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# FOLLOW-ON BIOLOGICS ARE SET UP TO FAIL

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## I. INTRODUCTION

I would like to thank the Editors of the Illinois Law Review for inviting me to comment on Professors Michael Carrier and Carl Minniti's article, "Biologics: The New Antitrust Frontier."<sup>1</sup> Carrier and Minniti's article is important for at least three reasons. First, it provides a comprehensive review of the various kinds of antitrust violations that beleaguer pharmaceutical markets in the United States. Second, the article examines the applicability of these anti-competitive behaviors to biopharmaceutical ("biologics") markets. And third, in so doing, the article alerts regulators and courts to potential anti-competitive behaviors and antitrust violations in the emerging area of follow-on biologics.<sup>2</sup> Carrier and Minniti's article does a meticulous job of mapping out types of anti-competitive behaviors and providing recommendations for limiting such behavior in biologics markets. It will, no doubt, serve as a valuable guide for regulators, judges, and practitioners.

Yet, while highlighting numerous risks to competition in follow-on biologics markets, Carrier and Minniti appear to share in an optimism about the prospects of such markets: that if we just policed these markets properly, com-

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1. Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 ILL. L. REV. 1.  
2. "Follow-on biologics" are biopharmaceutical products seeking marketing approval based on their clinical and/or structural similarity or identity to already-approved products. In the United States, follow-on biologics include, but are not limited to biosimilars under 42 U.S.C. § 262(i)(2), interchangeable biosimilars under 42 U.S.C. § 262(i)(3), and otherwise substitutable versions of established biologics approved under the Biologics Price Competition and Innovation Act (BPCIA), Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–23 (2010), or any other relevant existing or future laws.

petition could be guaranteed and, with it, prices would drop significantly.<sup>3</sup> Such optimism is unwarranted.

The legislative and regulatory efforts to instill competition into biologics markets have been fraught, from their outset, with persistent and mostly successful counter-efforts by the brand-name pharmaceutical industry<sup>4</sup> (“Industry”) to make follow-on biologics a limited and contained regulatory and commercial phenomenon. To that end, the Industry—with its lobbying spearheads, BIO and PhRMA—and its many allies in Congress, state legislatures, and state and federal administrations, have been waging war to maintain existing and erect new regulatory obstacles to the development, approval, and marketing of follow-on biologics.<sup>5</sup> The full implications of their many successes in doing so are being and will continue to be felt by patients, healthcare providers, and payors for many years to come as access to affordable versions of biologics remains stunted.

The Industry’s continuing success in undercutting the emergence of truly competitive<sup>6</sup> follow-on biologics markets in the United States<sup>7</sup> rests on four pil-

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3. See e.g., Carrier and Minniti, *supra* note 1, at 4, 77 (“With biosimilar entry poised to be unleashed in crucial multi-billion-dollar markets, there is no time to waste.”).

4. The pharmaceutical industry includes the brand-name pharmaceutical and biopharmaceutical industries, their numerous official and unofficial lobbying arms under the leadership of the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Innovation Organization (BIO), industry-funded patient groups, researchers, research institutions, medical salespersons, and more. Notably, when it comes to biologics the “battle lines” between brand-name and follow-on/generic parts of the industry are not as clear as they are in the small-molecule context. Still, with a few notable exceptions, it is possible to speak of efforts led by and on behalf of the brand-name biopharmaceutical industry, which are opposed to the interests of those parts of the industry that are focused on making follow-on biologics.

5. See *infra* Parts I.A–I.D; see also *Building a Wall Against Biosimilars*, 31 NATURE BIOTECHNOLOGY 264, 264 (2013) (describing Industry efforts to “do[] everything they can to make the US market for biosimilars as awkward for incomers as possible” and arguing that these efforts have been “helping to fortify the market brick by brick against biosimilars”).

6. By “truly competitive” and “competitively robust” biologics markets, I mean levels of competition sufficient to drive down the cost of biologics (and follow-on versions thereof) significantly for payors and patient-consumers, well beyond the 15-30% price drops currently typical of biologics markets subsequent to follow-on products’ entry. See W. Nicholson Price II, *Regulating Secrecy*, 91 WASH. L. REV. 1769, 1798 (2016) (discussing the high costs of developing biosimilars and that “biologics are expected to remain much more expensive, with drops of only 20–30 percent in price once competitive biosimilars enter the market”). For comparison, in the context of small-molecule drugs, significant price drops of more than 70% are typical subsequent to the entry of five or more generic products into a specific drug market. See *Generic Competition and Drug Prices*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm129385.htm> (last visited Apr. 4, 2018).

