

# THE ILLUSION OF INTERCHANGEABILITY: THE BENEFITS AND DANGERS OF GUIDANCE-PLUS RULEMAKING IN THE FDA’S BIOSIMILAR APPROVAL PROCESS

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This is the patent age of new inventions, for killing bodies, and for saving souls, all propagated with the best intentions.

—Lord Byron<sup>1</sup>

#### INTRODUCTION: REDUCING THE COSTS OF PRESCRIPTION DRUGS VIA A NEW GENERIC BIOLOGIC PATHWAY

On March 23, 2010, President Obama signed into law the ambitious Patient Protection and Affordable Care Act.<sup>2</sup> While media attention focused largely on the sweeping changes the bill makes to the nation's healthcare system,<sup>3</sup> there was also a less-noticed rider to the bill, the Biologics Price Competition and Innovation Act of 2009 (Biosimilars Act).<sup>4</sup> The Biosimilars Act grants the Food and Drug Administration (FDA) broad new authority to create an accelerated premarket approval pathway for

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1. GEORGE GORDON BYRON, DON JUAN 39 (Leslie A. Marchand ed., Riverside Press 1958) (1819) (Canto I, Stanza CXXXII).

2. Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148, 124 Stat. 119 (2010) (to be codified as amended at scattered sections of the Internal Revenue Code and 42 U.S.C.) (better known as the Healthcare Reform Act).

3. See, e.g., Sheryl Gay Stolberg et al., *The Long Road Back: Tactics, Perseverance and Luck Resurrected a Bill*, N.Y. TIMES, Mar. 21, 2010, at A1 (discussing the political battle that preceded the passage of the PPACA).

4. Biologics Price Competition and Innovation Act of 2009 (Biosimilars Act), Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010) (to be codified throughout 42 U.S.C.). The Biosimilars Act will be codified as an amendment to the Public Health Service Act (PHSA), Pub. L. No. 78-410, ch. 373, 58 Stat. 682 (1944) (codified as amended at 42 U.S.C. §§ 262–300jj (2006 & Supp. III 2009)), which grants biologics approval to the Food and Drug Administration (FDA).

generic competition to biologics<sup>5</sup> in an attempt to drive biologic drug prices down and reduce the overall costs of health care.<sup>6</sup>

Traditionally, inventors of medical products such as drugs and devices obtain patent protection at the United States Patent and Trademark Office (USPTO) for a twenty-year exclusive term<sup>7</sup> and simultaneously must seek FDA approval to market their invention<sup>8</sup> and for a trademark for their brand name.<sup>9</sup>

Because of the complicated and thorough approval process the FDA conducts, it is often expensive and time-consuming for the initial innovator to bring a drug to market.<sup>10</sup> Likewise, it is often prohibitively expensive for a generic follow-on company to bring an analogue to market, after patent protection has expired, through duplicative and costly reapproval of the

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5. See *infra* note 22 and Part II.C (discussing the old and amended definition of *biologics*).

6. See Randy Osborne, *Brand Biologics Grab 12 Years' Exclusivity, for Now*, 27 NATURE BIOTECHNOLOGY 677, 677–78 (2009) (decrying the twelve-year data exclusivity provisions of the bill as a coup for the innovator industry).

7. See 35 U.S.C. § 154(a)(2) (2006) (granting statutory authority to issue twenty-year patents).

8. Statutory authority for drug approval is found under § 505 of the Food, Drug, & Cosmetic Act (FDCA), Pub. L. No. 75-717, ch. 675, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.). Devices are regulated under § 510(k) of the Medical Devices Amendments of 1976 (MDA), Pub. L. No. 94-295, 90 Stat. 539 (codified as amended in scattered sections of 21 U.S.C.), and biologics are generally regulated under PHS Act § 351, with historic exceptions for insulin, human growth hormone, and a few others that qualify as both biologics and drugs, which are regulated as new drugs under FDCA § 505. See David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 154 (2005) (“In the 1940s, insulin was obtained in the same manner as many biologics, namely extraction from animals. Despite this similarity with biologics, insulin was regulated by FDA and not the Public Health Service.”).

9. Lanham Act, 15 U.S.C. § 1051 (2006) (granting statutory authority over trademarks). Thus, despite being codified at different section numbers, drug approvals are commonly referred to as § 505 approvals, biologics as § 355, and devices as § 510(k). Abbreviated approvals under Hatch–Waxman are referred to as § 505(b)(2) approvals.

10. Compare Joseph A. DiMasi, Ronald W. Hansen, & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166 (2003) (estimating the cost of research and development (R&D) for new drugs at \$403 million), and Pharm. Research & Mfrs. of Am. (PhRMA), *Drug Discovery and Development*, PHRMA, <http://www.phrma.org/research/drug-discovery-development> (last visited Aug. 14, 2011) (estimating the R&D for a new drug is more than \$800 million and can top \$1 billion), with MERRILL GOOZNER, *THE \$800 MILLION PILL: THE TRUTH BEHIND THE COST OF NEW DRUGS* 244–46 (2004) (maintaining these numbers are inflated and citing studies that estimate the true cost at \$115–240 million).

innovator drug, and it would be unethical to subject further human subjects to unneeded clinical trials.<sup>11</sup>

To deal with these problems, in 1984 Congress enacted a law called the Price, Competition, and Patent Term Restoration Act, which is commonly referred to as the Hatch–Waxman Act.<sup>12</sup> The Act allows generic follow-on drugs to seek accelerated approval by the FDA. In exchange, the law grants limited data exclusivity<sup>13</sup>—and hence, often de facto market exclusivity<sup>14</sup>—for the original brand-name innovator.<sup>15</sup> The Act utilizes a preexisting compilation of all relevant drugs and their clinical indications, the *Orange Book*, to list generic analogues.<sup>16</sup> Most importantly, Hatch–Waxman allows generic drug manufacturers to use the same FDA approval data as the brand-name manufacturers had in an abbreviated approval application (thus eliminating the need for duplicative human trials and reducing cost for generic manufacturers).<sup>17</sup> The result has been a decrease

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11. See *supra* note 10.

12. Drug Price Competition and Patent Term Restoration (Hatch–Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. § 355(b), (j), (l); 35 U.S.C. §§ 156, 271, 282 (2006)).

13. See Jessica Wapner, *Can Data Exclusivity Lead to Immortality?*, WORK IN PROGRESS (Jan. 28, 2011), <http://blogs.plos.org/workinprogress/2011/01/28/can-data-exclusivity-lead-to-immortality/> (“‘Data exclusivity’ . . . refers to protection of not only the drug but also the data. Under data exclusivity, manufacturers of generic drugs are prevented from using the original clinical trial data to support approval of their ‘biosimilar. . .’”).

14. Market exclusivity is literal—it means simply having no competition for a product in the marketplace. *Cf. id.* (“[T]he new law gives new biologics at minimum 2.5 years and at most 7 years of additional solo time on the market.”).

15. See Hatch–Waxman Act, 21 U.S.C. § 355(c)(3)(E), 355(j)(5)(F) (2006) (awarding data exclusivity to innovator and first-to-file generic applicants).

16. See *id.* § 355(j)(2)(A)(iii)–(v) (requiring listings). Generic drugs are those that are therapeutically equivalent with the original brand-name drug. The *Orange Book* is a listing of the levels of therapeutic equivalence and interchangeability. FDA, ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (2011), <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf> (so called because the original *Orange Book* had an orange cover).

17. See FDCA, 21 U.S.C. § 355 (codifying the Hatch–Waxman Act’s amendment of § 505(2)(b) of the FDCA). These Abbreviated New Drug Applications, or ANDAs, are regulated under § 505(2)(b), and also allow for patent dispute resolution between the innovator and the follow-on, as well as an added 180-day “follow-on” market exclusivity over second or third follow-on companies as a financial incentive to provide the initial funding for the costly approval process. Applicants can also file “paper new drug applications,” or Paper NDAs, which allow a generic applicant to rely on publicly available scientific papers in lieu of self-funded studies. For more, see *infra* notes 124–26 and accompanying text. See also Dudzinski, *supra* note 8, at 216 (mapping out § 505(b)(2) for the differences between NDAs, Paper NDAs, and ANDAs approval pathways and generic versus innovator drugs).

in the cost of prescription drugs due to increased price competition after the expiration of the original drug's patent term.<sup>18</sup>

However, the FDA maintained that the pathway applied only to single-molecule drugs, so there were large exceptions for other types of analogous medical therapies.<sup>19</sup> For instance, the FDA generally approves medical devices (such as pacemakers or stents)<sup>20</sup> under a separate pathway.<sup>21</sup> There is also another category of therapeutic substances known as biologics, which includes nearly anything derived from living organisms, such as vaccines, blood, or cellular products.<sup>22</sup> Importantly, a therapy can be both a "drug" and a biologic at the same time, such as insulin, human growth hormone, or other small-protein biologics.

Biologics are traditionally harder to produce and regulate than synthetically created single-molecule drugs because of their complexity, unpredictability (i.e., their ability to mutate or change shape),<sup>23</sup> and the fact

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18. See Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1293 (2006) (discussing Hatch–Waxman's long-term cost savings as it relates to potential biosimilars savings). Similarly, price competition for biologics could significantly lower the cost of health care. See Dawn Willow, *The Regulation of Biologic Medicine: Innovators' Rights and Access to Healthcare*, 6 CHI.-KENT J. INTELL. PROP. 32, 36–37 (2006) (projecting cost savings).

19. Cf. FDCA, 21 U.S.C. § 355(j) (codifying the Hatch–Waxman Act's amendment of § 505(2)(b) of the FDCA (providing abbreviated approval for generic drugs). The FDA had taken the position that § 505(b)(2) of the FDCA (as amended by the Hatch–Waxman Act) gave it a pathway to approve "more than 80 section 505(b)(2) applications for drugs for indications ranging from cancer pain to attention deficit disorder." See Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation and Research, to Katherine M. Sanzo et al. 4 (Oct. 14, 2003) [hereinafter FDA Interpretation], available at <http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-c000001-exhibit-29-vol4.pdf> (position mooted by Biosimilars Act).

20. See, e.g., U.S. Patent No. 7,135,038 (filed Sept. 30, 2002) (drug eluting stent); U.S. Patent No. 5,243,977 (filed June 26, 1991) (pacemaker).

21. 21 U.S.C. § 360(k) (codifying the Medical Devices Amendments of 1976, Pub. L. No. 94–295, 90 Stat. 539, § 510(k), and granting the FDA authority for device review).

22. 42 U.S.C. § 262(i) (2006) (granting jurisdiction over "viruses, therapeutic serums, toxins, antitoxins, or analogous products," and more that were intended for the "prevention, treatment, or cure of a disease or condition of human beings"); see *infra* Part II.C (discussing the amended definition of biologics). The FDA interprets *analogous* to include therapeutic proteins, monoclonal antibodies, and immunoglobulins. James N. Czaban et al., *Panacea or Poison Pill? Making Sense of the New Biosimilars Law*, 8 BNA PHARM. L. & INDUSTRY REP., May 2010, at 1, 2, available at [http://www.bna.com/pdf/plir\\_05032011.pdf](http://www.bna.com/pdf/plir_05032011.pdf) (categorizing the FDA's interpretation as "broad").

23. The three-dimensional structure of proteins affects how they bind to cells and other proteins. Imagine a long chain of magnets; a chain of identically opposite magnets would bind well with it. If the chain is twisted or overlapped, however, the binding changes drastically. See KATHERINE J. DENNISTON ET AL., GENERAL, ORGANIC, AND BIOCHEMISTRY

that they are often vaccines derived from live viruses with the potential to wreak large-scale havoc if they are not closely regulated.<sup>24</sup>

But what was originally a largely separate category for those rare treatments that required live precursor sources (such as vaccines or sera) has today morphed into an over \$52 billion arm of the drug industry,<sup>25</sup> fueled in part by the creation of recombinant DNA technology and the so-called genomics revolution.<sup>26</sup> Recombinant DNA technology allowed for the laboratory creation of large amounts of proteins and other cellular products from living precursor cells, providing vast opportunities for biotechnology firms to create products on a commercial scale that are both “biologics” and “drugs” under the law.<sup>27</sup> Further, with the mapping of the human genome, scientists predict that emerging biologic drugs will be personalized

554–55 (3d ed. 2001) (describing the complicated structural interactions and the forces that can alter them). Each protein—like the pie-shaped character in Shel Silverstein’s *The Missing Piece*—has an often-unique object it wants to bind with. Cf. SHEL SILVERSTEIN, *THE MISSING PIECE* (1976).

24. See *infra* notes 49–51 and accompanying text (explaining how, prior to regulation, faulty batches of biologics caused a number of deaths).

25. WENDY H. SCHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., RL 33901, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 1 (2009).

26. See generally FRANCIS S. COLLINS, *THE LANGUAGE OF LIFE: DNA AND THE REVOLUTION IN PERSONALIZED MEDICINE* (2010) (discussing the future of genetics and the biotech industry).

27. Compare the statutory definition of *drug*:

The term “drug” means . . . articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

FDCA, 21 U.S.C. § 321(g)(1) (2006), with the statutory definition of *biologic*:

*The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.*

PHSA, *id.* § 262(i) (2006) (amendments italicized) (as currently amended by Biosimilars Act § 7002(b)). Noticeably, the definitions are not co-exclusive, and hence it is possible for the FDA to classify a biologic as both a biologic and a drug and to approve such a “biologic drug” under either an NDA or a Biologics License Application (BLA). See *supra* note 17 (NDAs) and *infra* note 162 (BLAs). Like a Venn diagram, there is substantial overlap between the two definitions—nearly all biologics, if read broadly enough, qualify as drugs. Indeed, this is what has led to some of the confusion and wargaming. For instance, some innovator drugs approved under an NDA would have preferred approval under a BLA, so their potential generic competition could not avail themselves of § 505(b)(2) abbreviated approval.

to an individual's own genetic traits and could vastly improve the quality of care over the current "one size fits all" model of chemically synthesized drug treatment.<sup>28</sup>

Biologic drugs generally cost far more to manufacture than their single-molecule and chemically synthesized ("non-biologic") counterparts, because they are either "alive" or of a highly sensitive nature and must be created and closely monitored in a laboratory environment.<sup>29</sup> Additionally, the lack of a pathway for generic competition and rigorous, expensive, and ever-changing scientific standards for approval often result in de facto market exclusivity for the original brand-name manufacturer, further driving up the cost.<sup>30</sup> Biologic drugs average between \$10,000 to \$20,000 per patient, per year<sup>31</sup> and can be as expensive as \$10,000 for a single dose.<sup>32</sup> Hence, they significantly contribute to the cost of health care.<sup>33</sup> Industry experts and lawmakers expect the new regulatory pathway to increase price competition and decrease the cost of these drugs.<sup>34</sup>

While it will be almost a decade before the FDA fully implements the new biosimilars law and issues controlling guidelines for industry practice,<sup>35</sup> debate has already begun over the feasibility of determining interchangeability and biosimilarity for biologics.<sup>36</sup> Indeed, the FDA has

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28. See COLLINS, *supra* note 26, at XXIII–XXIV, 231–35, 237–50 (discussing biologics treatments targeted to individuals' genomes).

