

# FOLLOW-ON BIOLOGICS: LEGAL, SCIENTIFIC, AND POLICY CONSIDERATIONS

JEREMIAH J. KELLY\*

## INTRODUCTION

In the face of extreme costs to patients for brand-name, or “innovator,” therapeutic biologics, momentum is building to provide the U.S. Food and Drug Administration (FDA) with the statutory authority to approve abbreviated applications for follow-on biologics. FDA defines *follow-on biologics*, also termed *biosimilars*, *follow-on protein products*, or *subsequent entry biologics*, as therapeutic protein and peptide products that are intended to be sufficiently similar to a product already approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)<sup>1</sup> or licensed under section 351 of the Public Health Services Act (PHSA)<sup>2</sup> to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the previously approved product for approval of the current product.<sup>3</sup> The purported benefit to patients of follow-on biologics, assuming a highly similar safety and efficacy profile to the innovator product, is their reduced cost.<sup>4</sup> Such savings are the expected result of lower costs associated with bringing a follow-on biologic to market.<sup>5</sup>

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\* Mr. Kelly is an Associate in the food and drug and commercial litigation practices at the law firm of Whiteford, Taylor & Preston in Baltimore, Maryland. Mr. Kelly is a former legislative analyst at the U.S. Food and Drug Administration, where he served in the Office of Legislation and the Office of the Chief Counsel. Mr. Kelly was a member of FDA’s Working Group on Follow-on Protein Products. J.D., 2008, University of Maryland School of Law (Baltimore, MD); M.P.P., 2003, George Washington University (Washington, D.C.).

1. 21 U.S.C. §§ 301–399 (2006 & West Supp. 2009).

2. 42 U.S.C. §§ 201 to 300ii-4 (2006).

3. *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. 20, 24–25 (2007) (statement of Dr. Janet Woodcock, Deputy Comm’r & Chief Med. Officer, Food & Drug Admin.), available at [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110\\_house\\_hearings&docid=f:40500.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_house_hearings&docid=f:40500.pdf) [hereinafter Woodcock Statement I].

4. See, e.g., Henry Grabowski et al., *The Market for Follow-on Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1291 (2006) (discussing assumptions about the economic impact of developing a market for follow-on biologics).

5. See *id.* at 1292–93 (explaining the costs associated with new drug development and that follow-on entrants might not incur all of the costs associated with clinical trials); Kevin Outterson & Aaron S. Kesselheim, *How Medicare Could Get Better Prices on Prescription Drugs*, 28 HEALTH AFF. w832,

The debate over follow-on biologics is multi-faceted. Interested parties dispute FDA's assertion that it lacks statutory authority to approve such products,<sup>6</sup> the ability of scientific characterization methods to inform whether follow-on biologics can be proven similar enough to the innovator product to be safe,<sup>7</sup> the utility and duration of market exclusivity to promote innovative new biologics,<sup>8</sup> and the need to provide incentives to spur a follow-on biologics industry.<sup>9</sup> This Article provides an overview of the current follow-on biologics debate and describes Congress' movement towards creating an abbreviated approval pathway for follow-on biologics.<sup>10</sup>

### I. THE CURRENT LEGAL FRAMEWORK

Other governments, including those of the European Union and Canada, have implemented an abbreviated approval pathway for follow-on biologics.<sup>11</sup> Many commentators have called for the United States to do the same.<sup>12</sup> The existing legal hurdle to such a pathway is peculiarly American. Unlike the statutory schemes for drug approval in other countries, the current U.S. legal framework for drug approval consists of two distinct statutes: the FD&C Act and the PHSA. Full-scale new drug applications (NDAs) for chemically-synthesized drugs are approved by FDA under section 505(b)(1) of the FD&C Act,<sup>13</sup> whereas biologics license applications (BLA) for therapeutic biologics are approved under section 351 of the PHSA.<sup>14</sup> Generally, approval of an NDA or BLA depends on the results of three

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w837 (2009), available at <http://content.healthaffairs.org/cgi/reprint/28/5/w832> (noting estimate savings of \$9.2 to \$12 billion over the next decade if federal laws are expanded to include follow-on biologics).

6. 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, 116 (2009).

7. See Joshua Boger, *Follow-on Biologics: Balancing Innovation and Cost Savings*, HEALTH CARE COST MONITOR, Nov. 12 2009, available at <http://healthcarecostmonitor.thehastingscenter.org/joshuaboger/follow-on-biologics-balancing-innovation-and-cost-savings/> (noting that the determination as to how similar a follow-on product must be to be considered "safe and effective" is a debate ideally settled via scientific analysis by the FDA).