7. While this Comment focuses on the Industry’s efforts in the United States, it is important to recognize that these efforts are not limited to this country alone and that local efforts are part of larger, well-coordinated strategies aimed at limiting follow-on biologics as a regulatory and commercial phenomenon worldwide. See e.g., Evelien Moorkens et al., *Overcoming Barriers to the Market Access of Biosimilars in the European Union: The Case of Biosimilar Monoclonal Antibodies*, 7 FRONTIERS PHARMACOLOGY 1, 3–5 (2016) (discussing the barriers for biosimilar introduction, including the differing laws of interchangeability within each European Union member state); Patricia Van Arnum, *Biologics Exclusivity and Trade*, DCAT (Oct. 21, 2015), <https://www.dcatvci.org/11-value-chain-insights/89-biologics-exclusivity-and-trade> (discussing BIO and PhRMA’s vehement urging of the United States Trade Representative to conform the Trans-Pacific Partnership agreement (from which the United States eventually withdrew) to the United States’ twelve-year exclusivity for reference biologics rather than a five- to eight-year exclusivity); *Building a Wall Against Biosimilars*, *supra* note 5, at

lars: (1) an Industry-favorable, obstructed pathway for the approval of follow-on biologics; (2) acceptance and upholding of the view that regulatory filings submitted to the FDA are proprietary and confidential; (3) state laws making onerous the substitution of biologics with follow-on versions thereof; and (4) efforts to block any and all specific attempts to make, gain approval for, and sell follow-on biologics. Of these four pillars, the area of antitrust law (and, thus, Carrier and Minniti's article) addresses mostly the fourth. Yet, the emergence of competitively robust follow-on biologics markets requires dismantling more than one pillar. Until then, efforts to open biologics markets to competition will continue to be no more than a rearguard battle over the approval and marketing of a small number of follow-on versions of a mere handful of original products with limited substitutability. The price, as always, will be borne by payors, patients, and ultimately, the public.

In this Comment, I will briefly discuss each of the four pillars supporting the Industry's success in inhibiting the development, approval, and marketing of follow-on biologics. I show that unlike the story of the Hatch-Waxman Act, that of the Biologics Price Competition and Innovation Act ("BPCIA")<sup>8</sup> does not and probably will not have a happy ending,<sup>9</sup> that if the goal is to significantly lower biologics' prices, then the paradigm of approval of follow-on biologics in the United States needs to change.

## II. FOUR PILLARS OF NON-COMPETITIVE FOLLOW-ON BIOLOGICS MARKETS

### *A. BPCIA: An Industry-Favorable, Obstructed Pathway for Follow-On Biologics*

Efforts to establish regulatory pathways for approval of follow-on biologics go back at least as far as the late 1990s, well before the enactment of BPCIA, in March 2010. These efforts were initially prompted by applications

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264 (describing Industry efforts in Europe to hinder the penetration of follow-on biologics and stating that "[t]hus far, [the Industry has] played the game so well that biosimilar products are not only penetrating European markets at a glacial pace but also failing to provide savings anywhere near those of generic small molecules").

8. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119 (2010). BPCIA was enacted as Title VII, Subtitle A of the Affordable Care Act. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119, 804–21 (2010).

9. While the Hatch-Waxman Act has generally been considered successful in fostering competition and lowering drug prices, it has also been far from problem-free and what Carrier and Minniti call "regulatory abuse." *See e.g.*, Carrier and Minniti, *supra* note 1 at 37–40. Nor has the Hatch-Waxman Act been a panacea against high drug prices and price increases. *See e.g.*, U.S. GOV'T ACCOUNTABILITY OFFICE, REPORT TO CONGRESSIONAL REQUESTERS, PART D GENERIC DRUG PRICES DECLINED OVERALL, BUT SOME HAD EXTRAORDINARY PRICE INCREASES, GAO-16-706 (2016) (finding that out of 1,441 established generic drugs analyzed, more than 300 had at least one extraordinary price increase of 100 percent or more between first quarter 2010 and first quarter 2015); U.S. SENATE SPECIAL COMM. ON AGING, SUDDEN PRICE SPIKES IN OFF-PATENT PRESCRIPTION DRUGS: THE MONOPOLY BUSINESS MODEL THAT HARMS PATIENTS, TAXPAYERS, AND THE U.S. HEALTH CARE SYSTEM (2016) (documenting the strategies used by pharmaceutical companies to raise prices of older essential drugs).