29. Jeremiah J. Kelly & Michael David, *No Longer "If," but "When": The Coming Abbreviated Approval Pathway for Follow-on Biologics*, 64 FOOD & DRUG L.J. 115, 119 (2009) ("[B]iological drug products are typically produced in vivo (in a biological system) and, as a result, are complex and less well understood."). Further, the manufacturing process has a serious effect on the final product—purification is required. *Id.*

30. *Id.* at 115 (advocating lowering the cost of prescription drug prices).

31. For example, as of 2005, the "annual cost of Raptival [was] over \$12,000 . . . annual cost of Rebif [was] over \$13,000 . . . annual cost of Humiral [was] over \$15,000 . . . Kineret costs over \$15,000." Dudzinski, *supra* note 8, at 144 n.5.

32. "[A] single dose of Xigris costs approximately \$10,000." *Id.*

33. See *The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 1, 24–25 (2004) (statement of Carole Ben-Maimon, President and CEO, Barr Research, Inc.) [hereinafter *2004 Hearing*].

34. See, e.g., Czaban et al., *supra* note 22, at 2 n.8, 3 (citing a Congressional Budget Office estimate of \$6–7 billion in cost savings over ten years, but cautioning that drug prices may not fall significantly).

35. The FDA is not required to issue biosimilar guidelines until at least 2020. See Biosimilars Act, Pub. L. No. 111-148, § 7002(e)(2)(B)(ii), 124 Stat. 119, 817 (to be codified at 42 U.S.C. § 262). For now, applicants "may" use § 505 for biologics applications. *Id.* § 7002(e)(2).

36. The FDA has already begun to gather public, industry, and academic input on how the guidelines ought to be fashioned. See *infra* note 45 and accompanying text.

already set aside \$5.7 million for fiscal year 2011 toward the development of a biosimilars program,<sup>37</sup> and one senior FDA official has announced publicly that at least one guidance document will be released “by the end of the year, without question.”<sup>38</sup>

Some critics argue that any new biologics pathway will be so restrictive that it will do little to improve price competition.<sup>39</sup> Others argue it is a scientific impossibility to achieve interchangeability between some biologics (due to their variable nature as living organisms) and so the FDA’s efforts are doomed.<sup>40</sup> The traditional model for interchangeability under Hatch–Waxman (bioequivalence) is based on the assumption that a single-molecule drug may be chemically synthesized by another laboratory and will have the same effect.<sup>41</sup> With biologics, however, protein folding, cellular mutation, and environmental factors (such as storage temperature or even light exposure) can all contribute to wildly unpredictable results in any given final product.<sup>42</sup> Therefore, any determinations of interchangeability

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37. Cathy Dombrowski, *FDA Biosimilars Program Gets Seed Money in Administration’s FY ‘11 Budget*, THE PINK SHEET (Feb. 8, 2010) (on file with author).

38. *BioCentury This Week: Biosimilars: Will the Path Work?* (WUSA, CBS affiliate television broadcast May 1, 2011) (comments of Rachel Behrman, Assoc. Dir., Medical Policy in the FDA’s Ctr. for Drug Evaluation and Research), available at <http://biocenturytv.com/fullplayer.aspx> (activate “Expand Video Library” hyperlink; activate “BC Show 33” hyperlink; follow “BioCentury 05.01.11 – [1] The Pathway” hyperlink).

39. See Letter from Bernie Sanders, Senator, Vermont, to Margaret Hamburg, Comm’r, FDA (Nov. 2, 2010), <http://www.fdalawblog.net/files/bcpi-act---sanders-ltr-11-2010.pdf> (calling the twelve-year period of data exclusivity a “defect” in violation of Article 20 of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects).

40. See, e.g., Letter from Arthur D. Levinson, Chairman and Chief Exec. Officer, Genentech, Inc., to Genentech Stockholders, in GENENTECH, INC., GENENTECH 2003 ANNUAL REPORT 4 (2003), <http://www.gene.com/gene/about/ir/historical/annual-reports/2003/editorial/lettertostockholders.pdf> (“Genentech does not believe that the technology currently exists to prove a generic biotech product safe and effective . . .”). Representative Jay Inslee’s (R-WA) proposal in the 110th Congress did not include determinations of interchangeability. See Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 2(a)(2).

41. Shein-Chung Chow et al., *Statistical Methods for Assessment of Biosimilarity Using Biomarker Data*, 20 J. BIOPHARM. STAT. 90, 91 (2010) (“[T]he assessment of bioequivalence as a surrogate for evaluation of drug safety and efficacy is based on the *fundamental bioequivalence assumption* that if two drug products are shown to be bioequivalent in average bioavailability, it is assumed that they will reach the same therapeutic effect or they are therapeutically equivalent.”) (emphasis in original).

42. See Kelly & David, *supra* note 29 (“A chief argument against abbreviated approval of follow-on biologics is the scientific difficulty in measuring the structural differences, and their effects, between the innovator and the follow-on product.”).

should not be premised on the old model, and it would be scientifically disingenuous or dangerous to regulate them so.

By formulating the Hatch–Waxman Act broadly, Congress has given the FDA wide flexibility to regulate. It has mandated the use of guidance documents, a less costly and time-consuming form of regulating than formal or even informal rulemaking.<sup>43</sup> This guidance mandate has the advantage of increased flexibility and a faster turnaround time than traditional notice-and-comment rulemaking.<sup>44</sup> Nevertheless, if the FDA does not use that flexibility judiciously, the Biosimilars Act may not achieve actual reductions in the cost of prescription biological drugs or significantly affect the cost of health care.<sup>45</sup>

Part I of this Comment discusses the Hatch–Waxman amendments, analogous foreign biosimilars pathways, and the history of biologics approval. Part II discusses the new bill, compares the Hatch–Waxman pathway with the potential biosimilars pathway, and explores key differences between the two that could delay access to both innovator and generic drugs. Part III recommends using notice-and-comment procedures to establish product-class-specific guidance, while retaining flexibility within product classes for clinical requirements, and discourages the FDA from using two-sided biostatistical testing.

## I. BACKGROUND

### A. *History of Biologics Regulation*

In the nineteenth century, the United States and manufacturers developed and used vaccines (to prevent medical conditions such as smallpox) and antitoxins (to treat ailments like diphtheria).<sup>46</sup> These

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43. See Administrative Procedure Act, 5 U.S.C. §§ 552, 553 (2006) (laying out procedural requirements for formal, informal, and other forms of agency rulemaking).

44. See *id.* The problem with supposedly “informal” rulemaking is that it has become “ossified.” See Jeffrey S. Lubbers, *The Transformation of the U.S. Rulemaking Process—For Better or Worse*, 34 OHIO N. U. L. REV. 469, 471–72 (2008) (discussing the ossification of informal rulemaking).

45. The FDA recently held a public meeting on biosimilars. FDA Public Meeting, Approval Pathway for Biosimilar and Interchangeable Biological Products (Nov. 2–3, 2010), <http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm> [hereinafter FDA Public Meeting] (calling for stakeholder input before issuing biosimilarity and user-fee guidelines).

46. See JONATHAN LIEBENAU, MEDICAL SCIENCE AND MEDICAL INDUSTRY: THE FORMATION OF THE AMERICAN PHARMACEUTICAL INDUSTRY 3, 11 (1987) (discussing antitoxins); Rohit K. Singla, *Missed Opportunities: The Vaccine Act of 1813*, FOOD AND DRUG LAW: AN ELECTRONIC BOOK OF STUDENT PAPERS, 31 (Peter Barton Hutt ed., 2004),

therapies presented a host of problems as small patent medicine makers rushed to produce similar products that often had little or no effect, or were in fact harmful to consumers' health.<sup>47</sup> However, the regulation of drugs was widely thought to be a state law matter, and states were reluctant to spend money on something that was widely perceived as encroaching on personal liberties.<sup>48</sup>

Without regulation of the sources of these treatments, mislabeling, fraud, and deaths were inevitable. For instance, in 1901 thirteen children died from tetanus.<sup>49</sup> Officials eventually attributed their deaths to a diphtheria antitoxin obtained from the blood of a local horse.<sup>50</sup> Coincidentally, a similar tragedy occurred in New Jersey around the same time—nine children died from tetanus after receiving a contaminated smallpox vaccine.<sup>51</sup> This provoked Congress to regulate biologics under the 1902 Biologics Control Act, also known as the Virus–Toxin Law.<sup>52</sup> Thus, Congress created the first premarket approval in United States history for biologics, but synthetic drugs and patent medicines remained largely unregulated.

Soon thereafter, the publication of Upton Sinclair's novel *The Jungle*,<sup>53</sup> with its grisly depictions of conditions in the Chicago meatpacking industry, led to the passage of the Pure Food and Drug Act of 1906 (PFDA).<sup>54</sup> The Act included grants of power to regulate drugs as well as food and granted those powers to the Bureau of Chemistry, thus splitting statutory regulation of biologics and drugs at an early juncture.<sup>55</sup> Congress had originally

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<http://leda.law.harvard.edu/leda/data/229/rsingla.pdf> (discussing early smallpox vaccinations).

47. FRAN HAWTHORNE, *INSIDE THE FDA: THE BUSINESS AND POLITICS BEHIND THE DRUGS WE TAKE AND THE FOOD WE EAT* 36 (2005).

48. Singla, *supra* note 46, at 30–40 (discussing the early widespread opposition to mandatory vaccination).

49. Linda Bren, *The Road to the Biotech Revolution: Highlights of 100 Years of Biologics Regulation*, *FDA CONSUMER*, Jan.–Feb. 2006, at 50, 50–51.

50. *Id.*

51. *Id.*

52. Pub. L. No. 57-244, ch. 1378, 32 Stat. 728 (1902) (previously codified at 42 U.S.C. §§ 141–148, repealed and replaced by PHSA, Pub. L. No. 78-410, ch. 373, 58 Stat. 682 (1944) (codified as amended at 42 U.S.C. §§ 262–300jj (2006 & Supp. III 2009)) (creating the Center for Biologics Evaluation and Research (CBER) and regulating biologics).

53. UPTON SINCLAIR, *THE JUNGLE* (Bantham Reissue ed., Bantham Books 2003) (1906).

54. Pub. L. No. 59-384, ch. 3915, 34 Stat. 768 (1906).

55. *Id.*; *About FDA: History*, U.S. FOOD & DRUG ADMIN. (last updated July 29, 2010), <http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm>.

granted the Hygienic Laboratory, the predecessor of the National Institutes of Health (NIH),<sup>56</sup> the limited power to review biologics applications. However, after Congress passed the Public Health Service Act of 1944 (PHSA),<sup>57</sup> which was essentially a recodification of the earlier Biologics Control Act,<sup>58</sup> biologics review standards came to include “safety, purity, and potency.”<sup>59</sup>

Meanwhile, the Food, Drug, and Insecticide Administration (FDIA) was created in 1927 to deal with drug regulation; it was eventually renamed the FDA.<sup>60</sup> As the need for broader drug regulation grew, in 1938 Congress vested the Secretary of Agriculture with the power to review new drugs and notify the public that they were safe under the Federal Food, Drug, and Cosmetic Act (FDCA), but preexisting drugs could be sold without premarket approval.<sup>61</sup> This statutory grant of drug review and approval authority solidified the uneven two-track approach to approval of the two analogous (and sometimes overlapping) medical therapies. However, the usefulness of insulin, and the realities of the need for widespread production and sale of this biologic drug soon led to these two tracks crossing paths.

Insulin, which is a protein that naturally occurs in the body, was first discovered, understood, and isolated over a period from the latter half of the nineteenth century to 1921.<sup>62</sup> In 1922, insulin was finally isolated in an injectable form in Canada.<sup>63</sup> Its usefulness at treating diabetes led to the widespread sale of insulin.<sup>64</sup> Soon after the patent expired, Congress passed the Insulin Amendments, which expressly required the FDA to approve

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56. PETER BARTON HUTT ET AL., FOOD AND DRUG LAW 879 (3d ed. 2007).

57. Pub. L. No. 78-410, ch. 373, 58 Stat. 682 (1944) (codified as amended at 42 U.S.C. §§ 262–300j (2006 & Supp. III 2009)).

58. Biologics Control Act, Pub. L. No. 57-244, 32 Stat. 728 (1902) (previously codified at 42 U.S.C. §§ 141–148 (1942), repealed in 1944 by the PHSA).

59. PHSA, § 351(d), 58 Stat. at 702 (1944).

60. *Dudzinski*, *supra* note 8, at 151–52.

61. Federal Food, Drug, & Cosmetic Act (FDCA), Pub. L. No. 75-717, ch. 675, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.).

62. See Ian Murray, *Paulesco and the Isolation of Insulin*, 26 J. HIST. OF MED. AND ALLIED SCI. 150, 150–57 (1971).

63. See *id.* at 153.

64. See Frederic J. Geissel, *The U.S. Food and Drug Regulatory Process: Administrative Aspects of Certification of Insulins*, in INSULINS, GROWTH HORMONE, AND RECOMBINANT DNA TECHNOLOGY 201 (John L. Gueriguian et al. eds., 1981) (explaining the insulin industry’s growth).

insulin and insulin analogues despite the fact that developers derived it from animals, which qualified it as biologic as well as a drug.<sup>65</sup>

Later in 1948, Congress transferred biologics responsibility from the Hygienic Laboratory to the National Microbial Institute in NIH.<sup>66</sup> In 1955, after some mishaps with polio vaccine, Congress transferred biologics again to the newly formed Division of Biologics Standards (DBS) within NIH.<sup>67</sup>

In 1962, Congress finally authorized a true “premarket” approval process for drugs in response to the Thalidomide crisis, greatly expanding the FDA’s regulatory authority and bringing it in line with the longstanding premarket approval requirements of biologics.<sup>68</sup> Still, the two pathways were regulated by separate agencies.