8. See, e.g., Kelly & David, *supra* note 6, at 138–39 (detailing arguments for and against market exclusivity made by biologics innovators, the Department of Health and Human Services (DHHS), and the Generic Pharmaceutical Association (GPhA)).

9. See *id.* (noting that both biologics innovators and DHHS advocate rather lengthy periods of market exclusivity as an incentive to follow-on competition, while the GPhA argues that such an incentive is not needed); Bruce S. Manheim et al., *'Follow-on-Biologics': Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFF. 394, 401–02 (2006) (discussing the need for incentives above and beyond the current patent scheme as it relates to the follow-on biologic industry).

10. See *infra* Parts I–IV.

11. Kelly & David, *supra* note 6, at 116.

12. *Id.* at 116–17; see also Manheim et al., *supra* note 9, at 395 (noting that Congress must act since the FDA is not authorized to make such approvals).

13. 21 U.S.C. § 355(b)(1) (2006 & West Supp. 2009). Section 505 of the FD&C Act is codified at § 355 of Title 21 of the United States Code.

14. 42 U.S.C. § 262(a) (2006 & West Supp. 2009). Section 351 of the PHSA is codified at § 262 of Title 42 of the United States Code.

phases of clinical study and an FDA finding that the benefits of the drug outweigh the risks for a particular use.<sup>15</sup>

The FD&C Act includes two abbreviated approval mechanisms whereby applicants need not perform the full-scale testing required for NDA or BLA approval. First, section 505(j) of the FD&C Act provides for the abbreviated new drug application (ANDA) for generic drugs.<sup>16</sup> A generic applicant may submit an ANDA under section 505(j) of the FD&C Act and receive approval if the applicant proves pharmaceutical equivalence to an innovator product (called the “reference” product) listed in *The Orange Book*.<sup>17</sup> The ANDA applicant does not have to perform clinical trials to support its application, but rather relies on the drug’s therapeutic equivalence to the innovator product for approval.<sup>18</sup> Therefore, generic drugs are the “same” as their reference innovator product. Generally, generic drugs cost less than the innovator product because, without the need for clinical trials, the

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15. See 21 C.F.R. § 314.50 (2009) (outlining the NDA application process); Bryan A. Liang, *Regulating Follow-on Biologics*, 44 HARV. J. ON LEGIS. 363, 384–85 & n.152 (2007) (stating that the goal of the NDA process is to assure that the FDA has enough information to determine: “(1) whether the drug is safe and effective for its proposed uses; (2) whether the drug’s benefits outweigh its risks; (3) whether the drug’s proposed labeling is appropriate; and (4) whether the methods used in manufacturing the drug are adequate to assure its identity, strength, quality, and purity”). In order to submit an NDA, the applicant must first perform pre-clinical animal and *in vitro* studies focusing on the toxicology of the drug as well as previous human experience with the investigational drug. 21 C.F.R. §§ 312.2, .20, .23(a)(8)–(9). These studies, along with numerous additional, required documents, are submitted to the FDA for its approval under an Investigational New Drug (IND) application. See *id.* § 312.23 (outlining the requirements of an IND application). If the FDA approves the application, the applicant must then complete three phases of human clinical trials. *Id.* § 312.21. After this process is complete, the applicant is permitted to submit an NDA. See 21 C.F.R. § 314.50 (requiring those submitting an NDA to include “reports of all investigations of the drug product sponsored by the applicant,” as well as a “summary of the clinical data section of the application, including the results of statistical analyses of the clinical trials”).

16. 21 U.S.C. § 355(j). Generic drugs are therapeutically equivalent to and substitutable for the innovator product. Kelly & David, *supra* note 6, at 136. Therapeutic equivalents “can be expected to have the same clinical effect and safety profile” as the brand-name product when administered to patients and receive an “A” rating in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as *The Orange Book*). OFFICE OF GENERIC DRUGS, U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at iv, x (30th ed. 2010), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf> [hereinafter THE ORANGE BOOK]. Section 505(j) of the FD&C Act requires the ANDA applicant to provide information to show that the proposed generic is: (i) pharmaceutically equivalent (has the same active ingredient, dosage form, route of administration, strength, conditions of use); and (ii) is bioequivalent (the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug) to the listed reference product. 21 U.S.C. § 355(j)(2)(A)(iii)–(v), (8)(B).

