADMIN., *supra* note 36, at 16.. The adequacy is determined on the endpoint that the study is focused on. Certain endpoints call for smaller sample sizes than others. *Id.*

73. *Id.* at 20. The FDA expects studies designed to establish statistical evidence that the proposed product is neither inferior or superior to the reference product.

“that the proposed product is neither inferior” nor superior to the reference product.<sup>74</sup> The FDA strongly suggests having multiple meetings with the sponsor during the biosimilar manufacturing process.<sup>75</sup> For instance, meeting with the FDA at the beginning of the process is very important so that FDA can establish a “schedule of milestones that will serve as landmarks for future discussions with the Agency.”<sup>76</sup> Once the sponsor has completed the comparative clinical studies, they can submit their data to the FDA for approval.

The sponsor must submit a 351(k) application with the FDA in order to seek approval for a biosimilar product.<sup>77</sup> The 351(k) application requires the sponsor to show the similarity between their product and the reference product. To show this, the sponsor is required to show that the product: 1) is biosimilar to the reference product; 2) utilizes that same mechanisms of action for the proposed condition of use; 3) condition of use proposed in labeling have been previously approved for the reference product; 4) has the same route of administration, dosage form, and strength as the reference product; and 5) is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent.<sup>78</sup> The Public Health Service Act (PHSA) mandates that all necessary information is derived from analytical studies, animal studies, and clinical studies.<sup>79</sup> The FDA will license the biological product if they determine that the information submitted is sufficient to show that the product is either biosimilar or interchangeable to the reference product.<sup>80</sup> The applicant must also consent to inspection of the facility where the product was manufactured to receive a license.<sup>81</sup> The reference product must have four years or more on the market before a biosimilar manufacturer can submit a 351(k) application and the application will not be made effective until twelve years after the reference product was first licensed.<sup>82</sup>

### *C. Biosimilars in the European Union*

In Europe, the EMA regulates biosimilars through Directive

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74. *Id.*

75. *Id.* at 23.

76. *Id.*

77. Christl, *supra* note 17, at 9.

78. *Id.*

79. *Id.* at 10.

80. *Id.* at 11.

81. *Id.*

82. 42 U.S.C. 262(k)(7) (2010).

2001/83/EC and Directive 2004/27/EC.<sup>83</sup> The 2004 Directive amendment provided a general explanation of biosimilar requirements, only providing three sentences on the topic.<sup>84</sup> The amendment requires biosimilar manufacturers to provide information with respect to the differences between the biosimilar and the reference product.<sup>85</sup> The EMA released three guidelines following the Directives, explaining in more detail the requirements for biosimilar approval including an overarching guideline containing greater detail than the legislation.<sup>86</sup> The EMA has used the guideline method of regulating biosimilar approval to create a thriving market with twenty-five different biosimilars.<sup>87</sup>

The Directive 2004/27/EC amendments created the EMA approval process for biosimilar products and was further elaborated in subsequent guidelines.<sup>88</sup> The European approval process is distinct from the United States' because these guidelines enumerate separate steps to approval for each biologic product-type.<sup>89</sup> The EMA has released eight product-specific guidelines for biosimilars which include guidelines for recombinant follicle-stimulating hormone, interferon beta, monoclonal antibodies, and recombinant *erythropoietins*.<sup>90</sup> This method gives a very specific process for manufacturers to follow.

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83. *Biosimilars in the EU*, GENERIC PHARMACEUTICAL ASS'N, <http://www.gphaonline.org/gpha-media/gpha-resources/biosimilars-in-the-eu> (last visited on Apr. 4, 2016).

84. Council Directive 136/34, art. 10, 2004 J.O. (L136) 4 (EC). "Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided." *Id.*

85. *Id.*

86. Guideline on Similar Biological Medicinal Products, EUROPEAN MEDS. AGENCY, CHMP/437/04, Oct. 2005. *See also*, Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues, EUROPEAN MEDS. AGENCY, EMEA/CHMP/BMWP/42832/2005 Rev1, Dec. 2014. *See also*, Guideline On Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (revision 1), EUROPEAN MEDS. AGENCY, EMEA/CHMP/BWP/247713/2012 (May 2014).