In 1972, amid charges of conflict of interest and agency capture,<sup>69</sup> the DBS was given broader authority and was finally subsumed by the FDA and became the Bureau of Biologics.<sup>70</sup> This eventually morphed into the current Center for Biologics Evaluation and Research (CBER).<sup>71</sup>

Because of the way the FDA and the two-track approach to regulation has developed historically and the way that the FDA uses Centers to

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65. See Insulin Amendments, Pub. L. No. 77-366, ch. 613, 55 Stat. 851 (1941) (codified at 21 U.S.C. § 356).

66. HUTT ET AL., *supra* note 56, at 879.

67. *Id.*

68. Drug [Kefauver–Harris] Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C.) (creating premarket approval for all drugs requiring safety and efficacy testing in response to the Thalidomide crisis).

69. See Nicholas Wade, *Division of Biologics Standards: Scientific Management Questioned*, 175 SCIENCE 966, 968 (1972) (charging Division of Biologics Standards (DBS) with agency capture); see also Dudzinski, *supra* note 8, at 158 (“In the early 1970s, DBS was criticized after a series of well-publicized incidents where relatively ineffective vaccines reached the market.”).

70. Dudzinski, *supra* note 8, at 159.

71. See generally *Vaccines, Blood & Biologics*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/BiologicsBloodVaccines/default.htm> (last visited Aug. 14, 2011) (listing the CBER resources and linking to guidance). When an innovator first seeks approval of a medical therapy at the FDA, the FDA must determine where the agency should examine the medical therapy. See *supra* note 8 (discussing the statutory authority for separate approval pathways). For example, the FDA generally sends devices to the Center for Device and Radiological Health (CDRH), while they generally send biologics to CBER and drugs to the Center for Drug Evaluation and Research (CDER). CBER handles reviews of most biologic applications, and the three Centers often work in conjunction on combination products. See generally *Combination Products*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/CombinationProducts/default.htm> (last visited Aug. 14, 2011) (providing guidelines for where examinations should take place).

generally handle certain technologies, when applicants seek premarket approval for a medical therapy, strategically they must ask (and FDA officials must answer) the following three important questions. The results are often confusing.

First, the *definitional question*: how is the product defined by statute?<sup>72</sup> Second, the *examination question*: at what Center within the FDA will the product be examined?<sup>73</sup> Third, the *approval pathway question*: under what statutory premarket approval pathway should the product be regulated?<sup>74</sup>

Until 1972, those questions were relatively easy to answer. Treatments derived from living precursors, for the most part, went to DBS (and later CBER at the FDA) and were approved under Biologics License Applications (BLAs).<sup>75</sup> Most chemically synthesized single-molecule drugs went to the FDA and the Center for Drug Evaluation and Research (CDER)<sup>76</sup> and were approved under New Drug Applications (NDAs).<sup>77</sup> Advances in biotechnology, however, soon blurred those lines.

### B. History of Recombinant DNA Protein Products

For thirty years after World War II, the small-molecule drug sector grew rapidly, ballooning into a lucrative industry that treated all sorts of ailments, from infections and allergies to bad breath and bursitis.<sup>78</sup> Meanwhile, the field of biologics lagged far behind in generating new therapeutically effective products.<sup>79</sup>

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72. Is the product a drug, a biologic, or both? For the statutory definitions and a discussion of their substantial overlap, see *supra* note 27 and accompanying text. Or, is it a device or some combination thereof? See *generally Combination Products, supra* note 71.

73. Should the product go to CBER, CDER, or CDRH? See *supra* note 71 and accompanying text (naming the different centers and how the Office of Combination Products makes these determinations).

74. Should my product be examined under an NDA, an ANDA, or a Paper NDA? See *supra* note 17 and accompanying text. A BLA? See *infra* note 162 and accompanying text. A new Abbreviated Biologics License Application (ABLA)? See *infra* note 156 and accompanying text.

75. See *infra* note 162 and accompanying text.

76. See *supra* note 71 and accompanying text.

77. See *supra* note 17 and accompanying text.

78. Dudzinski, *supra* note 8, at 154 (“As American firms began to churn out dozens of new antibiotics, the period immediately after World War II heralded their collective embracing of the ‘small molecule paradigm’ as the *sine qua non* of the modern pharmaceutical industry and the birth of the ‘chemotherapeutic revolution.’”).

79. *Id.* at 160 (“Despite continuous scientific advancements and financial successes of the small molecule paradigm, dominance of the paradigm would be challenged by the biotechnology industry, especially after the late 1970s.”).

That is, until 1972, when the field of recombinant DNA was born.<sup>80</sup> Just a year prior, a paper published by Hamilton Smith, Daniel Nathans, and Walter Arber showed that you could cleave viral DNA with a specific enzyme.<sup>81</sup> Then in 1972, Stanford Professor Paul Berg conducted a groundbreaking experiment where he used the enzyme to splice a segment of DNA from one organism into another organism (a prokaryote—a single-celled bacterium lacking a nucleus).<sup>82</sup> In doing so, his team of scientists changed the genetic makeup of the organism. Thus, using this “recombinant” process, scientists could now modify or tailor the genes of host cells to turn bacteria into “living factories” that produced custom therapeutic proteins.<sup>83</sup>

For instance, scientists quickly learned how to recombine insulin DNA in a particular way and then insert it into the DNA of a single cell bacterium.<sup>84</sup> In 1982, a company named Genentech developed such a process to produce a “better,” faster-acting form of insulin.<sup>85</sup> Around the same time, scientists also found a way to produce monoclonal antibodies<sup>86</sup> (human immune proteins meant to attack and neutralize viruses and bacteria).<sup>87</sup> They did so by taking a human immune cell called a *B cell*, which produces only one type of antibody, and fusing it with a cancer cell to engineer an immortal cell line which endlessly created one type of antibody.<sup>88</sup>

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80. See David A. Jackson, Robert H. Symons, & Paul Berg, *Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Eschericia coli*, 69 PROC. NATL. ACAD. SCI. U.S. 2904, 2904 (1972) (announcing the development of biochemical techniques to covalently join any two DNA molecules); see also Bo G. Malström, Professor, Royal Academy of Sciences, Award Ceremony Speech for the Nobel Prize in Chemistry (1980), <http://www.nobel.se/chemistry/laureates/1980/presentation-speech.html> (awarding the prize to Berg).

81. See WILLIAM S. KLUG & MICHAEL R. CUMMINGS, *CONCEPTS OF GENETICS* 577 (Sheri L. Snavely ed., 6th ed. 2000).

82. Jackson et al., *supra* note 80, at 2904 (explaining the experimental procedure).

83. Dudzinski, *supra* note 8, at 161. *Contra Corporate Chronology*, GENENTECH, <http://www.gene.com/gene/about/corporate/history/timeline.html> (last visited Mar. 2, 2011) (claiming Genentech founders Robert Swanson and Dr. Herbert Boyer pioneered the field).

84. Dudzinski, *supra* note 8, at 161 (“Genentech . . . immediately began development of recombinant insulin . . .”).

85. *Corporate Chronology*, *supra* note 83.

86. Dudzinski, *supra* note 8, at 161.

87. See KLUG & CUMMINGS, *supra* note 81, at 567–70 (explaining antibodies).

88. Dudzinski, *supra* note 8, at 161 (noting that Centocor was founded in 1979 to exploit such technology).

The discovery revolutionized the field of therapeutic biologic drugs.<sup>89</sup> Scientists, no longer forced to find sources in larger living creatures such as pigs, dogs, rats, or horses, could now culture single-celled bacteria that could produce small molecule therapeutic protein biologics on a commercial scale.<sup>90</sup> Indeed, the ensuing method was so easy that “high school pupils could easily learn it.”<sup>91</sup> A field that had consisted almost solely of vaccines, blood, and insulin soon became crowded with new biologic protein drugs like erythropoietins (i.e., Epogen), and new “biotech” companies like Genentech, Amgen, and Biogen began to spring up.<sup>92</sup> The FDA responded to the explosion of recombinant DNA research and the inevitable flood of applications by hiring a large number of new employees to increase expertise.<sup>93</sup>

Further, in 1983, scientists at Columbia University, under the direction of Professor Richard Axel, developed a procedure that inserted the first recombinant DNA into larger-celled, more complex organisms (i.e., eukaryotes—whose cells have nuclei).<sup>94</sup> This quickened the pace of innovation by allowing scientists to mass-produce larger complex biologics as well.

Unfortunately for generic competition, however, the biologic drug industry was only in the nascent stages of development in 1982 and was little-discussed when Congress tackled the problem of escalating drug costs in the more heavily developed single-molecule drug industry.<sup>95</sup> They passed what is now widely known as the Hatch–Waxman Act and revolutionized how the FDA approves generic single-molecule drugs.<sup>96</sup>

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89. See KLUG AND CUMMINGS, *supra* note 81, at 577 (“Biotechnology is an outgrowth of recombinant DNA technology.”).

90. *Id.* at 593–97.

91. GOOZNER, *supra* note 10, at 21 (footnote omitted).

92. See *id.* at 16–29 (describing the growth of Amgen and the discovery and marketing of Epogen—artificial erythropoietin).

93. Dudzinski, *supra* note 8, at 161 (The FDA “recognized the ascendancy of recombinant DNA technology and anticipated commercialization of recombinant DNA products and regulatory findings; in response, FDA hired many physicians and scientists in order to amass institutional scientific expertise . . .”).

94. Eukaryotes are usually more complicated organisms that, like the human body, often require complicated intracellular structures to achieve their cellular functions. They are capable of building much more complicated protein structures and hence, capable of providing much more complicated therapeutic biologics through prokaryotic recombinant DNA processes. Dudzinski, *supra* note 8, at 166.

95. *Id.* at 167–68.

96. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355(b), (j), (l); 35 U.S.C. § 156, 271, 282).

*C. Hatch–Waxman*

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch–Waxman Act.<sup>97</sup> The Act gave the FDA broad and well-defined authority to issue abbreviated approval to generic drugs after approval of a brand-name drug.<sup>98</sup> Rather than having to wait for the first innovator drug's patent to expire and then having to repeat the process of approval all over again, generic companies could now file an abbreviated new drug application before patent expiration.<sup>99</sup> This allowed generic companies to lower their cost of entry to the market, increasing competition and hence lowered drug prices.<sup>100</sup>

The effect of Hatch–Waxman on the prices of prescription drugs in the United States has been tangible and significant.<sup>101</sup> For instance, “when Eli Lilly lost patent protection on the antidepressant drug Prozac (fluoxetine) in 2001, generic competitors garnered 70% of Prozac's market within 2 months.”<sup>102</sup> The industry now estimates that generic drugs make up over 75% of total prescriptions filled in the United States.<sup>103</sup>

Unfortunately, biologics had escaped the notice of lawmakers. In part because there was little generic competition once the FDA finally approved their biologic protein products, innovator companies were able to keep their drug costs high. In some cases, they currently charge upwards of

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97. *Id.*

98. *Id.*; see also Kelly & David, *supra* note 29, at 115 (“Hatch–Waxman aimed to strike a critical balance in the Food, Drug & Cosmetic Act (FDCA) between incentives for drug innovation and the need for lower drug prices through increased competition.”).

99. FDCA, 21 U.S.C. § 355(j) (2006).

100. See Grabowski et al., *supra* note 18, at 1291 (discussing the effect of Hatch–Waxman and offering that proponents of the Hatch–Waxman approach predict that follow-on biologics will similarly lower prices).

101. See *id.*; see also Kevin Outterson & Aaron S. Kesselheim, *How Medicare Could Get Better Prices on Prescription Drugs*, 28 HEALTH AFF. w832, w837 (2009), <http://content.healthaffairs.org/content/28/5/w832.full.html> (predicting large cost savings from follow-on biologic legislation).

102. Richard G. Frank, *Regulation of Follow-on Biologics*, 357 N. ENGL. J. MED. 841, 842 (2007).

103. Press Release, Generic Pharmaceutical Ass'n (GPhA), GPhA Tells FDA that Science-Based Biogeneric Approval Process Is Needed to Assure Lower Costs for Patients (Nov. 3, 2010), available at <http://www.gphaonline.org/media/press-releases/2010/gpha-tells-fda-science-based-biogeneric-approval-process-needed-assure-low> (noting that 75% of prescriptions filled are for generics, but they make up only 22% of total drug spending).

\$20,000 per year for biologic drug treatments,<sup>104</sup> supposedly to recoup the extensive start-up costs it takes to approve, market, and manufacture biologics.<sup>105</sup> At such high prices, it is clear that biologic drug prices have contributed significantly to rising healthcare costs.<sup>106</sup>

In 2003, the European Union enacted the world's first regulatory system for follow-on biologics.<sup>107</sup> The European Medicines Evaluation Agency (EMA) Guidance on the Regulation of Biosimilars established a new nomenclature for generic competition: "similar biological medicinal products."<sup>108</sup> In 2008 Health Canada (HC) followed with Guidance on Regulation of Subsequent Entry Biologics, Canada's framework for the review of abbreviated applications for biologics.<sup>109</sup>

In sum, the success of Hatch–Waxman, the growth of the biologics industry, and the international examples made the eventual statutory creation of a biologics generic pathway seemingly inevitable.<sup>110</sup>

#### D. Preexisting Legal Framework

In 1997, Congress passed the Food and Drug Administration Modernization Act, which under § 123(f) required the agency to conform

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104. See *supra* notes 29–32 and accompanying text (describing the exorbitant cost of some biologic treatments).

105. See *Biologics and Biosimilars: Balancing Incentives For Innovation: Hearing Before the Subcomm. on Courts and Competition Policy of the H. Comm. on the Judiciary*, 111th Cong. 2 (2009) (statement of Rep. Henry Johnson, Jr., Chairman, Subcomm. on Courts and Competition Policy) ("Estimates put average development costs as much as \$1.37 billion. It is also without a doubt that the cost of pharmaceutical products, and in particular biologics, is huge.").

106. See *id.* ("In 2007, pharmaceutical expenditures accounted for \$231.3 billion in health care costs, and biologics represented \$40.3 billion of this total.").

107. Council Directive 2004/27, art. 10, 2004 O.J. (L 136) 34, 39 (EC).

108. European Medicines Agency, Comm. for Medicinal Products for Human Use, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Non-Clinical and Clinical Issues; Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin*, 3, EMA/CHMP/BMWP/32775/2005 (Feb. 22, 2006), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003957.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003957.pdf).

109. See generally Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs), Canadian Minister of Health: Health Products and Food Branch (Jan. 30, 2008), available at [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/consultation/2009-03-seb-pbu-notice-avis-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/consultation/2009-03-seb-pbu-notice-avis-eng.pdf).