for marketing approval of follow-on versions of specific, highly-lucrative, off-patent biologics.<sup>10</sup> The regulatory and legal battles that resulted from these attempts drove legislators to begin exploring the idea of generic biologics.<sup>11</sup> With the establishment of a regulatory pathway for the approval of follow-on biologics in the European Union, in 2003,<sup>12</sup> and actual approval, starting in 2006, of several follow-on biologics in Europe,<sup>13</sup> doubts regarding the scientific and practical feasibility of such a pathway, which dominated the debate in the United States, became less convincing. So, in 2006, nearly a decade after the beginning of the discussion regarding the establishment of a regulatory pathway for the approval of follow-on biologics, legislative efforts to establish such pathway in the United States began in earnest.

The legislative efforts to establish a regulatory pathway for the approval of follow-on biologics were marked, from their outset, with determined opposition from the Industry and its allies in Congress. The first proposal for a follow-on biologics pathway was introduced in September 2006 by Representative Henry Waxman—one of the two primary co-sponsors of the Hatch-Waxman Act.<sup>14</sup> The Industry’s “response” came in the form of a bill introduced shortly thereafter which explicitly foreclosed the designation of two biological products as therapeutically equivalent.<sup>15</sup> The bill sought to make the approval of follow-on biologics exceedingly difficult (if not wholly impracticable),<sup>16</sup> and provided original product developers with an unprecedented market exclusivity period of twelve to fifteen years.<sup>17</sup> Since then, through the enactment of BPCIA in March 2010, at least three versions of the First Waxman Bill were introduced in the House, Senate, or both.<sup>18</sup> And every such bill was met with an Industry-sponsored “counter-bill”<sup>19</sup> as well as self-styled bipartisan bills.<sup>20</sup> This, of

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10. See Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 685–86 (2010).

11. *Id.* at 697.

12. Directive 2001/83/EC of the European Parliament and Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, Annex I, pt. II, ¶ 2, 2001 O.J. (L 311), 1, 152, as amended by Directive 2003/63/EC, Annex I, pt. II, ¶ 4, 2003 O.J. (L 159) 46, 78–79.

13. List of biosimilar products reviewed by the European Medicines Agency (EMA), obtained from European Public Assessment Report (EPAR) website, [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124) (last visited Dec. 6, 2017), on file with author.

14. Access to Life-Saving Medicine Act, H.R. 6257, 109th Cong. (2006) (the First Waxman Bill). A related bill was introduced in the Senate by Senator Charles Schumer, S. 4016, 109th Cong. (2006).

15. Patient Protection and Innovation Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 351(k)(2)(D) (2007) (PPIBMA) (unenacted) (“The Secretary may not approve, under any other provision of law, a product that is claimed to be similar to or the same as a reference product.”). The unenacted PPIBMA was introduced to amend the Public Health Service Act § 351, 42 U.S.C. § 262 (2012).

16. *Id.* § 351(k)(4)–(6) (introduced to amend the Public Health Service Act § 351, 42 U.S.C. § 262 (2012)).

17. *Id.* § 351(k)(3) (introduced to amend the Public Health Service Act § 351, 42 U.S.C. § 262 (2012)).

18. Access to Life-Saving Medicine Act, H.R. 1038, 110<sup>th</sup> Cong. (2007) (ALSMA), which again was accompanied by a related bill in the Senate, S. 623, 110<sup>th</sup> Cong. (2007); Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111<sup>th</sup> Cong. (2009) (PIALSMA).