17. 21 U.S.C. § 355(j)(2)(A)(iv); THE ORANGE BOOK, *supra* note 16, at iii–iv.

18. See 21 U.S.C. § 355(j)(4)(F) (explaining that drugs that are not the pharmaceutical equivalent to their innovator product will not be approved).

costs to bring the generic to market are less.<sup>19</sup> These savings are passed on to the patient.<sup>20</sup>

Secondly, section 505(b)(2) of the FD&C Act provides for abbreviated approval where the amount of data required to support the application is less than that required by the NDA, but more than that required under the ANDA.<sup>21</sup> Generally, applicants seeking approval of their product under section 505(b)(2) of the FD&C Act perform original clinical studies to support their application.<sup>22</sup> For approval, a section 505(b)(2) applicant also relies, in part, on FDA's finding of safety and efficacy for the innovator product.<sup>23</sup> FDA has also used section 505(b)(2) as an approval pathway for a narrow group of follow-on biologic products, such as follow-on versions of human growth hormone and insulin, where, for historical reasons, the innovator products have been regulated as drugs under the FD&C Act.<sup>24</sup> FDA has not found therapeutic equivalence for recent section 505(b)(2) approvals, such as Omnitrope (somatotropin) and hyaluronidase products,<sup>25</sup> and it may be said that these follow-on biologics are similar, but not the same as their reference innovator products.<sup>26</sup>

The legal dilemma facing follow-on biologics in the U.S. is that there is no abbreviated approval pathway for biologics licensed under section 351 of the PHSA. In other words, section 505(j) and section 505(b)(2) are not available to an applicant seeking to produce a follow-on version of a therapeutic biologic licensed under section 351 of the PHSA.<sup>27</sup> Again, those provisions are only available to an applicant seeking to market a follow-on version of a product approved under

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19. See U.S. Food & Drug Admin., U.S. Dep't of Health & Human Servs., Abbreviated New Drug Application (ANDA): Generics, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm> (last visited June 1, 2010) (noting that abbreviated approval pathways allow for less expensive generic drugs because they do not require "costly and duplicative clinical trials").

20. See *id.* (suggesting that patients benefit from generic drug production because generic prescription drugs cost less).

21. See 21 U.S.C. § 355(b)(2) (providing that an NDA applicant may rely on the results and reports of investigations conducted for a previously approved reference drug); Harriette L. Nadler & Damaris DeGraft-Johnson, *Demystifying FDA's 505(b)(2) Drug Registration Process*, REG. FOCUS, Oct. 2009, at 24, 25 (detailing the shared attributes of sections 505(b)(2) and 505(j) application processes for drugs, and noting that section 505(b)(2) applications may rely on FDA's prior findings of efficacy and safety).

22. See 21 U.S.C. § 355(b)(5)(B)–(C) (2006) (providing that an applicant shall meet with FDA in order to reach an agreement as to the size and design of clinical trials conducted to form the basis of a safety and efficacy claim); Scott Gottlieb, *Biosimilars: Policy, Clinical, and Regulatory Considerations*, 65 AM. J. HEALTH-SYS. PHARMACY (SUPP. 6) S2, S4 (2008), available at [http://www.aei.org/docLib/20080730\\_Biosimilars.pdf](http://www.aei.org/docLib/20080730_Biosimilars.pdf) ("Even under section 505(b)(2), some formal clinical efficacy and safety studies are typically needed for approval of each product.").

23. Kelly & David, *supra* note 6, at 117–18.

24. *Id.* at 116.

25. Woodcock Statement I, *supra* note 3, at 37–38.

26. *Id.* at 30.

27. *Id.* at 24.

section 505(b)(1) of the FD&C Act.<sup>28</sup> Under current law, an applicant attempting to “follow-on” to a biologic licensed under section 351 of the PHSA must submit a full-scale BLA for approval in order to compete with the licensed innovator biologic.<sup>29</sup>

Strong arguments have been made that FDA could approve follow-on versions of biologics licensed under section 351 of the PHSA. One such argument is that the definition of *drug* under the FD&C Act is broad enough to include the term *biologic*.<sup>30</sup> Under the deference likely given to FDA for such a reasonable interpretation following the Supreme Court’s decision in *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*,<sup>31</sup> approval under section 505(b)(2) is permissible.<sup>32</sup> Legal commentators have also argued that FDA could create an abbreviated BLA by notice and comment rulemaking on similar legal grounds.<sup>33</sup> However, the FDA has chosen the conservative path and consistently asserted a lack of statutory authority to approve abbreviated versions of biologics licensed under section 351 of the PHSA.<sup>34</sup> Accordingly, the statutory scheme in the U.S. presents a unique problem that Congress is attempting to resolve.