110. As Senator Hatch said, "When we adopted the 1984 Hatch–Waxman law, we were in an era of small molecule medicine and large patient population blockbuster drugs. Times have changed. It appears that we are rapidly entering an era of large molecule medicine and small patient population drugs." 148 CONG. REC. 15,677 (2002).

the drug (NDA) and biologic (BLA) approval processes in parallel.<sup>111</sup> Among other significant changes,<sup>112</sup> the Act did away with the expensive and cumbersome requirement for biologics license applicants to obtain a separate Establishment License Application (ELA) for their manufacturing facilities.<sup>113</sup>

Currently, the FDA approves drugs and some biologics under the so-called § 505 NDAs,<sup>114</sup> while most biologics are approved with § 351 BLAs.<sup>115</sup> That would traditionally mean that CDER handles the § 505 NDA applications and CBER handles the § 351 BLA applications. However, in the years running up to the new law, the FDA began transferring authority over certain classes of products from CBER to CDER, such as chemically synthesized biologic-analogues,<sup>116</sup> monoclonal antibodies, and therapeutic proteins.<sup>117</sup> The transfer likely reflected an FDA understanding that, given the growth of the biologic drug industry, some biologic drugs would be better regulated by CDER as a drug. It also reinforced the need for a generic biologics pathway to bring the two parallel pathways closer in line with one another.

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111. Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, § 123(f), 111 Stat. 2296, 2324 (codified at 21 U.S.C. § 355) (“The Secretary of Health and Human Services shall take measures to minimize differences in the review and approval of products required to have approved [BLAs] . . . and products required to have approved [NDAs] . . .”).

112. The FDAMA did far more than require parallel approval processes:

FDAMA also completely rewrote 42 U.S.C. § 262(a) by codifying the BLA requirement for all biologics, [and] reaffirmed that all biological products are subject to the FDCA . . . . Section 123(g) of FDAMA, which stated that no licensed biologic requires a section 505 application, sparked controversy in that it could possibly be interpreted to mean that biologics could use the ANDA provisions of FDAMA. In response, the House passed a technical amendment clarifying that this section could not be construed to apply ANDA provisions to biologics, although this bill did not reach the Senate for consideration.

See Dudzinski, *supra* note 8, at 177.

113. Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products, 61 Fed. Reg. 24,227 (May 14, 1996); Elimination of Establishment License and Product License, 64 Fed. Reg. 56,441 (Oct. 20, 1999).

114. 21 U.S.C. § 355 (2006).

115. *Id.* Devices are approved under 21 U.S.C. § 360.

116. FDA, INTERCENTER AGREEMENT BETWEEN THE CENTER FOR DRUG EVALUATION AND RESEARCH AND THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (1991), available at <http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm> [hereinafter INTERCENTER AGREEMENT].

117. See Drug and Biological Product Consolidation, 70 Fed. Reg. 14,978, 14,978 (Mar. 24, 2006) (explaining that the FDA transferred regulatory responsibility for protein products away from CBER to CDER).

For drugs, there are three approval pathways—a follow-on applicant can file (1) a normal NDA,<sup>118</sup> (2) a Paper NDA,<sup>119</sup> or (3) an Abbreviated New Drug Application (ANDA) (the so-called § 505(b)(2) approval), which uses the FDA's earlier finding of safety and efficacy of the brand-name drug.<sup>120</sup>

For biologics not considered an exception to the rule (e.g., human growth hormone),<sup>121</sup> there is currently only one approval plan—a follow-on applicant must file a complete BLA.<sup>122</sup> The follow-on applicant must then repeat all the clinical trials that the innovator conducted and cannot rely on old approval data to support the abbreviated application, with certain exceptions (e.g., Avonex approval, a rare exception that tends to prove the rule).<sup>123</sup>

Full biologic approval is a significant and costly regulatory burden.<sup>124</sup> The applicant must file extensive pharmacology, pharmacokinetics, toxicokinetics, and tissue-distribution studies; toxicology studies; and a separate Good Laboratory Practices requirement.<sup>125</sup> Further, applicants

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118. 21 U.S.C. § 355(b)(1); Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,950 (Apr. 28, 1992).

119. Publication of "Paper NDA" Memorandum, 46 Fed. Reg. 27,396, 27,396–97 (May 19, 1981).

120. 21 U.S.C. § 355(j)(1)–(2)(A).

121. These exceptions may be historical accident, although the statutory definitions of biologic and drug overlap:

Thus, by May 1981, FDA had divided protein-based therapeutics between the Bureaus, with human insulin, human growth hormone (and analogues), thymosin, ACTH, and endorphins under the purview of the Bureau of Drugs, while interferons, vaccines (for hepatitis B and influenza), and serum albumin fell under the jurisdiction of the Bureau of Biologics. There is little evidence of the deliberations and motivations for these distinctions, although one notes that the products in the Bureau of Drugs are physically smaller, and less complex proteins.

Dudzinski, *supra* note 8, at 163.

122. For more information on the pre-application process see James G. Kenimer et al., *Biologics*, in *FDA REGULATORY AFFAIRS: A GUIDE FOR PRESCRIPTION DRUGS, MEDICAL DEVICES, AND BIOLOGICS* 129, 137 (Douglas J. Pisano & David Mantus eds., 2004) (discussing clinical requirements in detail).

123. Avonex is a follow-on interferon beta-1b biologic. Biogen used comparability data with the first-to-file product, Betaseron, and received approval under § 505 from the FDA, despite the fact that the two have a different number of amino acids, one is glycosylated while the other is not, and there are two amino acid differences in the chain. *See Berlex Lab., Inc. v. FDA*, 942 F. Supp. 19, 21–22 (D.D.C. 1996) (unsuccessfully challenging the abbreviated approval).

124. *See* Grabowski et al., *supra* note 18, at 1292–93 (discussing R&D costs for drugs and biologics in terms of the Hatch–Waxman Act).

125. For an excellent discussion of those requirements, see Kenimer, *supra* note 122, at 129–52.

have to repeat the many requirements of Phase I (small trials meant to demonstrate safety only), Phase II (larger trials meant to demonstrate safety and efficacy), and Phase III human clinical trials (large, complex trials meant to demonstrate how safe and effective the treatment is compared to existing treatments).<sup>126</sup> Hence, the FDA needed an abbreviated approval pathway for biologic drugs to help alleviate this burden, spur competition, and increase widespread access to medicines.

## II. THE BIOSIMILARS ACT AND THE HATCH–WAXMAN ACT: THE TWO PARALLEL PATHWAYS, COMPARED

### A. Legislative History

In the years before the passage of the Biosimilars Act, legal scholars began arguing somewhat convincingly that the Hatch–Waxman Act itself authorized a generic pathway for biologics that qualified as drugs, regardless of whether the innovator product had been approved under § 351.<sup>127</sup> However, the FDA maintained that the Hatch–Waxman Act did not apply to generics of biologic products approved under § 351.<sup>128</sup> This led to the inevitable question: With all the advances in biotechnology, why would Congress not create a generic pathway for biologics?

Many detractors of a generic pathway argued to Congress that protein therapies and other biologics were simply too complex to safely allow for abbreviated generic follow-on applications.<sup>129</sup> Biotech companies have even argued that producing a generic biologic could not “be done because of the difficulty in producing biologics. In fact, they don’t believe there is such a thing as a generic biologic.”<sup>130</sup>

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126. *Id.*

127. *See, e.g.,* Dudzinski, *supra* note 8, at 171 (“It is questionable whether Title I of Hatch–Waxman applies only to ‘new drugs’ and excludes biologics because there was no biotechnology industry per se when it was enacted nor was the Act motivated by apparent concerns for generic biologics.”).

128. *See* FDA Interpretation, *supra* note 19 (finding so partly because the predictable atomic structure of single-molecule drugs allowed for a reliable determination of bioequivalence, while biologics, even small-protein biologic drugs, are harder to predict); *see also supra* text accompanying note 19.

129. *See 2004 Hearing, supra* note 33, at 72–73 (Statement of Dr. William Hancock) (arguing that results would always vary from batch to batch due to posttranslational modifications).

130. Deirdre Davidson, *Reform Eyed for Landmark Drug Law*, NAT’L L.J. LEGAL TIMES, Sept. 11, 2000, at 1.

On the other hand, advocates for the law countered that the FDA's standards for safety could remain high while "eliminating unnecessary requirements"<sup>131</sup> and that it "will be essential" to create generic competition in order "to reduce costs to consumers and health care providers, and to stimulate continued innovation."<sup>132</sup> Further, mechanisms of production and purification of biologics have progressed at a rapid pace, new technology has developed quickly, and advocates now argue that generic versions of biologics are well within a follow-on company's technical grasp.<sup>133</sup>

Regardless of the arguments, the drive to legislate a new generic biologics pathway began in earnest in 2007 with the 110th Congress. The 110th Congress debated four competing bills, each variously generous to the innovator or generic industry.<sup>134</sup> By the end of the term, it appeared that members had reached a compromise deal. However, the bill failed passage when key members of the generic industry withdrew their support pending the election of Barack Obama, hoping instead for a better bill under a Democratic Administration, House, and Senate.<sup>135</sup>

The Biosimilars Act was reintroduced in the 111th Congress in 2009 in modified form, and Congress finally passed it as part of the healthcare reform bill in 2010.<sup>136</sup>

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131. One of the FDA's primary institutional mandates (if not *the* primary one) is consumer safety. See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) ("Viewing the FDCA as a whole, it is evident that one of the Act's core objectives is to ensure that any product regulated by the FDA is 'safe' and 'effective' for its intended use.").

132. *2004 Hearing, supra* note 33, at 60 (statement of Dr. Carole Ben-Maimon, President and CEO, Barr Research, Inc.).

133. *Id.*

134. See Kelly & David, *supra* note 29, at 124–30 (discussing—complete with tables and charts—the four bills; the Inslee bill, *supra* note 40; the Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. (2007); the Pathway for Biosimilars Act, H.R. 5629, 110th Cong. (2008); and the Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007)).

135. Czaban et al., *supra* note 22, at 2. Whether the bill they ended up getting was in fact better remains to be seen.

136. See *supra* notes 3–4 and accompanying text (discussing the new Healthcare Reform Act). Senator Edward Kennedy originally introduced the bill during the 110th Congress, and it was reintroduced and adopted by the 111th Congress with a number of significant changes adopted from Eshoo's competing bill. Compare Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. § 2(a)(2) (2007) (Kennedy bill) (defining biosimilar as "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product"), with Pathway for Biosimilars Act, H.R. 5629, 110th Cong. § 101(a)(2) (2008) (Eshoo bill) (adding that "biosimilar[s]" must be "highly similar"). Ironically, Congress largely rejected the bill put

*B. The Biosimilars Act, Generally*

The Biosimilars Act amends the definition of *biologic* under § 262(i) of the PHSA,<sup>137</sup> grants the FDA statutory authority to issue biosimilar and interchangeable determinations, and gives the agency broad deference in determining the procedural details of the scheme.<sup>138</sup> It also sets up a patent-challenge system<sup>139</sup> and offers exclusivity incentives for the first follow-on applicant to file.<sup>140</sup> It grants the agency ten years to come up with a comprehensive pathway to encourage and expedite follow-on generic applications in an effort to drive down the cost of health care.<sup>141</sup> Additionally, the bill grants biologics innovator applicants twelve years of data exclusivity for their clinical studies.<sup>142</sup> Further, the Act includes a complex patent-challenge system administered through the FDA, which is intended to reduce costly litigation by resolving patent disputes before they reach court.<sup>143</sup> Lastly, there is a user-fee provision that grants the FDA fee-setting authority in order to recoup some of the costs of the new regulations.<sup>144</sup> The twelve-year provision, the patent challenge system, and the fee-setting provisions are beyond the scope of this Comment.<sup>145</sup>

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forth by Rep. Henry Waxman, the eponymous sponsor of the Hatch–Waxman Act, perhaps because it granted only a three-year data exclusivity term. *See* Access to Life-Saving Medicines Act, H.R. 1038, 110th Cong. (2007).

137. 42 U.S.C. § 262(i) (2006) (defining “biological product”); Biosimilars Act, Pub. L. No. 111-148, § 7002(b), § 351(i), 124 Stat. 119, 814–15 (2010) (to be codified at 42 U.S.C. § 262(i)).

138. Biosimilars Act § 7002(a)(2)(k).

139. *Id.* § 7002(a)(2)(l).

140. *Id.* § 7002(a)(2)(k)(6).

141. *Id.* § 7002(e).

142. *Id.* § 7002(a)(2)(k)(7).

143. *See id.* § 7002(a)(2)(l) (laying out the new patent-challenge system). For more on the loopholes, quirks, and vagaries the new system presents, see Czaban, *supra* note 22, at 5–9 (calling the new patent challenge system the “Kabuki Theater of Biologics Patent Litigation”).

144. Biosimilars Act § 7002(f). The Prescription Drug User Fee Act (PDUFA) expires in 2012 and is limited to user fees for prescription drugs, but is anticipated to be reapproved in expanded form. *See* Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (1992) (codified at 21 U.S.C. §§ 301, 343-1, 376, 379 (2006)) (detailing the strictures of the PDUFA); *see also* Alicia Mundy, *Generic Drug Makers Line Up Behind Proposal for FDA Fees*, WALL ST. J., Feb. 16, 2011, at B1 (“The Obama administration has supported user fees for generic drugs . . . . Obama’s budget . . . included \$40 million in anticipated revenue from such fees in 2012. Any such plan would require approval from Congress.”).

145. The contentious twelve-year data exclusivity provision in effect creates a strong new form of intellectual property protection for innovator biologics. *See* Interview with Hans Sauer, Assistant Chief Counsel, Biotechnology Indus. Org., in Washington, D.C. (Jan. 21,

### C. Definition of Biologics

The Biosimilars Act changed the statutory definition of a biologic under the PHSA. The old definition, with the relevant amendments italicized, is as follows:

The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, *protein (except any chemically synthesized polypeptide)*, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.<sup>146</sup>

The addition of the language concerning proteins is vital, as the majority of biologic drugs approved as drugs in the past under § 505 with an NDA (e.g., insulin, human growth hormone) are variants of recombinant DNA proteins that occur naturally in the body.<sup>147</sup> Other than those grandfathered in,<sup>148</sup> it would appear that, moving forward, all innovator protein therapies not chemically synthesized will now likely be approved again under § 351 of the PHSA as biologics, using a BLA.<sup>149</sup> Whether CDER will retain examination authority over them remains to be seen.

Here, Congress granted the FDA an expanded definition of *biologics*, one that would encompass nearly all therapeutic protein products. The FDA

2011) (“It is a sad commentary on the state of the patent system that biotech firms felt the need to lobby hard for this alternative form of intellectual property to run to.”) (on file with author). However, the twelve-year provision is now statutory, and so the debate is largely academic. Besides, legal authors have already commented on the twelve-year provision *ad nauseum*. See, e.g., Maxwell R. Morgan, *Regulation of Innovation Under Follow-on Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanism*, 11 COLUM. SCI. & TECH. L. REV. 93 (2010) (supporting the twelve-year provision).