87. Generics and Biosimilars Initiative, *Biosimilars approved in Europe*, GABI ONLINE (Jan. 13, 2017), <http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe>.

88. Council Directive 136/34, *supra* note 84.

89. Guideline on Similar Biological Medicinal Products, *supra* note 86.

90. *Multidisciplinary: Biosimilar*, EUROPEAN MEDS. AGENCY (2016), [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000408.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp).

Following the Directive 2004/27/EC amendments creating the approval process, the general requirements for biosimilar approval were established in three guidelines.<sup>91</sup> First, the Guideline of Similar Biological Medicinal Products outlined the basic principle to be applied to biosimilar products.<sup>92</sup> In this guideline, the EMA describes the difference between biological products and other drugs and the difficulties in creating similar products to biologics.<sup>93</sup> The guideline also requires that manufacturers of biosimilar products meet the EMA standards for quality, safety, and efficacy.<sup>94</sup> The guideline requires that the reference product be used for comparative quality, safety, and efficacy studies.<sup>95</sup> The active substance must be similar to the reference product on a molecular and biological level.<sup>96</sup> The pharmacological form, strength, and route of administration should also be the same as the reference product's, and, if it is not the same, the difference must be justified by appropriate studies on a case-by-case basis.<sup>97</sup>

The second guideline addresses quality issues for biosimilars and provides the requirements for comparability testing against the reference product.<sup>98</sup> During a comparability test, the safety and efficacy of the biosimilar product are considered and assessed for implications against safety or efficacy of the reference product. The guidance lists considerations for the comparability test to assure the quality of the product.<sup>99</sup> These considerations take into account the suitability of available analytical methods, validation of analytical methods, physicochemical properties, biological activity, and purity and impurities.<sup>100</sup> The comparability test applies to both the level of medicinal properties and the active substances.<sup>101</sup>

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91. *Biosimilars in the EU*, GENERIC PHARMACEUTICAL ASS'N 2013, *supra* note 83.

92. Guideline on Similar Biological Medicinal Products, *supra* note 88.

93. *Id.* at 4.

94. *Id.* at 3.

95. *Id.* at 4.

96. *Id.* at 5. For example, the similar biological product must have the same active component as the reference product and not just a version of the active component. *Id.*

97. *Id.*

98. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues, EUROPEAN MEDS. AGENCY, EMEA/CHMP/BWP/49348/2005, 3 (Feb. 2006).

99. *Id.* at 5.

100. *Id.* at 6–7.

101. Kuala Lumpur, *Biosimilars in the European Union—Regulatory Perspectives*, EUROPEAN MEDICINES AGENCY: SCIENCE, MEDICINES, HEALTH, 25 (May 30–31, 2011), [http://www.ich.org/fileadmin/Public\\_Web\\_Site/Training/ASEAN\\_Q5C\\_workshop\\_May\\_2011/SESSION\\_IVa\\_Biosimilars.pdf](http://www.ich.org/fileadmin/Public_Web_Site/Training/ASEAN_Q5C_workshop_May_2011/SESSION_IVa_Biosimilars.pdf).

The third guideline provides non-clinical and clinical data requirements in biosimilar approval.<sup>102</sup> Non-clinical data should be collected, from both in vitro studies and in vivo studies, before initiating clinical studies.<sup>103</sup> In vitro studies, typically cell-based assays or receptor-binding assay studies, “establish comparability in reactivity and the likely causative factor(s) if comparability cannot be established.”<sup>104</sup> The in vivo studies are performed in animals and are designed to maximize the information obtained before beginning clinical studies.<sup>105</sup> Once the non-clinical data is collected, the manufacturer can begin the clinical studies.