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28. Kelly & David, *supra* note 6, at 117.

29. 42 U.S.C. § 262(a) (2006 & West Supp. 2009).

30. Many biologics would satisfy the definition of *drug* under the FD&C Act. See 21 U.S.C. § 321(g)(1), (p) (2006) (defining *drug* and *new drug*); *Establishing a Regulatory Pathway for Generic Biotechnology Pharmaceuticals: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 118–19 (2004) (statement of Carole Ben-Maimon, President & Chief Operating Officer, Barr Research, Inc.) (contending that many biologic products have been misclassified and actually fall under the FD&C Act); Edward L. Korwek, *What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis*, 62 FOOD & DRUG L.J. 257, 260 (2007) (arguing that the FD&C Act’s definitions of *drug* and *device* are broad and could capture many biologics products).

31. 467 U.S. 837 (1984); see *id.* at 843–44 (explaining that regulations created by legislative agencies are given controlling weight, “unless they are arbitrary, capricious, or manifestly contrary to the statute”).

32. See *id.* at 843–44 (indicating that, where “Congress has explicitly left a gap for [an] agency to fill,” courts are to defer to an agency’s authority to “elucidate a specific provision of [a] statute by regulation”); Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics Under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 80 (2007) (arguing that “all biologics should be regulated as ‘drugs,’” and that approval under section 505(b)(2) should, therefore, be available to generic biologics).

33. See, e.g., 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, 200, 202 & n.450 (2005) (arguing that FDA’s approval of Avonex opened the door for the administrative BLA based on the decision in Berlex Labs., Inc. v. Food & Drug Admin., 942 F. Supp. 19 (D.D.C. 1996)).

34. Kelly & David, *supra* note 6, at 116 (citing *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway, Hearing Before the H. Comm. on Oversight and Government Reform*, 108th Cong. 19, 20 (2007) (statement of Dr. Janet Woodcock, Deputy Comm’r & Chief Med. Officer, Food & Drug Admin.) [hereinafter Woodcock Statement II]).

## II. FOLLOW-ON BIOLOGICS PRESENT UNIQUE SCIENTIFIC CHALLENGES

In addition to the legal hurdle facing follow-on biologics, it is important to note the significant differences between small-molecule drug products and large-molecule biological drug products. Generally, drug products have a chemical origin, are small molecules (e.g., a statin weighs about 400 Daltons), have simple chemical structures, and have chemical properties that are known and easily reproducible.<sup>35</sup> Therapeutic biologics, on the other hand, are derived from living cells, often through recombinant DNA technology, are significantly larger (e.g., 5,000 to 300,000 Daltons), are complex structures, present challenges to characterize with existing scientific methods, and are difficult to reproduce.<sup>36</sup> Furthermore, therapeutic biologics have stronger immunogenic properties than small molecule drugs, potentially leaving patients irreparably harmed by an adverse immune response.<sup>37</sup> It will be challenging for FDA to determine how “similar” a follow-on product must be to the innovator for approval and what impact on patient health any differences will have.<sup>38</sup> Accordingly, the need to conduct clinical studies for approval may not be significantly reduced when compared to a full-scale BLA, depending on the complexity of the follow-on biologic. Consequently, the more complex the follow-on is, the more robust its application will need to be for approval.

## III. LESSONS FROM HATCH-WAXMAN

Many commentators have cited the Drug Price Competition and Patent Term Restoration Act of 1984,<sup>39</sup> commonly referred to as “Hatch-Waxman,” as a potential model for an abbreviated pathway for follow-on biologics.<sup>40</sup> Hatch-

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35. See FED. TRADE COMM’N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 8 (2009), available at <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf> [hereinafter FTC REPORT] (commenting on the small size of drug products as compared to biologic products); Melissa R. Leuenberger-Fisher, *The Road to Follow on Biologics: Are We There Yet?*, 23 BIOTECHNOLOGY L. REP. 389, 395 (2004) (discussing differences between drugs and biologics and noting that “[r]eproducing chemical drug products is generally straightforward”).

36. FTC REPORT, *supra* note 35, at 3 n.1, 8–9 & n.20.

37. See Kelly & David, *supra* note 6, at 121 & n.48 (noting that differences between the innovator and follow-on could provoke a harmful immunogenic response from a patient).