146. 42 U.S.C. § 262(i) (as amended by Biosimilars Act § 7002(b)).

147. See *supra* Part I (discussing the history of regulation before the Hatch–Waxman Act).

148. See Biosimilars Act § 7002(c) (“An application for a biological product may be submitted under section 505 of the [FDCA] if [it] is . . . the subject of an application approved under such section 505 no later than the date of enactment of this Act.”).

149. The primary exception is directed at biologic-analogues of chemically synthesized drugs like Miacalcin, approved in 2005 before the legislation was drafted. Miacalcin is a “chemically synthesized polypeptide . . . cited as the reference product in the section 505(b)(2) application for Fortical, a recombinant salmon calcitonin product. The Fortical application was approved in 2005 . . . Congress thus had this precedent before it when drafting the language in question.” Jim Shehan, Vice President, Legal, Gov’t & Quality Affairs, Novo Nordisk, Inc., Address at the FDA Public Meeting (Nov. 2, 2010), [http://www.novonordisk-us.com/Images/PDF/NN\\_Shehan\\_Testimony\\_October\\_27\\_FINAL.pdf](http://www.novonordisk-us.com/Images/PDF/NN_Shehan_Testimony_October_27_FINAL.pdf).

has traditionally interpreted the “or analogous product” clause broadly,<sup>150</sup> including such things as monoclonal antibodies, therapeutic proteins, and immunoglobulin products. By specifically defining *proteins*, Congress has assumed this interpretation and made it statutory—making it clear that protein products are squarely biologics and will be subject to § 351 as amended, not § 505. So while many biologics will still qualify as drugs under the statutory definition, they most likely will be regulated under the new § 351(k) approval rules.

#### D. Bioequivalence, Biosimilarity, and Interchangeability

The Hatch–Waxman Act resulted in a highly detailed procedural pathway (the ANDA) that asks generic applicants to show their drug is “bioequivalent” to corresponding innovator drugs, meaning therapeutically equivalent.<sup>151</sup> The FDA lists innovator and generic drugs in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*), with an appropriate “equivalence” grade (generally, an A-type or B-type rating).<sup>152</sup>

In contrast, the Biosimilars Act creates two statutory determinations for a follow-on biologic product: biosimilar and interchangeable. These can be analogized to the distinction in single-molecule drugs between products that are bioequivalent (i.e., those that receive a B rating in the *Orange Book*), versus products that are both bioequivalent and interchangeable (i.e., those that receive an A rating). In the former case, bioequivalence generally means the generic drug can only be prescribed for the same indications as the innovator, not substituted for it.<sup>153</sup> In the latter, the pharmacists can switch a patient’s prescription of one for the other without asking.<sup>154</sup> Further, the legislation gives the FDA the power to decide *not* to allow for

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150. 21 C.F.R. § 600.3(h) (2010) (defining *analogous products*).

151. Hatch–Waxman Act, Pub. L. No. 98-417, § 101(2)(A)(iv), 98 Stat. 1585, 1586 (1984) (codified at 21 U.S.C. § 355(b), (j), (l); 35 U.S.C. § 156, 271, 282 (2006)). The applicant must provide “information to show that the new drug is bioequivalent to the listed drug referred to in clause (i)” with the exception that if the applicant admits the drug has a different active ingredient, additional studies are needed. *Id.*

152. ORANGE BOOK, *supra* note 16.

153. RICHARD R. ABOOD, PHARMACY PRACTICE AND THE LAW 141 (6th ed. 2011) (“For example, if the *Orange Book* lists four pharmaceutically equivalent drugs, two with a B rating and two with an A rating, the pharmacist may interchange the two drugs with A ratings.”).

154. *See id.* (cautioning that switching is only allowed if the drug is therapeutically equivalent or bioequivalent to the prescribed drug).

either biosimilar or interchangeable determinations for some classes of biologics.<sup>155</sup>

Thus, the new law will lead to the creation of what is in essence an Abbreviated Biologics License Application (ABLA),<sup>156</sup> with the two standards resulting in far different, more unpredictable results than Hatch–Waxman.

### 1. *Biosimilarity*

The Biosimilars Act defines *biosimilarity* to require: (1) a follow-on product must be “highly similar” to the reference product in terms of structure, and (2) there can be “no clinically meaningful differences” between the biological product in terms of safety, purity, and potency.<sup>157</sup> This broad language allows the FDA to fashion clinical testing requirements based on (1) similar chemical structure and (2) statistical bioequivalence in clinical outcomes and efficacy. For instance, the FDA must define “clinically meaningful.”

To compare, for drugs NDAs must include data relating to (1) chemistry, (2) manufacturing, (3) controls, (4) labeling, (5) testing, (6) animal studies, (7) clinical studies, and (8) bioavailability<sup>158</sup> requirements.<sup>159</sup> ANDAs, on the

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155. Biosimilars Act, Pub. L. No. 111-148, § 7002(a)(2)(k)(8)(E)(i), 124 Stat. 119, 808 (2010) (to be codified at 42 U.S.C. § 262(k)(8)(E)(i)).

156. Note that I have created the Abbreviated Biologics License Application (ABLA) term. Others have hypothetically called this future pathway “§ 351(k) approval” in keeping with the common practice of referring to approvals by their original statutory section number. *E.g.*, Steven A. Nash & Rebecca Workman, *A New Pathway for Follow-on Biologics*, 20 FED. CIR. B.J. 193, 194 (2010) (“[T]his Article will refer to an application for licensure of a biosimilar or interchangeable product as a ‘351(k) application.’”).

157. The PHS Act was amended to include the following definition of *biosimilar*:

(2) The term ‘biosimilar’ or ‘biosimilarity,’ in reference to a biological product that is the subject of an application under subsection (k), means—

(A) that the biological product is *highly similar* to the reference product notwithstanding minor differences in clinically inactive components; and

(B) 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.

Biosimilars Act, § 7002(b) (emphasis added) (internal quotation marks omitted).

158. See 21 U.S.C. § 355(j)(8) (2006) (defining bioavailability as “the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action”).

159. This is derived from the FDA’s applications for drugs or biologics, which uses different nomenclature. See David J. Pizzi & Janet C. Rae, *Formatting, Assembling, and Submitting the New Drug Application (NDA)*, in FDA REGULATORY AFFAIRS: A GUIDE FOR PRESCRIPTION DRUGS, MEDICAL DEVICES, AND BIOLOGICS 81, 81–115 (Douglas J. Pisano & David Mantus eds., 2004) (including a chart mapping the various study requirements).

other hand, require (1)–(5) but can prove bioequivalence<sup>160</sup> comparative to the innovator drug in lieu of any of (6)–(8).<sup>161</sup> Somewhat analogously, BLAs must submit data relating to (1)–(8) and must further submit establishment standards.<sup>162</sup>

The Biosimilars Act provides that the FDA will derive determinations of biosimilarity from: (1) analytical studies showing the biological product is highly similar, (2) animal studies, including [an] assessment of toxicity, and (3) clinical studies sufficient to demonstrate safety, purity, and potency in relation to the innovator biologic.<sup>163</sup>

These factors are analogous to drug bioequivalence, animal studies, clinical studies, and bioavailability requirements. This seems to encompass the full requirements, with an additional required showing of “highly similar.” However, a clause makes any of these three requirements optional at the FDA’s discretion.<sup>164</sup> Additionally, the ABLA applicants must submit data showing four other factors.<sup>165</sup>

Thus, the burden of evidence for generic biologic applicants could be far higher than it is for generic drugs under Hatch–Waxman, even in relation to the higher burdens of biologics innovators.<sup>166</sup> ABLA applicants will also

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160. See 21 C.F.R. § 320.24 (2010) (describing methods to demonstrate bioequivalence, including (1) pharmacokinetic studies, (2) pharmacodynamic studies, (3) comparative clinical trials, and (4) in vitro studies). For statutory authority, see 21 U.S.C. § 355(j)(8)(B).

161. Animal studies, clinical studies, and bioavailability studies are a combination of the precursor toxicology studies, phase I–III clinical trials, and pharmacokinetics, toxicokinetics, and tissue distribution studies. See Kenimer et al., *supra* note 122, at 136–43 (detailing clinical requirements).

162. See 21 C.F.R. § 601.2 (general BLA requirements); *id.* § 601.12 (2010) (supplements or changes to an existing license or BLA); see also Kenimer & Jessop, *supra* note 122, at 146–52 (explaining at BLA data requirements, including the data showing the establishment can reproduce batches in a safe, clinically pure, and consistent manner).

163. Biosimilars Act, Pub. L. No. 111-148, § 7002(a), 124 Stat. 119, 804 (2010) (to be codified at 42 U.S.C. § 201).

164. See *id.* § 7002(a)(2)(k)(2)(A)(ii) (“The Secretary may determine, in the Secretary’s discretion, that an element described [above] is unnecessary in an application submitted under this subsection.”).

165. *Id.* § 7002(a)(2)(k)(2)(A)(i). The four other factors are: (1) the products have the same mechanism of action (but only to the extent that it is known); (2) the intended conditions for use have been previously approved for the reference product; (3) the products have the same route of administration, dosing, and strength; and (4) the facilities used to process and package the product meet certain standards. *Id.*

166. See Grabowski et al., *supra* note 18, at 1293 (“Given that biologics made with different cell lines or manufacturing facilities might exhibit different efficacy and safety characteristics, it is likely that some clinical trial data will be required before a follow-on biologic is approved.”).

have to submit studies related to purity, manufacturing studies, mechanism of action, and possibly further animal, human, and other trials. In effect, ABLA applicants may be required to submit most or all of these data again just to achieve a biosimilar determination. ABLA applicants have reason to be hopeful, however. In July 2010 (after the passage of the Biosimilars Act), the FDA approved a generic of a complex carbohydrate drug without the need for any clinical trials proving safety or efficacy.<sup>167</sup> While the drug was technically not a biologic according to the FDA,<sup>168</sup> at least one senior FDA official has cited its approval as an example of how permissive the FDA's thinking on biologics abbreviated approval could be.<sup>169</sup>

It also appears from the plain language that the highly similar determination itself is a much higher bar than Hatch–Waxman's bioequivalent standard. The biosimilars standards outlined above will require additional studies showing that the physical chemical structures of the two biologics are highly similar.<sup>170</sup> The FDA can waive toxicity or certain Phase II and Phase III trials upon a “good enough” showing of chemical similarity, but in practice the FDA is unlikely to waive most of these requirements, erring on the side of caution.<sup>171</sup> This could mean applicants will have a relatively harder—and costlier—time achieving a biosimilarity determination than they currently have getting bioequivalent determinations for single-molecule drugs.<sup>172</sup> Until the FDA issues guidance and grows comfortable with the process, these ABLAs are not likely to

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167. *See Momenta Receives OK for Generic Version of Lovenox*, ABC NEWS.COM (July 23, 2010) (on file with author) (describing FDA approval of a generic version of enoxaparin (trade name Lovenox), a low molecular weight heparin, without requiring any safety or efficacy studies).

168. *Id.* (“Lovenox is technically not a biologic drug—a complex medicine made inside special, live cells rather than by combining chemicals. However, ‘functionally and effectively it is’ . . . because it is derived from animal materials and is heavily processed and purified.”) (quoting Tim Anderson, Analyst for Berstein Research).

169. *See BioCentury This Week: Biosimilars: Will the Path Work?*, *supra* note 38 (statement of Dr. Rachel Behrman, Assoc. Dir. for Med. Pol’y in CDER). Behrman cited Momenta's approval of M-Enoxaparin as exemplary of U.S. thinking on generic clinical requirements, as opposed to Europe, where they often require new safety and efficacy testing. As she stated, “We may be able to take the European experience [with biosimilars] and go one step further.” *Id.*

170. *See supra* note 157 (citing the highly similar standard).

171. *See generally* Supplements and Other Changes to an Approved Application, 69 Fed. Reg. 18,728, 18,729 (Apr. 8, 2004) (discussing the FDA's adoption of a risk-based approach to the regulation of pharmaceuticals to enhance safety).

172. *See* Grabowski et al., *supra* note 18, at 1293 (estimating costs of the average ADNA at \$1–2 million and estimating that costs of the average generic biologic approval have been \$10–40 million in Europe).

provide significant—if any—application cost savings.<sup>173</sup> That will probably take decades.

## 2. *Interchangeability*

Putting the lower-bar biosimilar determinations aside, the additional interchangeability standards seem even more difficult to meet, and the costs may not outweigh the benefits associated with generic status. The statute defines interchangeable as a biological product that “(i) is biosimilar to the reference product; [and] (ii) can be expected to produce the *same clinical result* as the reference product in any given patient.”<sup>174</sup>

This is a higher clinical standard than the biosimilar “no clinically meaningful differences” standard.<sup>175</sup> Now the FDA must determine the level of statistical tolerance it will assign to the word interchangeable as opposed to equivalent.<sup>176</sup>

Ironically, this could also indicate that biologics that have a *better* clinical result cannot achieve interchangeable status, regardless of evidence that the mechanism of action is the same, the dosage is the same, and the structure is identical. That remains true even if the generic is a slight improvement over the innovator biologic.

However, that is not the end of the interchangeability requirements. In addition:

for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of *alternating or switching between* use of the biological product and the reference product [*must*] *not [be] greater than* the risk of using the reference product without such alternation or switch.<sup>177</sup>

Ostensibly, this additional “switching” test data requirement is out of a fear that an interchangeable determination could result in patients switching between biologics. Congress could have addressed this concern

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173. See Bruce Babbitt, White Paper, *The Dawn of Biosimilar Development in the United States: Key Legislative Aspects and Next Steps for BioPharma Manufacturers*, 5 (PAREXEL Consulting 2010) (on file with author) (noting at present “very few companies are expected to pursue the interchangeability option as presented in the [Biosimilars] Act”).

174. Biosimilars Act § 7002(a)(2)(k)(4)(A)(i), (ii) (2010) (emphasis added).

175. *Id.* § 7002(a)(2)(k)(2)(A)(i)(I)(aa) (allowing biosimilarity to be shown through analytical studies showing the follow-on is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” (emphasis added)).