19. Pathway for Biosimilars Act, H.R. 5629, 110<sup>th</sup> Cong. (2008) (PFBA); Pathway for Biosimilars Act, H.R. 1548, 111<sup>th</sup> Cong. (PBA).

course, is not unusual for legislative battles in Congress. It was, however, widely anticipated that some sort of a mutually agreeable arrangement would eventually be worked out—like the one reached in the Hatch-Waxman Act—which would potentially open biologics markets to meaningful competition. These expectations, though, were frustrated with the passage of the highly Industry-favorable BPCIA.<sup>21</sup> While it is not entirely clear *how* things turned out the way they did,<sup>22</sup> it appears that Industry allies within the Democratic Party in the House were able to add BPCIA language to the then-pending Affordable Care Act (“ACA”) bill<sup>23</sup> at a key point in the legislative efforts to pass the ACA.<sup>24</sup> In so doing, the Industry was able to force the arm of its Congressional Democrat opponents, despite their protests, to pass BPCIA’s Industry-favorable positions as part of the ACA.<sup>25</sup> It is unknown whether a backroom deal to that effect was struck, yet, it appears that BPCIA language was allowed to stay in the ACA bill as a price to be paid for the votes of those Industry allies who added BPCIA language to the bill. The resulting BPCIA, in its enacted form, included *almost everything* for which the Industry had lobbied, short of tossing the idea of follow-on biologics altogether.<sup>26</sup>

Since then, BPCIA’s drafters and proponents have sought to portray BPCIA as a “meaningful compromise” which represents a “middle ground between innovator and generic interests.”<sup>27</sup> As discussed above, BPCIA’s legislative history belies this description, as do BPCIA’s highly Industry-favorable arrangements. BPCIA affords an unprecedented twelve- to twelve-and-a-half-year term of market exclusivity in original biologics, during which the FDA is not allowed to approve follow-on versions of such products.<sup>28</sup> Notably, this

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20. Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. (2007); *see also* Hessler Carver et al., *supra* note 10, at 746–64, 776–78, and 784–87; Press Release, *Senators Kennedy, Hatch, Clinton, Enzi Announce FDA Biologics Agreement* (June 22, 2007), <https://www.help.senate.gov/ranking/newsroom/press/senators-kennedy-hatch-clinton-enzi-announce-fda-biologics-agreement>.

21. Biologics Price Competition and Innovation Act, Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010).

22. Accounts of the legislative efforts that led to the enactment of BPCIA as part of the Affordable Care Act (ACA) do not provide explanations as to why BPCIA language was kept in the ACA draft despite strong and explicit opposition by the White House, the Generic Pharmaceutical Association (GPhA), and other stakeholders. *See* Hessler Carver et al., *supra* note 10, at 802–03, 805–06.

23. Senator Harry Reid amended the ACA bill by substitute on November 19, 2009. H.R. 3590, 111th Cong. (2009) (as amended by S. Amend. 2786). This was the first amendment of the bill in the Senate.

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

25. *See* Hessler Carver et al., *supra* note 10, at 802–03.

26. The Industry’s initial position regarding follow-on biologics, as reflected in the PPIMBA, would have foreclosed follow-on biologics as an economically feasible prospect. *See supra* notes 15–16 and accompanying text.

27. *See* Hessler Carver et al., *supra* note 10, at 671, 817 (arguing that “[BPCIA] represented a true compromise of competing interests”); Ude Lu, *Biologics Price Competition and Innovation Act: Striking A Delicate Balance Between Innovation and Accessibility*, 15 MINN. J.L. SCI. & TECH. 613, 614 (2014) (concluding “that the current design of BPCIA tips too favorably toward innovation and compromises accessibility”); Mark Metzke, *Increasing Follow-on Biologics Competition with A New Biologics Act*, 39 AIPLA Q.J. 357, 383 (2011) (characterizing BPCIA as “favor[ing] protecting innovators”).

28. 42 U.S.C. §§ 262(k)(7)(A), (m)(2)(A). This long exclusivity term was the subject of much controversy during and even after the legislative proceedings that led to the enactment of BPCIA. *See e.g.*, FTC,

long exclusivity is afforded *in addition to* (rather than *in lieu of*) other exclusivities in the biological product.<sup>29</sup> At the same time, BPCIA does not offer *any* exclusivity to developers of biosimilar products. The only exclusivity afforded under BPCIA to developers of follow-on biologics is a one-year market exclusivity for products deemed *interchangeable*.<sup>30</sup> As explained below, not only has no product been approved as interchangeable to date, but the prospects of such approvals happening in the future are unclear, making BPCIA exclusivity for follow-on products mostly or entirely moot.<sup>31</sup>