38. See *id.* at 120 (discussing the various ways a biological drug product and its follow-on product may differ, including bioactivity and immunogenic properties of the drugs, and suggesting a need for “competent analysis” of similarities to the approved biologic).

39. Pub. L. No. 98-417, 98 Stat. 1585 (codified, in relevant part, as amended at 21 U.S.C. §§ 321, 355, 360cc).

40. See, e.g., Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-on Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 585–87 (2008) (discussing the possible benefits of an abbreviated approval pathway for follow-on biologics that is modeled on the Hatch-Waxman Act); Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, B.C. INTELL. PROP. & TECH. F., July 19, 2009, at 20–25 (discussing recent legislation that proposed to create an abbreviated

Waxman was the Congressional response to the high cost of innovator drugs.<sup>41</sup> These amendments balanced the need to lower drug cost to patients against the need for incentives to innovate for brand-name manufacturers.<sup>42</sup> To help achieve this balance, Hatch-Waxman created the section 505(j) ANDA approval pathway for generic drugs and provided 180-day market exclusivity for the first generic drug applicant to successfully challenge an innovator's patent.<sup>43</sup> The 180-day exclusivity provision provides that no other generic drug will be permitted to compete with the innovator for 180 days. This exclusivity provides a lucrative marketing window for the generic drug company.<sup>44</sup> In addition, Hatch-Waxman provided five years of market exclusivity for new chemical entities and three years of market exclusivity for a significant change in the innovator product,<sup>45</sup> while the Orphan Drug Act<sup>46</sup> provided seven years of marketing exclusivity for orphan drugs.<sup>47</sup> This new product exclusivity provides additional protection from competition whereby an innovator company can recover the costs of research and development it expended in bringing that product to market.<sup>48</sup>

While effectively permitting the entry of generic drugs at reduced costs to patients, Hatch-Waxman is not a perfect model for the follow-on biologic pathway because the economic model for follow-on biologics competition may not resemble the generic drug economic model. First, there is a concern that market exclusivity for the innovator company is not needed because of the low rate of market entry expected for follow-on biologics and the type of price competition that is likely to result.<sup>49</sup> Second, there is a significant concern that, because follow-on biologics

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pathway for follow-on biologics analogous to the one created for generic drugs by the Hatch-Waxman Act).

41. See Joyce Wing Yan Tam, Note, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 535, 540 (2010) (detailing the passage of the Hatch-Waxman Act, and noting that it has been successful in part because it has resulted in "substantial cost savings on lifesaving medicines").

42. See John A. Vernon et al., *Exploration of Potential Economics of Follow-on Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B.U. J. SCI. & TECH. L. 55, 62 (2010) (noting that the Hatch-Waxman Act sought "[t]o strike a balance between drug price competition and innovation").

43. 21 U.S.C. § 355(j)(5)(B)(iv) (2006 & West Supp. 2009).

44. *Id.*; see also Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 361 & n.67 (2007) (detailing the "controversial" 180-day exclusivity provision of the Hatch-Waxman Act, and noting that it is "[d]esigned to spur generic competition" by "granting valuable exclusionary rights").

45. 21 C.F.R. § 314.108 (2009).

46. Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

47. 21 U.S.C. § 360cc.

48. See Eisenberg, *supra* note 44, at 360 (suggesting that the FDA-administered exclusionary rights are provided "to encourage particular kinds of innovation in drug development rather than to protect consumers from unsafe or ineffective drugs").

49. See Kelly & David, *supra* note 6, at 116-17 (noting that price competition for biologics is dependent on a willingness to enter the market and, given the high costs of doing so, "results in *de facto*

will not be interchangeable or substitutable with their reference innovator products (e.g., merely *similar*, but not the *same* as are generics), cost savings to patients will be minimal.<sup>50</sup> In a June 2009 report, the Federal Trade Commission (FTC) found that: (i) competition between an innovator and a follow-on product will not resemble generic competition under Hatch-Waxman, but rather brand-to-brand competition;<sup>51</sup> (ii) cost savings from follow-on biologics will be hurt by the lack of automatic substitution between a follow-on and an innovator and will only range ten to thirty percent;<sup>52</sup> (iii) the high cost of follow-on biologic market-entry, as compared to generic drug market entry, will result in few follow-on biologic entrants;<sup>53</sup> and (iv) existing patent protection and market-based pricing are sufficient to foster brand-name innovation without providing innovator exclusivity.<sup>54</sup> There is criticism from both the innovator and follow-on sides of this debate over the findings of the FTC. The innovators insist that a period of twelve to fourteen years of market exclusivity is necessary to restore the incentives to innovate that will be eroded by follow-on competition.<sup>55</sup> Citing the FTC's criticism of the innovator economic model, the generic and follow-on industries argue that any innovator exclusivity will ultimately reduce competition and limit follow-on innovation.<sup>56</sup> The Obama Administration has argued that seven years of marketing exclusivity—the mid-point between the FTC analysis and the innovator position—