176. Cf. ORANGE BOOK, *supra* note 16, at x (using for drugs “a 0.05 level of [statistical] significance”).

177. Biosimilars Act § 7002(a)(2)(k)(4)(B) (emphasis added).

in other ways. For instance, it could have added labeling requirements that patients cannot switch from one biologic or follow-on once a system of treatment has begun, or then only with a doctor's approval. Or they could have counseled doctors to only prescribe certain biologics at the beginning of treatment or changed the law so that a determination of interchangeability only applies to the initial prescription filled, not subsequent courses of the medication. To be sure, this would not have eliminated the risk associated with switching completely; the only way to do that would be to require cumbersome testing. However, by requiring such a high switching bar in addition to other safety requirements, the FDA is again erring on the side of caution. Thus, the statute imposes an unnecessarily high burden on follow-on applicants seeking interchangeability determinations.

Ominously, the FDA has indicated in the past that the mechanisms of switching may make it *impossible* to achieve an interchangeable determination.<sup>178</sup> This indicates the FDA may be predisposed to deny applicants seeking interchangeability in cases where switching is likely.

#### *E. New Approval Procedures: What an ABLA Might Look Like*

Hatch–Waxman dictates stringent guidelines of what clinical data applicants must provide with an ANDA and explicitly states that the FDA does not have the authority to require more clinical data than the statute requires.<sup>179</sup>

Conversely, the Biosimilars Act grants the FDA exceedingly broad authority to increase or decrease the testing and data requirements. Indeed, the FDA can decide that science does not currently allow for *any* biosimilar or interchangeable determinations for non-protein products.<sup>180</sup>

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178. As one FDA official said in 2007, “For many follow-on protein products—and in particular, the more complex proteins—there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.” Janet Woodcock et al., *The FDA's Assessment Of Follow-on Protein Products: A Historical Perspective*, 6 NATURE REVS. DRUG DISCOVERY 437, 440 (2007).

179. Hatch–Waxman Act, 21 U.S.C. § 355(j)(2)(A)(viii) (2006) (“The Secretary may not require that an abbreviated application contain information in addition to that required by [the Act].”).

180. See Biosimilars Act § 7002(a)(2)(k)(8)(E)(i).

The Secretary *may* indicate in a guidance document that the science and experience, as of the date of such guidance, with respect to a product or product class (*not including any recombinant protein*) does not allow approval of an application for license as provided under this subsection for such product or product class.

This broad statutory grant will likely allow the FDA to adjust policies and procedural requirements as technology develops and requires different (and hopefully more efficient) testing methodologies to assure safety and efficacy of follow-on biologics.

It is currently unclear if the FDA will “rank” interchangeability determinations, the way Hatch–Waxman does equivalency, with an *Orange Book*-style rating.<sup>181</sup> It should. It would be confusing to have two separate working definitions of *biosimilar/interchangeable* and *therapeutically equivalent* within the medical treatment field in the two separate pathways. Instead, the prudent thing to do is adopt a parallel (or at least analogous) definition of *interchangeable* for biologics. Having an indexed listing of all biologics and their associated biosimilars and interchangeables will increase certainty, help avoid frivolous litigation, and reduce development costs by increasing the quality and ease of co-extant biologics research.

To do this, the FDA should begin by forming an analogous *Orange Book* (say, a *Purple Book*) for biosimilarity and interchangeability ratings and rank biologics accordingly.

#### F. *Notice-and-Comment or Guidance-Plus Rulemaking?*

Traditionally, the Administrative Procedure Act (APA)<sup>182</sup> confines agency rulemaking to one of three avenues: formal rulemaking, informal (notice-and-comment) rulemaking, and policy statements that do not have the force and effect of law.<sup>183</sup> Nonetheless, statutes can require more or less procedure and replace the rulemaking requirements of the APA.<sup>184</sup> Beyond the APA and the agency’s enabling statute, courts cannot normally impose further procedural requirements.<sup>185</sup> The agencies, however, are free to impose further procedures,<sup>186</sup> and the President, through the Office of

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*Id.* (emphases added).

181. See ORANGE BOOK, *supra* note 16, at xiii–xxi (listing levels and rankings of equivalents).

182. Pub. L. No. 79-404, 60 Stat. 237 (1946) (codified at 5 U.S.C. §§ 551–59, 701–06).

183. ANDREW F. POPPER ET AL., ADMINISTRATIVE LAW: A CONTEMPORARY APPROACH 66 (2d ed. 2010).

184. See *Marcello v. Bonds*, 349 U.S. 302, 310 (1955) (allowing exemptions from the Administrative Procedure Act (APA), but suggesting that they must be “express”).

185. *Vt. Yankee Nuclear Power Corp. v. Natural Res. Def. Council, Inc.*, 435 U.S. 519, 524 (1978) (stating that “the [APA] established the maximum procedural requirements which Congress was willing to have the courts impose upon agencies in conducting rulemaking procedures”).

186. *Id.* (“Agencies are free to grant additional procedural rights in the exercise of their discretion.”) See Recommendations of the Administrative Conference of the United States,

Management and Budget (OMB) and its rulemaking division, the Office of Information and Regulatory Affairs (OIRA) can and often does impose additional procedural hurdles.<sup>187</sup>

Due to the increasingly onerous and time-consuming nature of “informal” notice-and-comment rulemaking, agencies are increasingly using policy and guidance documents, which offer some notice or opportunity for public comment but lack the many “ossified” constraints of informal rulemaking.<sup>188</sup> For instance, many agencies issue “guidance documents,” which lack many of the procedural hurdles of normal notice-and-comment rulemaking.<sup>189</sup> Ostensibly, they do this in an attempt to get around notice-and-comment rulemaking requirements.

These guidance documents may claim to lack the force and effect of law but may de facto have significant legal impact.<sup>190</sup> Some argue agencies do this in an attempt to avoid judicial review<sup>191</sup> and to avoid other procedural

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Agency Policy Statements, Rec. 92-2, 1 C.F.R. § 305.92-2 (1992), available at <http://www.law.fsu.edu/library/admin/acus/305922.html> (recommending “the ‘circumstances of particular proceedings’ that should move agencies to consider such additional procedures”).

187. See, e.g., OFFICE OF MGMT. & BUDGET, EXEC. OFFICE OF THE PRESIDENT, OMB BULL. NO. 07-02, FINAL BULLETIN FOR AGENCY GOOD GUIDANCE PRACTICES (2007) [hereinafter FINAL BULLETIN], at 20–22 (imposing procedure on guidance documents).

188. See David L. Franklin, *Legislative Rules, Nonlegislative Rules, and the Perils of the Short Cut*, 120 YALE L.J. 276, 284 n.33 (2010) (citing Todd D. Rakoff, *The Choice Between Formal and Informal Modes of Administrative Regulation*, 52 ADMIN. L. REV. 159, 166 (2000) (asserting that agencies are “avoiding ‘ossification’ . . . by increased use of ‘interpretative rules’ and ‘policy statements’”)); see also Lubbers, *supra* note 44, at 473 (“This precipitous drop in final rules published in the *Federal Register*—and the even more dramatic drop in proposed rules published for comment—are clear indications of the ossification of rulemaking or at least increased agency reluctance to use the APA’s rulemaking process.”).

189. For procedural hurdles that guidance documents retain see generally FINAL BULLETIN, *supra* note 187.

190. See, e.g., *Gen. Elec. Co. v. EPA*, 290 F.3d 377 (D.C. Cir. 2002) (striking down polychlorinated biphenyl (PBC) risk assessment guidance as having legal effect and hence requiring notice and comment); see also COMM. ON GOV’T REFORM, NON-BINDING LEGAL EFFECT OF AGENCY GUIDANCE DOCUMENTS, H.R. REP. NO. 106-1009, at 9 (2000) (“[A]gencies have sometimes improperly used guidance documents as a backdoor way to bypass the statutory notice-and-comment requirements for agency rulemaking and establish new policy requirements.”).

191. Gwendolyn McKee, *Judicial Review of Agency Guidance Documents: Rethinking the Finality Doctrine*, 60 ADMIN. L. REV. 371, 372 (2008) (“Agencies increasingly issue guidance documents . . . in lieu of engaging in the more costly, and binding, informal rulemaking process that ultimately affords regulatees with opportunities for judicial review.”); Franklin, *supra* note 188, at 307 n.160 (noting the lack of any provisions allowing for judicial review as evidence of a possible attempt to avoid it). But see Connor N. Raso, Note, *Strategic or Sincere?*

hurdles imposed by the Executive Branch and Congress.<sup>192</sup> At a minimum, however, guidance documents allow agencies to make changes in their approval procedures with less unaccountability to the public.

This guidance practice has become particularly prevalent at the FDA in recent years.<sup>193</sup> In 1997, the FDA issued guidance laying out its so-called “Good Guidance Practices” (GGP).<sup>194</sup> The same year, Congress mandated that certain aspects of the 1997 GGP document become law and codified others.<sup>195</sup>

Congress did this via the Food and Drug Administration Modernization Act (FDAMA), which required the FDA to solicit public input before issuing guidance documents.<sup>196</sup> In doing so, Congress endorsed a new form of significant rulemaking—a sort of “guidance-plus” requiring public comment but not the full range of APA requirements.<sup>197</sup>

In 2007, the Executive Branch, through the OMB, took notice of the increasing use of these guidance documents by issuing the Final Bulletin for Agency Good Guidance Practices.<sup>198</sup> In it, OMB recognized that agencies often used guidance to produce significant regulation<sup>199</sup> and added

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*Analyzing Agency Use of Guidance Documents*, 119 YALE L.J. 782, 782 (2010) (arguing that agencies do not often use guidance documents to avoid judicial review).

192. See LOUIS FISHER, CONG. RESEARCH SERV., RL33151, COMMITTEE CONTROLS OF AGENCY DECISIONS 21, 31 (2005) (finding that even post-*Chadha*, Congress finds many ways to exert control, through committees and budgetary means, over agency action). See generally LOUIS FISHER, CONG. RESEARCH SERV., RS22132, LEGISLATIVE VETOES AFTER CHADHA (2005) (reviewing *Chadha* and its impact on the veto systems in various legislatures); FINAL BULLETIN, *supra* note 187, at 20–22 (requiring added procedural requirements for agency guidance documents).

193. See U.S. FOOD AND DRUG ADMIN., *Biologics Guidances*, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/ucm2006010.htm> (last visited Mar. 3, 2011) (collecting FDA guidance documents).

194. The Food and Drug Administration’s Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8961 (Feb. 27, 1997).

195. The FDA Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, § 405(h)(1)(A), 111 Stat. 2296, 2368 (codified at 21 U.S.C. § 371) (requiring the Secretary to publish a legislative rule codifying aspects of the 1997 GGP guidance).

196. *Id.* § 405(h)(1)(D) (“For guidance documents that set forth existing practices or minor changes in policy, the Secretary shall provide for public comment upon implementation.”).

197. See Nina A. Mendelson, *Regulatory Beneficiaries and Informal Agency Policymaking*, 92 CORNELL L. REV. 397, 401 (2007).

198. See, e.g., FINAL BULLETIN, *supra* note 187.

199. *E.g., id.* at 2 n.2 (citing S. REP. NO. 105-43, at 26 (2007) (raising concerns about public knowledge of, and access to, FDA guidance documents, lack of a systematic process for adoption of guidance documents and for allowing public input, and inconsistency in the use of guidance documents)).

additional procedural hurdles for “economically significant guidance documents,” which have an economic impact of more than \$100 million on the U.S. economy.<sup>200</sup> Notably, the bulletin stated that unless the guidance document is exempted due to an emergency or other appropriate consideration, the agency should observe the notice-and-comment procedures dictated by the bulletin.<sup>201</sup> The Judiciary has also voiced its displeasure at the practice of utilizing guidance documents to circumvent the legal requirements of rulemaking.<sup>202</sup> These rulemaking requirements are where Hatch–Waxman and the Biosimilars Act diverge significantly.

Hatch–Waxman demands that the FDA use notice-and-comment rulemaking procedures to implement the Act.<sup>203</sup> Coupled with the Supreme Court’s decision in *Vermont Yankee Nuclear Power Corp. v. Natural Resources Defense Council, Inc.*, which forbade courts from imposing additional procedural hurdles on rulemakings,<sup>204</sup> the FDA is required to use only notice-and-comment rulemaking to implement the provisions of Hatch–Waxman.

Conversely, the broad language of the Biosimilars Act confers sweeping authority to the FDA in regulating a detailed procedural pathway similar to

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200. *Id.* at 7.

201. *Id.* at 21. In general:

. . . when an agency prepares a draft of an economically significant guidance document, the agency shall:

- a. Publish a notice in the Federal Register announcing that the draft document is available;
- b. Post the draft document on the Internet and make it publicly available in hard copy . . .
- c. Invite public comment on the draft document; and
- d. Prepare and post on the agency’s website a response-to-comments document.

*But see id.* at 21 (subjecting these requirements to the discretion of the agency head).

202. As the D.C. Circuit has opined:

One guidance document may yield another and then another and so on. Several words in a regulation may spawn hundreds of pages of text as the agency offers more and more detail regarding what its regulations demand of regulated entities. Law is made, without notice and comment, without public participation, and without publication in the Federal Register or the Code of Federal Regulations.

*Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1020 (D.C. Cir. 2000) (emphasis added).

203. Hatch–Waxman Act, 21 U.S.C. § 355 (2006) (“The Secretary of Health and Human Services shall promulgate, in accordance with the notice and comment requirements of section 553 of title 5, United States Code, such regulations as may be necessary for the administration of section 505 of the Federal Food, Drug, and Cosmetic Act, as amended by sections 101, 102, and 103 of this Act, within one year of the date of enactment of this Act.”).

204. *Vt. Yankee Nuclear Power Corp. v. Natural Res. Def. Council, Inc.*, 435 U.S. 519, 524 (1978).

(or different from) the Hatch–Waxman pathways.<sup>205</sup> The Biosimilars Act includes language suggesting the Secretary issue “final guidance” with “opportunity for public comment,”<sup>206</sup> possibly endorsing this new guidance-plus form of rulemaking. Indeed, to the best of my knowledge, the FDA’s recent enabling statutes are unique in providing technically “nonbinding” guidance with public comment as a primary means of rulemaking authority.<sup>207</sup>

As such, the agency is encouraged to use these guidance-plus documents, which provide greater flexibility and avoid the burdens imposed by informal rulemaking but which some think unreviewable by courts.<sup>208</sup>

Significantly, the Biosimilars Act itself requires that the agency gather public comment before issuing any final guidance.<sup>209</sup> It is unclear, however, what an opportunity for public comment alone entails. Possibly, this is a codification of the OMB Bulletin’s “public feedback” requirement, which does not require the agency to respond to the comments (as notice-and-comment does).<sup>210</sup> Thus, Congress has created and endorsed a new form of rulemaking through the Biosimilars Act and the FDAMA—one significant enough to require public comment, but one that does not demand the procedural requirements of notice-and-comment rulemaking and is not subject to the judicial precedent that guides (and burdens) notice-and-comment rulemaking.