The purpose of the clinical studies is to produce comparable clinical data to the reference product.<sup>106</sup> This process is conducted in a step-wise procedure beginning with “pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety trials.”<sup>107</sup> In regards to biosimilars, the PK test is “is used to detect possible differences in the interaction with the body between the originator and the biosimilar.”<sup>108</sup> The PD studies concern the “magnitude and time course of the observed pharmacological effect.”<sup>109</sup> The markers for the PD test should be selected to demonstrate the efficiency of the product and the efficiency of the test should be compared in a population where the possible differences between the reference product and biosimilar product can best be observed.<sup>110</sup> These two studies can be combined in situations where certain requirements are met.<sup>111</sup>

Efficacy and safety trials can begin once the PK and PD studies

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102. European Medicines Agency, Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues, EMEA/CHMP/BMWP/42832/2005, 3 (Feb. 2006).

103. *Id.* at 4.

104. *Id.*

105. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins, *supra* note 86, at 4. These endpoints include pharmacodynamic effect, non-clinical toxicity, and any safety concerns. *Id.*

106. *Id.* at 5.

107. *Id.*

108. *Id.* at 8.

109. Points to Consider on Pharmacokinetics and Pharmacodynamics in the Development of Antibacterial Medicinal Products, EUROPEAN MEDS. AGENCY, CPMP/EWP/2655/99, 1 (July 2000).

110. Guideline of Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins, *supra* note 86, at 5–6.

111. *Id.* at 5–6. These requirements include if the PK of the reference medicinal product are well characterized; there is sufficient knowledge of the pharmacodynamics properties of the reference medicinal product; the relationship between dose/exposure and response/efficacy of the reference medicinal product is sufficiently characterized; and at least one PK marker is accepted as a surrogate marker for efficacy. *Id.*

are completed and shown to have similar results to the reference product.<sup>112</sup> The efficacy trials are necessary to demonstrate further the comparable clinical effects of the biosimilar product and reference product.<sup>113</sup> Once the biosimilar is shown to be effective, safety tests are still necessary before the product can be approved.<sup>114</sup> These studies obtain data from a number of patients to address adverse events compared to the reference product.<sup>115</sup> The immunogenicity of the product is observed and considered throughout the process, and if an applicant has an immune response different from the reference product, further analysis must be conducted for clinical safety, efficacy, and PK parameters.<sup>116</sup> These are the general requirements in the EMA for similar biologic products, with more specific requirements found in further guidelines tailored to each biologic product.

For biosimilar approval in the European Union, the sponsor must follow the same marketing application process as other drugs in addition to the biosimilar specific requirements.<sup>117</sup> For a normal drug marketing application with the EMA, the applicant must include the name of the medicinal product, name of the active substance, and pharmacotherapeutic group.<sup>118</sup> The strength of the product, pharmaceutical form, route of administration, container, and pack sizes must also be included.<sup>119</sup> The legal status of the product and whether it is subject to medical prescription is also required on the application.<sup>120</sup>

The EMA has created five modules in the organization of their application specific to biosimilar approval.<sup>121</sup> Module 1 requires the sponsor to provide a “concise document summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted is a similar biologic medicinal product.”<sup>122</sup>

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112. *Id.* at 6.

113. *Id.*

114. *Id.*

115. *Id.* at 6. Assuming the reference product has adverse effects, the similar biologic should be expected to have a similar rate of these effects. *Id.*

116. *Id.* at 7.

117. Notice to Applicants: Volume 2B-CTD, 12 (June 2006).

118. European Commission: Health and Consumers Directorate-General, Medicinal Products for Human Use: Volume 2B: Module 1.2: Administrative Information Application Form, Revision 12, EUROPEAN MEDS. AGENCY, 1 (Sept. 2015).

119. *Id.* at 17–18.

120. *Id.* at 19–20.

121. *Q&A 11-20: Similar Biological Product Application*, EUROPEAN MEDS. AGENCY, [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000126.jsp&mid=WC0b01ac0580533e0d](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000126.jsp&mid=WC0b01ac0580533e0d) (last visited Apr. 7, 2016).