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market exclusivity for the innovator companies”); Anthony D. So & Samuel L. Katz, *Biologics Boondoggle*, N.Y. TIMES, Mar. 8, 2010, at A23 (suggesting that “higher-than-normal barriers to entering the market” weighs in favor of a lesser period of market exclusivity for biologic drug makers).

50. See Grabowski et al., *supra* note 4, at 1298 (suggesting that physicians and patients will be slow to accept biogeneric products that are not thought to be “therapeutically equivalent” to the innovator product, and that this phenomenon will add to the cost of producing follow-on biologics).

51. FTC REPORT, *supra* note 35, at iii.

52. *Id.* at iv, vi.

53. *Id.* at iii–iv.

54. *Id.* at v–vi.

55. *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. 40, 72–73 (2009) (prepared statement of Jeffrey P. Kushan, Sidley Austin LLP, on behalf of the Biotechnology Industry Organization), available at [http://frwebgate.access.gpo.gov/cgi-bin/useftp.cgi?IPaddress=162.140.64.184&filename=51014.pdf&directory=/diska/wais/data/111\\_house\\_hearings](http://frwebgate.access.gpo.gov/cgi-bin/useftp.cgi?IPaddress=162.140.64.184&filename=51014.pdf&directory=/diska/wais/data/111_house_hearings).

56. See *Biotech Bottleneck: Congress Can Encourage Competition Within an Increasingly Important Class of Prescription Drugs*, WASH. POST, July 28, 2009, at A16 [hereinafter *Biotech Bottleneck*] (reporting that a FTC report suggested that no added exclusivity period is necessary for biologic innovations and that additional protection might “delay the entry of biogenerics and drive costs even higher”); Press Release, Generic Pharmaceutical Ass’n, GPhA Says BIO Cries Wolf on Senate Biogenerics Proposal (July 9, 2009), available at <http://www.gphaonline.org/media/press-releases/2009/gpha-says-bio-cries-wolf-senate-biogenerics-proposal> (noting that the FTC has suggested that little or no market exclusivity is needed because of the “extremely robust intellectual property protection” in the biotechnology industry).



is a reasonable compromise.<sup>57</sup> Objective economic analysis also supports a seven-year exclusivity period for innovators.<sup>58</sup>

While Hatch-Waxman provides many concepts to consider in creating an abbreviated approval pathway for follow-on biologics, it is not a ready-made model for this new pathway. The novel scientific challenges and interchangeability issues presented by follow-on biologics will create a much different model of competition than the generic drug competition model. Ultimately, Congress must decide the appropriate balance between promoting innovation and providing cost-competition as it constructs the abbreviated pathway for follow-on biologics.

#### IV. A PATHWAY FOR FOLLOW-ON BIOLOGICS ON THE HORIZON

With the progress of the Europeans and Canadians in implementing an abbreviated approval pathway for follow-on biologics, action by Congress on this issue is ripe. In the 111th Congress, two legislative proposals would create such an abbreviated approval pathway for follow-on biologics. First, H.R. 1548, *The Pathway for Biosimilars Act*, sponsored by Representative Anna G. Eshoo (D. California), would amend the PHSA to allow approval of biologic products based on their similarity to a reference product.<sup>59</sup> H.R. 1548 would permit, but not require, FDA, through the Secretary of Health and Human Services, to find a follow-on product interchangeable with the innovator.<sup>60</sup> This bill also provides the innovator BLA holder with twelve years of market exclusivity during which FDA may not approve a follow-on version of that product.<sup>61</sup> Second, H.R. 1427, *The Promoting Innovation and Access to Life-Saving Medicine Act*, sponsored by Representative Henry A. Waxman (D. California), Chairman of the House Committee on Energy and Commerce, would also amend the PHSA to allow approval of follow-on biologics based on their similarity to the reference product.<sup>62</sup> H.R. 1427 would provide five years of innovator exclusivity.<sup>63</sup> This bill would also

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57. Press Release, Generic Pharmaceutical Ass'n, GPhA: Obama Administration Says It Will Continue to Push for Seven Years of Market Exclusivity for Biogenerics (Sept. 17, 2009), available at <http://www.gphaonline.org/media/press-releases/2009/gpha-obama-administration-says-it-will-continue-push-seven-years-market-ex>; see also *Biotech Bottleneck*, supra note 56 (reporting that the Obama Administration regards a seven-year period of market exclusivity a "generous compromise").