In reality, the agency generally holds extensive public conferences and hearings and solicits comments from the public and stakeholders—indeed, it is in the FDA’s best interest to obtain as much input as possible when

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205. See Biosimilars Act § 7002(a)(2)(k)(8)(A), (B)(ii) (2010).

206. *Id.* § 7002(a)(2)(k)(8)(A), (B)(i).

207. See Mendelson, *supra* note 197 at 401 (“With the exception of these FDA procedures, however, no other statute requires [comment] procedures for agency guidance documents.”).

208. See McKee, *supra* note 191, at 372 (arguing FDA guidances are unreviewable by courts). *Contra* Raso, *supra* note 191, at 793–95, 801, 802 (arguing guidance is reviewable by the courts).

209. See Biosimilars Act § 7002(a)(2)(k)(8)(A) (including the statutory words “after the opportunity for public comment,” which require the agency to elicit comment before final guidance issues).

210. FINAL BULLETIN, *supra* note 187, at 15 (“Public comments submitted under these procedures on significant guidance documents are for the benefit of the agency, and this Bulletin does not require a formal response to comments . . . . In some cases, the agency, in consultation with the Administrator of Office of Management and Budget’s (OMB’s) Office of Information and Regulatory Affairs, may in its discretion decide to address public comments by updating or altering the significant guidance document.”).

crafting procedures and testing paradigms for biologics.<sup>211</sup> For the Biosimilars Act, it has already begun to do this.<sup>212</sup> But that does not undercut the fact that Congress has endorsed this new form of rulemaking as a way to escape the procedural rigors—and possibility of judicial review—associated with notice-and-comment rulemaking.

To be clear, Congress has provided that the FDA can issue extensive regulations with far-reaching economic effects over a period of ten years using only guidance-plus documents, which ostensibly have no binding legal effect. Such guidance-plus documents cannot be considered mere policy documents. Scholars and the Congressional Budget Office expect the guidances to have billion-dollar consequences.<sup>213</sup> As such, it would be prudent—and in line with executive suggestion<sup>214</sup>—for the FDA to issue full notice-and-comment rulemaking for the broad regulation implementing the statute.

### *G. Judicial Review and Legislative Rules*

Any future biosimilars guidance-plus documents may be exempted from the APA § 706 judicial review provisions<sup>215</sup> because the organic biosimilars statute mandates the use of the guidance procedure.<sup>216</sup> However, even if the guidance-plus documents are held reviewable, courts will likely rule that these guidance-plus documents are policy documents and do not require informal rulemaking.<sup>217</sup>

If the guidance-plus documents are ever challenged in court as invalid because they were not made pursuant to notice-and-comment procedures,

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211. The FDA benefits from the community's and stakeholders' expertise. Public input increases public trust and decreases the likelihood of legal challenge.

212. See, e.g., FDA Public Meeting, *supra* note 45 (discussing the Biosimilars Act).

213. See Czaban, *supra* note 22, at 2 n.8, 3 (discussing costs and expressing ambivalence about potential savings for the cost of health care but citing the Congressional Budget Office's estimate of \$6–7 billion in savings); Grabowski et al., *supra* note 18, at 1291, 1293 (discussing costs generally, and providing the \$10–40 million average cost of abbreviated approval in Europe as instructive).

214. FINAL BULLETIN, *supra* note 187, at 15 (Although “this Bulletin does not require agencies to provide notice and an opportunity for public comment on all significant guidance documents before they are adopted, but it is often beneficial for an agency to do so when they determine that it is practical.”).

215. APA § 10(b), 5 U.S.C. § 706 (2006).

216. See generally Biosimilars Act § 7002(a)(2)(k)(5) (2010).

217. See 21 C.F.R. § 10.115(d) (2010) (declaring guidance lacks the force and effect of law).

the courts will have to determine if the guidances qualify as substantive legislative rulemaking—that is, whether they have the force of law.<sup>218</sup>

To determine if an agency document qualifies as substantive rulemaking, the courts generally apply some form of a “legal effects test” like the one used in *Cement Kiln Recycling Coalition v. EPA*.<sup>219</sup> Here, potential clinical testing guidance documents will probably not have the force and effect of law because they only proscribe procedural, highly technical testing requirements for FDA approval.<sup>220</sup> Also, the fact that the FDA may opt not to allow for determinations of biosimilarity or interchangeability in most cases militates toward finding that those regulations lack the force and effect of law.

Indeed, the D.C. Circuit has held that similar guidance documents at another agency (the Mine Safety & Health Administration) are not legislative.<sup>221</sup> Under the test previously used by the D.C. Circuit, the FDA guidance documents are not legislative. This is because the FDA: (1) is acting only pursuant to the organic biosimilars statute,<sup>222</sup> (2) only publishes most guidance on the FDA website and in the *Federal Register*, but not in the *Code of Federal Regulations*,<sup>223</sup> (3) expressly disclaims any invocation of legislative powers,<sup>224</sup> and (4) amends prior guidance but cannot amend

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218. See *United States v. Mead Corp.*, 533 U.S. 218, 227 (2001) (acknowledging that agencies’ interpretive choices may influence courts but do not bind them in every case).

219. 493 F.3d 207, 226–27 (D.C. Cir. 2007). In this case, the court applied a three-factor test to determine if a guidance was a rulemaking. First, how did the agency characterize the action? Second, did the agency issue the guidance in the *Federal Register* or the *Code of Federal Regulations*? Third, did the guidance have a binding effect on the parties or the agency? *Id.*

220. Accord Kelly & David, *supra* note 29, at 132 (regarding the 2009 proposals for biosimilars laws, “On its face, the guidance described in proposed legislation likewise fails the legal effects test because it would not have the force and effect of law.”).

221. See *Am. Mining Cong. v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1112 (D.C. Cir. 1993). The four-part test announced by the D.C. Circuit is as follows:

(1) whether in the absence of the rule there would not be an adequate legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties, (2) whether the agency has published the rule in the Code of Federal Regulations, (3) whether the agency has explicitly invoked its general legislative authority, or (4) whether the rule effectively amends a prior legislative rule.

If the answer to any of these questions is affirmative, we have a legislative, not an interpretative rule.

*Id.* at 1112.

222. Biosimilars Act §§ 7002–7003(2010).

223. See *infra* note 239 and accompanying text (comparing rules published in the *Code of Federal Regulations* with good guidance only noticed in the *Federal Register*).

224. See, e.g., FDA, GUIDANCE FOR INDUSTRY: STATISTICAL APPROACHES TO ESTABLISHING BIOEQUIVALENCE 1 (Jan. 2001), <http://www.fda.gov/downloads/Drugs/>

prior legislative rules.<sup>225</sup> Therefore, any biosimilars guidance documents will likely be unreviewable by any court.<sup>226</sup>

However, even assuming for the sake of argument that the guidances are ultimately found to be reviewable and that a court might hold them invalid as legislative rules, the practical likelihood of court challenges is minimal.<sup>227</sup> Further, any court challenge would also have to overcome finality and ripeness requirements,<sup>228</sup> although the fact that the legislation calls for final guidance may undercut a finality challenge to some extent.<sup>229</sup>

As a result, the agency will likely be free to issue good guidance documents without the fear of judicial review or the threat of an adverse ruling, despite the fact that those documents will have an overwhelmingly substantive effect—for instance, if the agency determines that there can be no interchangeability for any class of biologics.

This means the agency has broad flexibility—and power—over the new biosimilar and interchangeable determinations. The Biosimilars Act gave the FDA the discretion to allow or deny *all* interchangeability determinations for *entire classes* of biologics.<sup>230</sup> If the past is any indication,<sup>231</sup> the FDA will be reticent to aggressively implement the legislation, instead erring on the side of caution.<sup>232</sup> If it issues difficult or

GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf. Like most guidance, it includes the following disclaimer:

This guidance represents the Food and Drug Administration's current thinking on this topic. *It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.* An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

*Id.* (emphasis added).

225. *See, e.g., id.* The FDA has since discarded this guidance.

226. *But cf.* *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1019 (D.C. Cir. 2000) (holding similar Environmental Protection Agency guidance reviewable). If the FDA couches the guidance documents in the imperative, courts may find that they are binding and notice-and-comment procedures must be observed. *See id.* at 1023 (“[T]he entire Guidance, from beginning to end . . . reads like a ukase. It commands, it requires, it orders, it dictates.”). *See generally* JEFFREY S. LUBBERS, A GUIDE TO FEDERAL AGENCY RULEMAKING 73–104 (2006) (detailing the many ways in which guidance documents are subject to review).

227. *See Raso, supra* note 191, at 802 (“On balance agencies face a lower litigation risk from guidance documents because the lower probability of engaging in litigation outweighs the greater probability of winning once challenged.”).

228. *Id.*

229. A more substantive discussion of the ripeness and finality doctrines is beyond the scope of this Comment.

230. Biosimilars Act §7002(2)(k)(3) (2010).

231. *See Woodcock et al., supra* note 178, at 437–42 (offering a historical perspective).

232. To be fair, unsafe yet approved products have killed consumers in the past (e.g., Vioxx), so the FDA has good reason to be cautious. *See Hawthorne, supra* note 47, at 109–22

impossible-to-meet biosimilarity and interchangeability guidelines, the FDA may fail to achieve the explicit statutory purpose of the Biosimilars Act—a significant reduction in prescription drug costs through generic competition.<sup>233</sup>

### III. RECOMMENDATIONS TO THE FDA

The FDA has ten years from March 3, 2010, to issue final guidelines for ABLA pathways under the amended § 351(k).<sup>234</sup> In that time, the FDA should continue to gather as many comments from the public, scientists, and interested parties as possible.<sup>235</sup> Then, it should provide notice in the *Federal Register* and allow further comment on proposed classifications and guidelines, following standard notice-and-comment procedures. Finally, it should issue clear notice-and-comment rules on product classifications and overall procedures but retain case-by-case guidance-plus flexibility in clinical testing requirements. Otherwise it runs the risk of attempting a major regulatory overhaul using only legally nonbinding policy documents. That would provide insufficient oversight and responsiveness to the public, which could lead to a regulatory scheme that does not fulfill the statutory purpose and actually hinders the growth of the generic biotech industry.

#### A. *Classifying Biologics Through Legislative Rules*<sup>236</sup>

First, the FDA should provide detailed notice-and-comment rules that indicate clearly how and where each individual type of biologic will be classified. Recently, the FDA issued a similar guidance for class-specific clinical testing in the drug field.<sup>237</sup> Indeed, the Biosimilars Act itself suggests this when it discusses “product class-specific guidance.”<sup>238</sup> These

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(discussing the difficult decision to allow thalidomide for HIV treatment even though it causes birth defects).

233. See *supra* note 18 and accompanying text (discussing cost savings).

234. Under the statute, the sponsor of an innovator biologic *may* submit an NDA instead of a BLA during the transition period that expires in 2020. Biosimilars Act § 7002(e).

235. The FDA has begun to do this. *E.g.*, FDA Public Meeting, *supra* note 45.

236. Legislative rules are regulations promulgated by informal notice-and-comment rulemaking.

237. CDER, GUIDANCE FOR INDUSTRY, BIOEQUIVALENCE RECOMMENDATIONS FOR SPECIFIC PRODUCTS 1 (June 2010), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072872.pdf> (stating future drug bioequivalence guidance will be tailored to product classes).

238. Biosimilars Act § 7002(a)(2)(k)(8)(D):

final rules should be issued following the notice-and-comment rulemaking requirements of the APA and should be published in the *Code of Federal Regulations*, in addition to the *Federal Register*,<sup>239</sup> to provide the biologics industry with a clear picture of the regulatory landscape, increase certainty in the market, and encourage generic manufacturers to apply for more licenses. The FDA has the authority to utilize stronger procedural safeguards than the statute requires, and the OMB has encouraged agencies to utilize full notice-and-comment procedures over guidance “whenever practical.”<sup>240</sup> This is just such a situation.

The FDA should be careful to make these categories clear and well defined. They should avoid case-by-case ad hoc approvals to prevent wasteful clinical research, reduce approval costs, and increase certainty, hence allowing more effective interchangeability determinations. This will encourage follow-on companies to submit narrowly tailored, detailed clinical tests. It will also cut down on the paperwork and bureaucratic delay.<sup>241</sup>

One common complaint with the FDA is a lack of predictability in the examination requirements<sup>242</sup>—a complaint the FDA can address by issuing clear guidelines with the force of law behind them. In fact, the industry has voiced fears that generic companies may not seek interchangeability determinations *at all* because of the high evidentiary bar<sup>243</sup>—something the FDA must work diligently to counteract. Doing so would also allow for judicial review of the broader substantive rulemaking involved, while

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If the Secretary issues product class-specific guidance . . . such guidance shall include a description of . . . the criteria that the Secretary will use to determine whether a biological product is highly similar to a reference product in such product class; and . . . the criteria, if available, that the Secretary will use to determine whether a biological product meets [interchangeability standards].

239. When a “good guidance” rises to the level of a major regulatory shift, the FDA will usually publish the regulations in the *Code of Federal Regulations*. Compare 21 C.F.R. § 320.24 (2010) (ADNA bioequivalence requirements), and 21 C.F.R. § 601.2 (general BLA requirements), with Supplements and Other Changes to an Approved Application, 69 Fed. Reg. 18,728, 18,729 (Apr. 8, 2004) (to be codified at 21 C.F.R. pt. 314) (adopting a risk-based approach to the regulation of pharmaceuticals to enhance safety).

240. FINAL BULLETIN, *supra* note 187, at 15 (“Pre-adoption notice-and-comment can be most helpful for significant guidance documents that are particularly complex, novel, consequential, or controversial.”).

241. See *Hawthorne*, *supra* note 47, at 94–95 (describing how, before electronic filing, paper applications often arrived at the FDA’s Rockville offices in full U-Haul trucks).

242. See *id.* at 128 (“They keep changing the rules.”).

243. See, e.g., Bruce Babbitt, *supra* note 173 (“[A]t this very early stage of biosimilar development in the US very few companies are expected to pursue the interchangeability option . . .”).

possibly preventing a legal challenge to the entire scheme that could result if the FDA utilized only guidance-plus documents to regulate biosimilars and maintained that none of them had the force and effect of law.

The FDA should use legislative rules to divide the separate classes of biologics—small proteins, insulin-like analogues, monoclonal antibodies, blood products, progenitor cells, and others.<sup>244</sup> In 2005, David Dudzinski catalogued the entire scope and various levels of complexity in protein biologic products.<sup>245</sup> While he published his work before Congress began debate on the Biosimilar Act, it is still highly relevant.