122. *Id.*

The summary should include the active substance and differences between the relevant attributes of the reference medicinal product. In showing the data, “the comparability exercise versus the reference medicinal product for quality, safety and efficacy should be described and the reference medicinal product . . . defined.”<sup>123</sup> Module 2 requires the overall summary of the quality study and clinical and nonclinical overviews.<sup>124</sup> Module 3 should include the regular requirements for medicinal product marketing approval along with a demonstration of comparability to the reference product.<sup>125</sup> This section should include information about “Facilities and Equipment and Safety Evaluation of Adventitious Agents” and the origin of animals used.<sup>126</sup> Module 4 and Module 5 provide that “results of pre-clinical and clinical studies should be provided.”<sup>127</sup> If any confusion in the application process exists, the EMA allows applicants to set up meetings to have the confusion clarified.<sup>128</sup>

## II. DIFFERENCES BETWEEN THE BIOSIMILAR APPROVAL PROCESSES

Even though the pathways for approval look similar, the success of the biosimilar program in the EU proves that there are still differences between the EMA and FDA. Two major differences in the programs are relevant to this issue: FDA’s emphasis on sponsor meetings during the development stage<sup>129</sup> and the EMA’s product-specific guidelines.<sup>130</sup> These differences show the contrasting approaches that each agency takes with respect to biosimilars. Overall, the FDA takes a broad regulatory approach and, through meetings, attempts to advise and facilitate the sponsor’s development.<sup>131</sup> The EMA has given greater regulatory guidance for biosimilar development, through product class-specific guidelines.<sup>132</sup> The sponsors are aware of what is required for their product to be approved through these guidelines and

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123. *Id.*

124. *Id.*

125. *Id.*

126. *Q&A 11-20: Similar Biological Product Application*, EUROPEAN MEDS. AGENCY, [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000126.jsp&mid=WC0b01ac0580533e0d](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000126.jsp&mid=WC0b01ac0580533e0d) (last visited Apr. 7, 2016).

127. *Id.*

128. *Id.*

129. Food and Drug Admin., U.S. Dep’t of Health and Human Serv., OMB Control No. 0910-0802, *Formal Meetings Between FDA and Biosimilar Biological Product Sponsors or Applicants: Guidance for Industry*, 1–2 (Nov. 2015).

130. *Multidisciplinary: Biosimilar*, *supra* note 90.

131. *See generally* OMB Control No. 0910-0802, *supra* note 129.

132. Jun Wang & Shein-Chung Chow, *ON the Regulatory Approval Pathway of Biosimilar Products*, 5 *PHARMACEUTICALS* 353, 360 (May 30, 2012).

therefore require less agency intervention. The FDA's hands-on approach to biosimilar approval appears to be less effective in approving biosimilar products compared to the EMA's regulatory guideline approach.

The FDA created five different formal meetings in the Biosimilar User Fee Act of 2012 for sponsors of biosimilar products being developed.<sup>133</sup> The sponsors of biosimilars are required to be a member of the Biosimilar Product Development (BPD) Program, a program created by the FDA, to request and participate in these meetings.<sup>134</sup>

These meetings start with an initial meeting to determine if a licensure under section 351(k) may be feasible.<sup>135</sup> The BPD Type 1 meeting is only necessary if the biosimilar development has stalled for either safety reasons or clerical mistakes.<sup>136</sup> This meeting allows the FDA to discuss how the sponsor can recover and what additional information is required to advance the approval process.<sup>137</sup> BPD Type 2 meetings target a specific issue or questions regarding an ongoing BPD program which the FDA can respond with targeted advice.<sup>138</sup> BPD Type 3 meetings are the most important for application approval. During the Type 3 meeting, the FDA conducts a substantive review of full study reports and includes information regarding the similarity between the biosimilar product being developed and the reference product and advice on additional studies needed.<sup>139</sup> BPD Type 4 meetings are held to discuss the content of the application<sup>140</sup> and are used to prepare the sponsor for submitting their application for approval.<sup>141</sup>

Though the BPD program appears to be a voluntary program created to benefit the biosimilar manufacturers, the totality of the evidence requirement for biosimilar approval, placed in the discretion of FDA scientists, makes it less beneficial.<sup>142</sup> The BPD program requires

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133. *Biosimilar Implementation: A Progress Report from FDA Before the S. Committee on Health, Education, Labor, and Pensions*, 114th Cong. (Sept. 2015) (statement of Dr. Janet Woodcock, Dir., CDER of FDA).