58. *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. 8–10 (2009) (prepared statement of Alex Brill, Am. Enterprise Inst.), available at <http://judiciary.house.gov/hearings/pdf/Brill090714.pdf>.

59. H.R. 1548, 111th Cong. sec. 101(a)(2) (2009).

60. See *id.* sec. 101(a)(2), § 351(k)(4)(A)–(B) (providing safety standards for interchangeability that dictate when the Secretary of Health and Human Services may determine that a biological product is interchangeable).

61. *Id.* sec. 101(a)(2), § 351(k)(7)(A).

62. H.R. 1427, 111th Cong. sec. 3(a)(2), § 351(k)(1) (2009).

63. H.R. 1427, sec. 3(a)(2), § 351(k)(10)(A); see also Wing Yan Tam, supra note 41, at 555–56 (discussing the comparatively weak exclusivity provisions in the Waxman bill and contrasting them with

permit, but not require, FDA to find a follow-on product interchangeable with a reference biologic.<sup>64</sup>

The Obama Administration's initial healthcare reform proposal included provisions substantially similar to H.R. 1548 at section 2575 of H.R. 3962, *The Affordable Healthcare for America Act*.<sup>65</sup> H.R. 3962 passed the House by a vote of 220-215 on November 7, 2009, and the Senate included a follow-on biologics pathway in H.R. 3590, as amended by S.A. 3298 on December 24, 2009. The healthcare reform package passed by Congress on March 21, 2010, was signed into law by President Obama on March 23, 2010, and included the follow-on biologics pathway as a key feature of the new law.<sup>66</sup> Accordingly, FDA has been granted authority to approve follow-on versions of products licensed under section 351 of the PHSA.

#### V. IMMEDIATE INFLUX OF MARKETED FOLLOW-ON BIOLOGICS UNLIKELY

Although FDA has received the statutory authority to approve abbreviated applications for follow-on biologics for innovator products licensed under section 351 of the PHSA, it is unlikely that the market will see an immediate influx of follow-on biologics because the data required to support an application will be substantial.

FDA's recent approval of Omnitrope (somatotropin),<sup>67</sup> a section 505(b)(2) approval, provides a good example of the type of data, experience, and knowledge about the scientific characteristics of the product's active ingredient that will be required to support a follow-on application.<sup>68</sup> The data submitted to support the Omnitrope application was extensive. FDA approved the Omnitrope application

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provisions in the Eshoo bill); Bob Braun, *A Search for Lifesaving 'Biologic' Drugs, A Fight to Cut Costs*, STAR-LEDGER (Newark, NJ), June 15, 2009, at 3 (reporting that Rep. Waxman "favors the same five-year period of market exclusivity in the generic prescriptions law").

64. See H.R. 1427, sec. 3(a)(2), § 351(k)(5)(B)-(C) (providing that the Secretary shall publish either that a biological product is interchangeable with the reference or that interchangeability has not been established).

65. H.R. 3962, 111th Cong. §§ 2575-2577 (2009).

66. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010).

67. See *F.D.A. Approves a Generic Biodrug*, N.Y. TIMES, June 1, 2006, at C5 (reporting the approval process for Omnitrope); Diedra Henderson, *FDA Clears a Generic Biotech Drug: Case Fails to Clarify the Approval Process*, BOSTON GLOBE, June 1, 2006, at D1 (reporting that the FDA approved Omnitrope, a generic human growth hormone).