He writes first that the FDA should recognize the distinction between: “‘*biologic*’ *biologics*” (i.e., vaccines, toxins, antitoxins, and viral and pathogen particles), which are highly unpredictable, truly dependent on source materials, and should not have generic analogues; and “‘*biologic*’ *drugs*” (i.e., protein macromolecules), which are more predictable, allow for independent manufacturers to arrive at the same result, and for which generics should be allowed.<sup>246</sup>

Dudzinski implicitly advocated for less strenuous biosimilarity and interchangeability standards for biologic drugs versus biologic biologics. The FDA should heed this advice and scale determinations of (and clinical requirements for) interchangeability and biosimilarity accordingly to streamline the application process. A classification matrix would allow the FDA the flexibility of determining varying testing standards within each class of macromolecule without making the process standardless and arbitrary. Otherwise, companies will have even less certainty about what they are required to file. Therefore, the FDA should institute a product classification system.

Indeed, the FDA’s recent behavior allowing small-molecule protein biologics to apply as drugs under § 505 indicates the FDA’s willingness to create a sliding scale of biologics categories.<sup>247</sup> Under the grandfather provisions of the Biosimilars Act, these small-molecule protein manufacturers will probably be able to file § 505 applications until the new regulations become effective.<sup>248</sup> However, biologic products that fall into similar categories but that the FDA has not previously approved under

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244. The FDA has begun to do this. See *supra* note 117 and accompanying text.

245. Dudzinski, *supra* note 8, at 154.

246. *Id.* at 185–87.

247. See INTERCENTER AGREEMENT, *supra* note 116 (allowing protein products to file NDAs).

248. See Biosimilars Act, Pub. L. No. 111–148, 124 Stat. 804, § 7002(e) (2010) (to be codified at 42 U.S.C.) (legislating a grandfather or “safe harbor” provision for ten years).

§ 505 should also be allowed to file with CDER in the interim to increase certainty in the approval process and avoid inequitable results.

Dudzinski also catalogs those biologic drugs that are most likely to benefit from an abbreviated approval pathway.<sup>249</sup> First, biological macromolecules can be broken down into four categories: polysaccharides, polynucleotides (DNA, RNA), lipids, and polypeptides (proteins). Amongst these known macromolecules, the easiest and most likely to benefit from generic pathway approval are polynucleotides and polypeptides, as they are the most widely used already and likely easiest to reproduce.<sup>250</sup>

He then divides known proteins with therapeutic benefits into categories based primarily on the size of the macromolecules, something the FDA should do. In shorthand, his five categories are (1) small proteins, (2) medium-sized proteins, (3) larger non-antibody-based proteins, (4) antibodies, and (5) very large molecules.<sup>251</sup> He bases the categories on complexity and ease of synthesis, in ascending order, and the FDA should do the same. By issuing clearly delineated product-class rules, the FDA can breathe certainty and efficiency into the regulatory process in a field where it is sorely needed. Laying out clear product classes with the force of law is the first step in creating a straightforward and predictable regulatory framework that puts generic applicants on notice of approval requirements and allows them to obtain FDA approval quickly and efficiently. Clear product classes will lead to lower healthcare costs and greater access to life-saving medicines for those who cannot afford brand-name prices.

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249. Dudzinski, *supra* note 8, at 185–87.

250. *Id.*

251. *See id.* at 185–87. Dudzinski’s categories are as follows:

Therapeutic peptides containing eight to ten amino acids that are small in size (1000–1300 daltons), such as oxytocin, somatostatin, or gonadotropin. These small proteins are reproducible through chemical synthesis rather than the recombinant DNA and so are more likely to generate widely repeatable results.

Medium-sized proteins (such as insulin, glucagons, or bivalirudin) usually contain between twenty and seventy amino acids (3000–7000 daltons). These are more appropriate for recombinant DNA, as they are mostly copies of human proteins.

Larger non-antibody protein-based therapeutics (15,000 to 100,000 daltons) (e.g., human growth hormone, erythropoietin) which are harder to synthesize, but have been widely made for years using recombinant DNA, with high purity and yield.

Larger antibodies that have large stretches of nonactive (or “variable”) regions and active or “constant” regions (approximately 150,000 daltons).

Very large molecules (e.g., Factor VIII, a coagulation factor) have always been regulated as biologics and contain over 2300 amino acids (over 200,000 daltons).

*Id.*

*B. Flexible Guidance for Interchangeability and Biosimilarity Determination Requirements*

Second, the FDA should use the flexibility of guidance-plus documents to issue individualized biosimilarity and interchangeability testing requirements within each classification. Advances in testing technology and biologic understanding will inevitably allow the FDA to make those determinations using fewer clinical tests in the future, and they must have the regulatory agility to react quickly to those changes in order to avoid undue delay or ossification in the rulemaking.<sup>252</sup>

To paraphrase Dudzinski, not all biologics are created equal.<sup>253</sup> Some will require less testing to prove interchangeability or biosimilarity. For instance, small macromolecules with eight amino acids and no glycosylation are currently easily reproducible in the laboratory.<sup>254</sup> There is no reason why a generic company cannot produce an identical macromolecule like this on an industrial scale; testing standards should reflect this scientific reality.<sup>255</sup> In the case of more easily predictable small-molecule proteins, studies of statistical bioequivalence are far less important than studies showing the chemical identities match.

Conversely, with some larger macromolecules where less is known about the mechanism of action, companies should be allowed to conduct large-sample population studies showing statistically bioequivalent outcomes that are at least as effective as the innovator biologic. However, for now the FDA should not grant extremely large macromolecules interchangeability (e.g., the very-large-class factor VII coagulants, live vaccines, and other endlessly unpredictable biologics). There is too much room for variability or mutation, and science cannot yet adequately predict the clinical effects of such biologics.<sup>256</sup> Indeed, one top FDA official has said as recently as 2007

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252. Rakoff, *supra* note 188 (claiming agencies can avoid ossification through the use of interpretative rules and policy statements).

253. Dudzinski, *supra* note 8, at 185.

254. FDA Public Meeting, *supra* note 45 (response of Jim Shehan, Vice President for Legal, Government & Quality Affairs, Novo Nordisk).

255. See *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing before the Subcomm. on Health of the H. Comm. On Energy and Commerce*, 110th Cong. 32, 35 (2007) [hereinafter Woodcock Statement] (statement of Janet Woodcock, Director of CDER) (finding the ability to predict clinical comparability of two products depends on their chemical structure and the ability to scientifically demonstrate structural similarity, using the Omnitrope approval as an example).

256. Proteins are subject to many unpredictable physical and chemical changes that can affect their efficacy. They are subject to post-translational modifications, three-dimensional structural changes (e.g., via their disulfide bonds), and protein aggregation. Even changing

that current science will allow for biosimilarity or interchangeability determinations for smaller but not larger protein products.<sup>257</sup>

In sum, issuing notice-and-comment rules for ever-changing scientific standards would be deleterious and should be avoided. Therefore, the FDA should instead employ guidance to lay out testing requirements.

*C. Fundamental Assumptions: Proposing a Balancing Test in Clinical Trials*

The FDA should also employ a balancing test between therapeutic and chemical biosimilarity. The FDA can scale the therapeutic testing based on the unpredictability of the macromolecule, thus maintaining a high level of consumer safety. For instance, for innovator biologics with a strong effect, unpredictable size and conformation, or wholly unknown mechanisms of action, the FDA should require further therapeutic clinical testing.<sup>258</sup> On the other hand, where the size is small, the conformation known, or the mechanisms of action relatively well understood, the FDA should require a lesser showing of therapeutic similarity for biosimilarity or interchangeability determinations.

The FDA bases drug bioequivalence on the fundamental assumption that equivalent average testing data proves therapeutic equivalence.<sup>259</sup> Similarly, the FDA should base biologic biosimilarity on the fundamental assumption that similar clinical outcome (i.e., more tolerant) average testing data balanced with data showing chemical structural similarity proves biosimilarity. Likewise, the FDA should premise biologic interchangeability on the fundamental assumption that biosimilar and safe average testing data proves that biologics will result in the same clinical outcome (i.e., interchangeability). This balancing of clinical data and chemical structural similarity reflects the spirit of the legislation and provides the most efficient regulatory pathway to generic competition. In addition, since the FDA will already have approved the innovator biologic for safety and it has probably

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the temperature of protein can alter the structure and utility through a process called “denaturing,” as when you cook an egg and then cool it down. *See* DENNISTON ET AL., *supra* note 23, at 533–64.

257. Woodcock Statement, *supra* note 255 (“Although [a generic pathway for biologics] currently may be possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.”).

258. *Accord* Grabowski et al., *supra* note 18, at 843 (“Analysts predict that more complicated molecules will have less competition from follow-on products, which will enter the market more slowly than traditional generic pharmaceuticals.”).

259. *See* CHOW ET AL., *supra* note 41, at 91 (defining the fundamental assumption).

been on the market for a number of years, there is a lesser need for a high showing of clinical safety in the biosimilar follow-on.

Importantly, the field of biostatistics has advanced rapidly in the past twenty years.<sup>260</sup> In 1997, the FDA issued guidance allowing generic manufacturers to use population (PBE), individual (IBE), and average bioequivalence (ABE) studies.<sup>261</sup> These different methods can produce better biostatistical results within variable subject matter.<sup>262</sup> The FDA retracted the use of IBE and PBE for drugs in 2003 because researchers found that population and individual bioequivalence studies could be manipulated through poorly conducted controls.<sup>263</sup> However, the FDA is now aware of these problems, can adjust to solve them, and so should use PBE, IBE, and scaled average BE, as well as other advanced statistical techniques, to anticipate high variability in biosimilar batches.<sup>264</sup>

The FDA should consider allowing follow-on biologics applicants to show PBE, or at least incorporate newer forms of biostatistical analysis as they emerge. These and other methods control for the inherent variability of results within biologic-drug-user populations. That is why they need flexibility to alter product-specific testing guidelines as appropriate statistical methods emerge—so the FDA can quickly implement them, creating certainty and letting generic company's statisticians utilize them to show biosimilarity and interchangeability. Using advanced statistical bioequivalence methods<sup>265</sup> that control for interpopulation variability is more appropriate for variable biologics than it is for drugs.

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260. See generally SHEIN-CHUNG CHOW ET AL., STATISTICS IN DRUG RESEARCH: METHODOLOGIES AND RECENT DEVELOPMENTS (2002) (discussing new bioequivalence statistical methods).

261. “The population [Bioequivalence (BE)] approach assesses total variability of the measure in the population. The individual BE approach assesses within-subject . . . as well as the subject-by-formulation interaction.” FDA, GUIDANCE FOR INDUSTRY: STATISTICAL APPROACHES TO ESTABLISHING BIOEQUIVALENCE 3 (Jan. 2001), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf>.

262. *Id.*

263. SCOTT PATTERSON & BYRON JONES, BIOEQUIVALENCE AND STATISTICS IN CLINICAL PHARMACOLOGY 179 (2006) (“After FDA reviewed data from application of such techniques in practice, the IBE and PBE methods were removed from their guidance in 2003.”).

264. *Id.* at 186–88 (describing scaled BE as being useful for highly variable drugs and citing characterizations of the average bioequivalence (ABE) requirements for highly variable subject matter as “too stringent.”).

265. See generally CHOW ET AL., *supra* note 260 (presenting new biostatistical methods).

Most importantly, the FDA should allow for product-specific equivalence boundaries.<sup>266</sup> Otherwise, the volatile nature of biologics (as compared with single-molecule drugs) will mean that aberrant or unexpected clinical results in certain tests, even if not statistically significant under some more advanced statistical models, could derail an abbreviated biologics application.

The FDA should use product-specific statistical equivalence boundaries (i.e., tolerance levels) similar to or more liberal than those they use for drugs<sup>267</sup> in order to encourage generic applicants to file and so that they do not set the bar too high. Indeed, the nature of the word *biosimilarity* suggests it should be a lower bar than therapeutic equivalence. If, on the whole, the follow-on is as equally effective (or even more so) as the innovator, it should be afforded interchangeability status under the Biosimilars Act, regardless of the known or unknown mechanism of action or the actual conformational structure. If the generic applicant can show the chemical structure is highly similar, the FDA should apply the balancing test and allow a more permissive statistical tolerance level. This effectively balances consumer safety with the regulatory realities and statutory purpose of the law—to speed biologic generics to market.

Lastly, because of the statutory language mandating the “same clinical outcome” for interchangeability status, some researchers have advocated “two-sided” biostatistical testing, where the follow-on applicant must prove that his drug is not “worse,” but also not “better” than the innovator.<sup>268</sup> Those in favor of two-sided testing argue that a biologic cannot be interchangeable if it does not produce a statistically equivalent outcome, even if that outcome is better.<sup>269</sup> They argue that such a result proves that the follow-on is not interchangeable, but rather is different (in some biobeneficial way), and so the product does not deserve interchangeable status. They caution against the dangers of such products, which could show differing adverse consequences years down the road.<sup>270</sup>

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266. Lei Lei et al., *Evaluating Statistical Methods to Establish Clinical Similarity of Two Biologics*, 20 J. BIOPHARM. STAT. 1, 62, 72 (2010) (“Given that biopharmaceutical products usually have more variation, product-specific equivalence boundaries may be the right choice.”).

267. ORANGE BOOK, *supra* note 16, at x (for drugs, “two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved”).

268. FDA Public Meeting, *supra* note 45 (response of Dr. Shein-Chung Chow). Statistical bioequivalence means using statistical regressions of population data to show that two groups are bioequivalent.

269. *Id.*

270. *Id.*

The FDA should not feel obligated to use two-sided testing. Where a follow-on biologic's clinical outcomes are more statistically effective than the innovator, the follow-on should be granted interchangeability status (as long as studies show that the follow-on is as safe as the innovator). This is well within a reasonable interpretation of the "same clinical outcome" language and better suits the statutory purpose of the Act—to allow generics to market.

#### CONCLUSION

It is up to the FDA to enforce Congress's will and vigorously pursue the explicit statutory purpose of the Biosimilars Act—lowering prescription drug costs by allowing for rigorous generic biologic competition. Accordingly, the FDA must work hard to allow generic competition with innovator products. It can do this through a well-defined classification system produced through notice-and-comment rulemaking that allows robust generic competition in the areas of biologics where barriers to market entry and cost of manufacture are high. This way, the FDA can encourage innovation *and* price competition while still maintaining the highest standards of consumer safety and remaining accountable to the public.