134. OMB Control No. 0910-0802, *supra* note 129, at 5.

135. *Id.* at 3.

136. *Id.*

137. *Id.*

138. *Id.* at 4.

139. *Id.*

140. *Id.*

141. *FDA Finalizes Guidance for Biosimilars Meetings*, GENERICS & BIOSIMILARS INITIATIVE (Jan. 29, 2016), <http://www.gabionline.net/Guidelines/FDA-finalizes-guidance-for-biosimilars-meetings>.

142. There are very few resources referencing the effects of the meeting requirements for

its members to pay an annual user fee.<sup>143</sup> As of December 2015, the annual fees are \$237,420<sup>144</sup> an amount that many generic drug companies find excessive.<sup>145</sup> If the biosimilar sponsor were to fall behind on these fees, the FDA is able to deny a meeting.<sup>146</sup> Also, scheduling the meetings with the FDA is a long process.<sup>147</sup> In the final guidance, released in November 2015, the FDA created timelines for when meetings should be scheduled following the submission of a request.<sup>148</sup> Prior to the release of this final guidance, other manufacturers complained that the draft guidance released by the FDA was in need for clarification and further detail.<sup>149</sup>

Since the totality-of-the-evidence approach focuses on “reviewing everything known about the applicant’s and the innovator’s products,” partaking in the BPD meetings greatly increases the chances of approval.<sup>150</sup> Currently, there is no information on whether the final guidance improved the biosimilar approval process for sponsors, though there have been no biosimilars approved within the three months following the release of the guidance.<sup>151</sup> Instead of expediting

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biosimilars, and none following the release of the Final Guidance for Formal Meetings Between the FDA and Biosimilar Product Sponsors. *See generally, Call for Clarity in FDA’s Draft Guidance on Biosimilar Meetings*, GENERICS & BIOSIMILARS INITIATIVE (June 2013), <http://www.gabionline.net/Biosimilars/General/Call-for-clarity-in-FDA-s-draft-guidance-on-biosimilar-meetings>.

143. OMB Control No. 0910-0802, *supra* note 129, at 5.

144. *Biosimilar User Fee Act (BsUFA)*, U.S. FOOD & DRUG ADMIN. (Dec. 30, 2015), <http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm>.

145. *Call for Clarity in FDA’s Draft Guidance on Biosimilar Meetings*, GENERICS & BIOSIMILARS INITIATIVE (June 2013), <http://www.gabionline.net/Biosimilars/General/Call-for-clarity-in-FDA-s-draft-guidance-on-biosimilar-meetings>. The generics company, Mylan, believes the user fees should be less than the fees required by PDUFA. *Id.*

146. OMB Control No. 0910-0802, *supra* note 129, at 9.

147. *Call for Clarity in FDA’s Draft Guidance on Biosimilar Meetings*, GENERICS & BIOSIMILARS INITIATIVE (June 2013), <http://www.gabionline.net/Biosimilars/General/Call-for-clarity-in-FDA-s-draft-guidance-on-biosimilar-meetings>. During the notice and comment period of the draft guidance, the drug manufacturer, Apotex, complained about the length of time the FDA takes to grant a meeting request. *Id.*

148. Zachary Mietus, *Formal Meetings with the FDA Regarding Biosimilars: What’s Changed*, WEINBERG GROUP (Nov. 24, 2015), <http://weinberggroup.com/formal-meetings-with-fda-biosimilars>. Type 1 meetings should be scheduled within 30 days, Type 2 should be scheduled within 75 days, Type 3 should be scheduled within 120 days, and Type 4 should be scheduled within 60 days. *Id.*

149. *Call for Clarity in FDA’s Draft Guidance on Biosimilar Meetings*, GENERICS & BIOSIMILARS INITIATIVE (June 2013), <http://www.gabionline.net/Biosimilars/General/Call-for-clarity-in-FDA-s-draft-guidance-on-biosimilar-meetings>.

150. 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).

151. *Biosimilars*, U.S. FOOD & DRUG ADMINISTRATION, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars> (last visited on Apr. 6, 2016) (showing that the most

the manufacturing process, these meetings cause the process to stall or take longer than needed.<sup>152</sup> This puts greater costs on sponsors of biosimilars which could have gone to the development of the medical product.