68. See generally Liang, *supra* note 15, at 393-97 (discussing in detail the FDA's approval of Omnitrope). In addition to requiring that the product's application contain "a significant amount of nonclinical and clinical testing," the FDA also "assessed Omnitrope's [application] based upon whether it was 'sufficiently similar' to other previously approved forms . . ." *Id.* at 396. The FDA further indicated that Omnitrope's application "included substantial original data establishing its profile as similar to Genotropin . . ." *Id.*; see also Catherine Hollingsworth, *Pharmaceuticals FDA Approves 'Follow-on' Biotech Omnitrope to Treat Growth Disorders*, Health Care Daily Rep. (BNA) (June 1, 2006) (reporting that Omnitrope was "the first recombinant copy of a biotech drug" approved pursuant to section 505(b)(2) of the FD&C Act, and that its approval was a "landmark decision").

based on several long-term clinical trials; the strong assessment of structural similarity between Omnitrope and its reference product, Genotropin; the fact that the mechanism of action for human growth hormone is well-understood; favorable comparative pharmacodynamic and pharmacokinetic information between the follow-on and the innovator; a thorough immunogenicity analysis; a wealth of experience using human growth hormone; and FDA's conclusion of safety and efficacy related to Genotropin.<sup>69</sup>

The same factors will guide FDA's review and approval of other follow-on biologics.<sup>70</sup> Considering that human growth hormone is a relatively simple follow-on biologic and requires a robust data submission for approval, it is clear that a more complex follow-on product will require more data to support an application for approval. FDA's review and approval of these products will likely require a case-by-case scientific analysis, and specific data requirements for the application will depend on the complexity of the follow-on biologic that is the subject of the application.<sup>71</sup> Combining the time it will take to generate the data necessary to support a follow-on application with the potential increase in time for FDA to review more complex applications, it could be years before patients see a marketed follow-on biologic that will compete with innovator products licensed under section 351 of the PHSA.<sup>72</sup>

#### CONCLUSION

The follow-on biologics debate presents interesting and complex legal, policy, and scientific questions. While Congress has taken action to create an abbreviated approval pathway for follow-on biologics, the pathway's success will ultimately depend on how the FDA uses the flexibility it is provided in the statute to inform its science-based decisions, the degree to which the statute will promote innovation and reduce drug prices, and the level of confidence that patients will have in substituting a follow-on biologic for their prescribed innovator product. While there

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69. Woodcock Statement II, *supra* note 34, at 35–36.

70. See Janet Woodcock et al., *The FDA's Assessment of Follow-on Protein Products: A Historical Perspective*, 6 NATURE REVS. DRUG DISCOVERY 437, 438, 440–41 (2007) (citing Omnitrope as an example of an approved protein product that illustrates the information that the FDA will likely use when evaluating other follow-on biologic products).

71. *Id.* at 441; see also Jessica R. Underwood, *What the EU Has that the U.S. Wants: An Analysis of Potential Regulatory Systems for Follow-on Biologics in the United States*, 10 DEPAUL J. HEALTH CARE L. 419, 455 (2007) (advocating that lawmakers create a biogeneric pathway that “defin[es] terms narrowly and evaluat[es] highly complex molecules on a case-by-case basis”).

72. See Elysa B. Goldberg, Note, *Fixing a Hole: Will Generic Biologics Find a Niche Within the Hatch-Waxman Act?*, 20 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 327, 348–49 (2009) (noting that, even if legislation is written to clarify the approval process, the inevitable challenges that will occur during that approval process will potentially compromise competition in the realm of innovative and follow-on biologics); So & Katz, *supra* note 49 (arguing that because a biologic manufacturer can extend the period of exclusivity by making “minor modifications,” current biologics-related legislation might delay competition beyond the provided-for periods of market exclusivity).

will be cost savings to consumers from the introduction of follow-on biologics,<sup>73</sup> it will take time before follow-on biologics are marketed to compete with licensed biologics.<sup>74</sup> FDA's review and approval of these products will likely be a case-by-case scientific analysis with the data required to support the application depending on the complexity of the follow-on biologic.

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73. See, e.g., Sarah Sorscher, Note, *A Longer Monopoly for Biologics?: Considering the Implications of Data Exclusivity as a Tool for Innovation Policy*, 23 HARV. J.L. & TECH. 285, 287–88 & n.20 (2009) (citing STEVE MILLER & JONAH HOUTS, EXPRESS SCRIPTS, INC., POTENTIAL SAVINGS OF BIOGENERIC IN THE UNITED STATES 1, 7 (2007), available at <http://www.express-scripts.com/research/studies/pharmacybenefitresearch/specialtypharmacyservices/docs/potentialSavingsBiogenicsUS.pdf>) (indicating that estimated savings related to the market entrance of generic biologics is about \$71 billion over a ten-year period).

74. See Gitter, *supra* note 40, at 587–88 (describing the temporal differences likely to occur between the competitive generic drug and follow-on biologics markets, and noting that eventually a “robust” follow-on market will develop).