Furthermore, BPCIA institutes and seeks to impose on developers of follow-on biologics an elaborate patent dispute resolution framework (“Patent Dance”) that would have placed them in considerable procedural and commercial disadvantage.<sup>32</sup> Chief among these disadvantageous aspects of the Patent Dance framework was the requirement that makers of follow-on biologics disclose to makers of original products the details of their follow-on product application, including the process of manufacturing their follow-on biologic.<sup>33</sup> Notably, BPCIA does not impose a similar, reciprocal requirement on makers of original products to provide their applications and manufacturing processes to makers of follow-on products. Another example, which is also discussed by

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EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, v–x (2009) (rejecting the conclusions of the study which was the basis for the determination of twelve years as the proper term for market exclusivity in original biologics and making the case that no additional non-patent exclusivity is necessary in order to provide sufficient incentives for innovation in biologics); ALEX M. BRILL, PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS: A CRITIQUE 11 (2008), available at <http://perma.cc/S825-8DVQ>; LAURENCE J. KOTLIKOFF, STIMULATING INNOVATION IN THE BIOLOGICS INDUSTRY: A BALANCED APPROACH TO MARKETING EXCLUSIVITY 6 (2008), available at <http://perma.cc/3TSM-8ZNG>; Brian F. McMahon, *The Biologics Price Competition and Innovation Act of 2009: Legislative Imprudence, Patent Devaluation, and the False Start of A Multi-Billion Dollar Industry*, 100 KY. L.J. 635, 671–75 (2012); *see also* Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. 299, 350–51 nn.228–34 and accompanying text (2015). *But see* Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERIES 479, Fig.6 (2008) (arguing, in a research supported by PhRMA, that the proper market exclusivity period for biologics should fall between 12.9 and 16.2 years).

29. *See* Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 461–71 (2012) (reviewing the potentially negative ramifications of awarding both kinds of exclusivities to biologics and suggesting making such exclusivities alternative to one another).

30. 42 U.S.C. § 262(k)(6)(A).

31. The FDA is currently in the process of developing guidelines for follow-on biologics developers who may wish to seek approval of their biosimilar products as interchangeable and has only recently issued proposed guidelines for public comments. *See* U.S. Food & Drug Admin., Considerations in Demonstrating Interchangeability with a Reference Product: Draft Guidance for Industry, 82 Fed. Reg. 5,579 (Jan. 18, 2017) [hereinafter *Interchangeability Draft Guidance*]. The comment period for the draft guidance ended on May 12, 2017, and FDA has yet to announce a final guidance. *See* U.S. Food & Drug Admin., Guidances (Drugs): Biosimilars, <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm> (last visited Jan. 28, 2018).

32. *See e.g.*, McMahon, *supra* note 28, at 675–76 (discussing how BPCIA patent dispute resolution framework might “permit far too many opportunities for skilled litigators to participate in gamesmanship”). Indeed, recent reports indicate that follow-on biologics makers seeking to follow the statutory Patent Dance framework have already encountered the kind of gamesmanship by the Industry of which commentators had warned. *See infra* notes 109–110 and accompanying text. *But see* Erika Lietzan, *A Solution in Search of a Problem at the Biologics Frontier*, 2018 U. ILL. L. REV. ONLINE 19, 21 (2018), <https://illinoislawreview.org/online/a-solution-in-search-of-a-problem-at-the-biologics-frontier/> (arguing that the Patent Dance framework is “stacked against” original biologics makers).

33. 42 U.S.C. § 262(l)(2)(A).

Carrier and Minniti, is BPCIA's mandating that makers of follow-on biologics would have to face makers of original products in court not once *but twice* prior to being able to actually launch their follow-on product.<sup>34</sup> A third example is the asymmetry in limitations on access to certain judicial proceedings that BPCIA imposes on makers of follow-on biologics for not complying with the stipulations of the Patent Dance framework, *but not* on makers of original products.<sup>35</sup> Indeed, BPCIA's language and arrangements leave little doubt regarding whose interests were on its drafters' minds. While courts, ultimately, held that engaging in BPCIA's patent dispute resolution was optional for makers of follow-on biologics,<sup>36</sup> that holding was a surprise for many and did not reflect the intention of BPCIA's drafters, who sought to impose that onerous framework on makers of follow-on biologics.<sup>37</sup>

Finally, BPCIA reflects an acceptance of the Industry's position that product developers' submissions to the FDA, including data from clinical trials and information regarding the process of manufacturing their products, is proprietary and confidential. Thus, BPCIA does not authorize the FDA to compare the process of making a follow-on biologic with the process of making the original product, which the follow-on product seeks to emulate.<sup>38</sup> In this regard, the constituting paradigm of BPCIA is similar to that of the Hatch-Waxman Act, which instituted the pathway for the approval of generic small molecule drugs. Yet, as explained below, that paradigm may well be unsuitable for biologics.