Instead of creating a system of voluntary meetings for the biosimilar sponsors, the EMA decided to put the information necessary for development in their guidelines. As of September, 2015, the EMA has published ten final biological product class-specific guidelines.<sup>153</sup> The complexity and diversity of biological product-classes necessitates a variety of different guidelines specific to each product.<sup>154</sup> These classes vary in their “benefit/risk profile, the nature and frequency of adverse events, the breadth of clinical indications, and whether surrogate markers for efficacy are available and validated.”<sup>155</sup> In creating the guidelines, “robust and thoughtful scientific discussion and deliberation drove decision-making.”<sup>156</sup> The comments for the guidelines include a wide variety of interested groups such as the scientific community, pharmaceutical manufacturers and patient organizations.<sup>157</sup> An example of a class specific guideline is the *Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor*.<sup>158</sup> This guideline gives specific requirements for the pharmacodynamic studies, toxicological studies, and clinical studies.<sup>159</sup> By making clear what is necessary for biosimilar sponsors to gain approval and licensure, they are able to focus more on the manufacturing of the biosimilar and will need less information from the agency regarding the manufacturing and approval process.

The FDA’s method may appear to be effective but is slowing the approval process down. Instead of creating general guidances and trying to meet and individually address the issues of the sponsors, the FDA should take the EMA’s approach and create biological product-

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recently mentioned biosimilar is Zarzio, the first biosimilar approved).

152. See Mietus, *supra* note 148 (including length of approval for each meeting type).

153. *Multidisciplinary: Biosimilar*, *supra* note 90.

154. Wang & Chow, *supra* note 132, at 360.

155. *Id.*

156. Barbara Mounho et al., *Global Regulatory Standards for the Approval of Biosimilars*, 65 FOOD & DRUG L.J. 819, 822 (2010).

157. *Id.*

158. See generally European Meds. Agency, EMEA/CHMP/BMWP/31329/2005, Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor (Feb. 22, 2006). G-CSFs are proteins that bind to cells to carry out specific reactions. generally European Meds. Agency, EMEA/CHMP/BMWP/31329/2005, Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor (Feb. 22, 2006)

159. *Id.* at 4–5.

class specific guidances.<sup>160</sup> This method gives the sponsors clear requirements necessary for approval and licensure of their product.<sup>161</sup> Clear and enumerated requirements may lead to an increase in the number of biosimilar approvals by the FDA.

### III. WAYS TO OVERCOME THESE BARRIERS

The FDA is still able to make improvements to the biosimilar market, even though many problems in the market are caused by outside sources. One area that was proven to be most effective in helping create a biosimilar market is the publishing of product-type specific guidances.<sup>162</sup> If the FDA was to follow the EMA's guidance driven approach, sponsors will know what is expected to achieve biosimilar licensure approval.<sup>163</sup> The FDA has been resistant to creating product-specific guidances for biosimilars, believing that applicants should not be required to perform the same analytical, preclinical, and clinical testing.<sup>164</sup> The FDA's reluctance to create product-specific guidances has made it more difficult for biosimilars to be approved in the United States and has delayed the access to these drugs to the people of the United States.

The FDA's current approach of having general guidances with the purpose of having meetings with biosimilar sponsors has cost these sponsors more time and money.<sup>165</sup> Creating a personalized method of biosimilar development through agency meetings with the product manufacturers appears to be ideal, but without the resources does not work. Instead, the FDA should adopt the EMA's approach of having individual guidances for each biological product-class.<sup>166</sup> This method has been called the gold standard for biosimilar approval and has been

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160. See Wang & Chow, *supra* note 132, at 360. The EMA's guideline driven biosimilar approval process is considered to be the "gold standard" for authorizing biosimilar products. *Id.*

161. See *id.*

162. *Id.* The EMA approval process is called the "gold standard for authorizing biosimilar products."

163. See Vinita Banthia, Note, *Biosimilar Regulation: Bringing the United States up to Speed with Other Markets*, 16 MINN. J.L. SCI. & TECH. 879, 890–891 (2015).