*B. Acceptance and Upholding of the Industry's Views on the Proprietary and Confidential Nature of Regulatory Filings*

The paradigm of increasing access to biomedical products through the approval of follow-on versions of these products is based on the idea that prices will only drop if there is sufficient competition in the market for such products. A precondition for prices going down, however, is that the original product and its follow-on version may serve as alternatives to one another. This, in turn, presents another prerequisite, namely that the two potentially-alternative-products be sufficiently alike to make consumer choice between them meaning-

34. *Id.* §§ 262(l)(6), (8).

35. *Id.* §§ 262(l)(9)(B)–(C).

36. *Sandoz Inc. v. Amgen Inc.*, 137 S.Ct. 1664, 1674 (2017) (affirming the Federal Circuit's holding that the maker of a follow-on biologic cannot be forced by injunction to follow with 42 U.S.C. § 262(l)(2)(A)).

37. *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. 9 (2009) (statement of Rep. Anna Eshoo) (discussing the intent to have the biosimilar applicant challenge the reference product's patent and the reference product's manufacturer's two-month timeline to enforce their patent); *see also* Hessler Carver et al., *supra* note 8, at 757 (discussing how the drafters of BPCIA chose a "mandatory information exchange process" over a plan that gave the reference-product sponsor and the follow-on applicant the mere "option to notify each other regarding patents they deemed relevant"); Nathan Mannebach, *We Shall Dance, Unless You Choose Not To*, 688 U. KAN. L. REV. 687, 700–05, 710 (discussing the legislative history behind BPCIA and concluding that BPCIA intended the Patent Dance to be mandatory).

38. 42 U.S.C. §§ 262(k)(2)–(4) (listing the types of information a follow-on product maker must submit with its application and the standard based on which such information ought to be evaluated).

ful *and* medically acceptable. In short, to increase access, follow-on products must be cheaper from the products with which they are meant to compete and they must be deemed clinically equivalent.

Yet, the need for clinical equivalence—assessed in the United States by the FDA—has faced a significant obstacle. The Industry’s longstanding position has been that the documents it submits to the FDA in connection with product marketing applications contain proprietary information and, as such, are not to be disclosed *or even used internally by the FDA* for the purpose of comparing original products with putative follow-on products.<sup>39</sup>

In fact, that same position was one of the main obstacles to the FDA’s ability to independently create a regulatory pathway for approval of generic pharmaceuticals prior to the passage of the Hatch-Waxman Act in 1984.<sup>40</sup> Yet, the Hatch-Waxman Act got around the Industry’s objection to making use of information from earlier regulatory filings by relying on the relative preciseness with which small-molecule drugs are synthesized, characterized and formulated. Thus, all the Hatch-Waxman Act requires in order to establish clinical equivalence is that (1) the active pharmaceutical ingredient (API) in the follow-on product be chemically the same as the API in the original product,<sup>41</sup> (2) the two products have the same route of administration, dosage form, and strength,<sup>42</sup> and (3) the follow-on product be expected to have the same therapeutic effect as the original product when administered to patients.<sup>43</sup> All of these pre-requisites could be easily, relatively cheaply, and independently ascertained by follow-on product-developers without having to utilize information from prior regulatory filings. Hence, once the abovementioned requirements are met, the Hatch-Waxman Act gives the FDA the authority to approve a fol-