164. Malkin, *supra* note 150, at 9.

165. See *Call for Clarity in FDA's Draft Guidance on Biosimilar Meetings*, *supra* note 145.

166. An example is the Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor. This Guideline led to the approval of Zarzio in 2009, the European Union equivalent of Zarzio. EUROPEAN MEDS. AGENCY, EMEA/CHMP/BMWP/31329/2005, Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor (June 2006).

copied by other governing bodies including the World Health Organization.<sup>167</sup> By only publishing general guidances, the FDA is creating more confusion for biosimilar developers. If the FDA were to start publishing more specific guidances related to product-class biosimilars, the biosimilar sponsors will have more clarity and will be able to expedite their development process.<sup>168</sup>

The FDA would not have to eliminate the totality of the evidence method of approval if the agency decided to create product-specific guidances.<sup>169</sup> While using this method, the FDA considers “structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical study(ies) data.”<sup>170</sup> These steps in analysis are required by both the FDA<sup>171</sup> and EMA<sup>172</sup> during the development stage of biosimilars. The FDA can continue to place greater weight on certain aspects of the approval process depending on the specificity of the biosimilar product. Creating product-specific guidances would not remove this feature of the FDA’s application considerations but will assist biosimilar sponsors to determine the specific data and analysis the FDA wants in assessing the application.<sup>173</sup>

The FDA can also continue to meet with biosimilar sponsors during the approval process even though there will be less necessity for these meetings. The FDA already suggests that sponsors should consider other sources of information applicable to their product development prior to requesting a meeting with the FDA.<sup>174</sup> The FDA’s main interest in making this request is to have sponsors be more efficient with FDA resources.<sup>175</sup> If the FDA were to make product-class specific guidelines, the biosimilar sponsors would have more information available for what is necessary in their approval process. This would require less meetings with the FDA, allowing the agency to use the resources allotted to it for other purposes. When necessary, sponsors would still be able to meet with the FDA, especially if problems arise

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167. Wang & Chow, *supra* note 132, at 360.

168. *Id.* at 361–362.

169. See Christl, *supra* note 17, 19–20. The totality of the evidence method is used by FDA scientist to evaluate information from the sponsor. The method of the sponsor’s research is not dependent on this approach.

170. U.S. FOOD & DRUG ADMIN., *supra* note 36, at 8.

171. *Id.*

172. Guideline on Similar Biological Medicinal Products, *supra* note 86.

173. See *infra* note 168.

174. OMB Control No. 0910-0802, *supra* note 129, at 7.

175. *Id.*

during the application process.<sup>176</sup>

#### IV. CONCLUSION

Five years since the passing of the BPCI Act, only four biosimilars have been approved.<sup>177</sup> The European Union and EMA have seen far greater success in biosimilar approval using a guidance approach and have had biosimilars on the market since 2006.<sup>178</sup> The FDA instead has used a sponsor meeting approach which has left many biosimilar manufacturers lacking clarity. As long as there is uncertainty in what is required for biosimilar approval, development of biosimilars will be stymied. Although the FDA faces other barriers to approval of biosimilars, including biologic patent extension<sup>179</sup> and the cost of development of biosimilars,<sup>180</sup> providing further clarity to biosimilar sponsors will improve the approval process. Based on the EMA's success in approving biosimilars, the best method of giving further clarity to biosimilar sponsors is through product-specific guidances. Until the FDA can publish product-specific guidances, biosimilar sponsors will continue to have difficulty gaining approval.

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176. This would put greater emphasis on BPD Type 1 and Type 2 meetings, where sponsors need answers to actual questions to continue their application process. OMB Control No. 0910-0802, *supra* note 129, at 3–4.

177. *Information on Biosimilars*, U.S. FOOD & DRUG ADMINISTRATION (Feb. 22, 2016), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars>.

178. *European Public Assessment Reports*, *supra* note 9.

179. Erwin A. Blackstone & Joseph P. Fuhr, *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFIT 469, 472 (2013).

180. *Id.* at 470–71. A biosimilar costs between \$100 million and \$250 million to develop. *Id.*