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39. See e.g., Hessler Carver et al., *supra* note 10, at 698 (“[Approval of] BLAs in reliance on preclinical and clinical safety and effectiveness data submitted in other BLAs . . . in the view of the authors, [is] inconsistent with . . . the Federal Trade Secrets Act, FDCA section 301(j), and the U.S. Constitution.”); Edward L. Korwek, *Towards Understanding the “Generic” Debate about Biologics*, 7 J. BIOLAW & BUS. 1, 5 (2004) (discussing the argument by the Biotechnology Industry Association (BIO) that the FDA’s reliance on “innovator information essentially involves misappropriation of the innovator’s trade secret and confidential business information, which is not permitted under the Takings Clause of the Fifth Amendment”); Letter from Robert A. Long, Jr., Partner, Covington & Burling, to Food & Drug Admin. 4–5, 8–10, 15–17 (July 13, 2005), <https://web.archive.org/web/20170211011252/http://www.fda.gov/ohrms/dockets/dockets/03p0176/03p-0176-c000003-01-vol3.pdf> (Docket Nos. 2004P-0171/CP and 2003P-0176/CP) (arguing that the Federal Trade Secrets Act prohibits a government employee from disclosing trade secrets discovered “in the course of his employment or official duties,” that the FDCA prohibits any person from “using to [their] own advantage, or revealing . . . any information . . . concerning any method or process, which, as a trade secret, is entitled to protection,” and that the Takings Clause and FDA policies “clearly support innovators’ reasonable, investment-backed expectation that trade secret data submitted to FDA would not be used in follow-on approvals”).

40. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2012)). Notably, the Industry has successfully asserted that same position later with respect to biologics, thus dissuading the FDA from attempting to develop a regulatory pathway for the approval of generic biologics based on its existing authorities under FDCA and the Public Health Service Act. See e.g., Hessler Carver et al., *supra* note 10, at 699, nn.219–25.

41. 21 U.S.C. § 355(j)(2)(ii).

42. *Id.* § 355(j)(2)(iii).

43. *Id.* §§ 355(j)(2)(iv).



low-on product based on the assumption that if the original product was proven clinically safe and effective, and the two products are the same, then the follow-on product is expected to be *equally* safe and effective. In this way, the Hatch-Waxman Act makes it possible to establish clinical equivalence, the most crucial pre-requisite for the approval of follow-on versions of biomedical products. And, it does so while dispensing with the need to disclose or directly use data submitted as part of earlier FDA filings. Unfortunately, this elegant solution does not work for biologics.

Biologic products are complex in both structure and composition,<sup>44</sup> and, at least presently, cannot be fully and precisely characterized in the same manner that small-molecule drugs can.<sup>45</sup> Indeed, Industry proponents have often argued that when it comes to biologics “the process [of making the product] is the product.”<sup>46</sup> Accordingly, it is broadly accepted that short of meticulously replicating the process of making a biologic under the same conditions, it is very difficult, if not impossible, to guarantee identity or near identity between that biologic and its follow-on version(s).<sup>47</sup> But, replicating the processes of making biologics simply cannot be done without using data submitted in earlier filings, which is something the Industry has—as discussed above—strongly opposed.<sup>48</sup> With no access to product manufacturing information, guaranteeing clinical equivalence of follow-on versions of biologics potentially necessitates robust comparisons, the exact nature and extent of which must be decided by the FDA

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44. With some exceptions (*e.g.*, human growth hormone and insulin), biologics typically consist of very large molecules having complex three-dimensional (and, possibly, quaternary) structures and appendages (*e.g.*, oligosaccharide chains) that are very difficult to precisely characterize using current scientific methods. Moreover, at least some biologic products consist of not a single molecule but a *collection or mixture* of structurally-related variations of a certain molecule in a certain ratio between the different variations. *See e.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY OF A THERAPEUTIC PROTEIN PRODUCT TO A REFERENCE PRODUCT 7 (2015), <https://www.fda.gov/downloads/drugs/guidances/ucm291134.pdf> (“Using multiple, relevant, state-of-the-art methods can help define tertiary protein structure and, to varying extents, quaternary structure and can add to the body of information supporting biosimilarity. At the same time, a protein’s three-dimensional conformation can often be difficult to define precisely using current physicochemical analytical technology.”); MANTEJ CHHINA, U.S. FOOD & DRUG ADMIN., OVERVIEW OF BIOLOGICAL PRODUCTS 8 (2013), <https://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM356666.pdf> (discussing how the structure of small molecules are known, yet in biological products the “[s]tructure may or may not be completely defined or known”).

45. *See supra* note 44.

46. *See* Hessler Carver et al., *supra* note 10, at 708–09 (describing the Industry’s position on “[w]hether the process is the product”).

47. *See* Price, *supra* note 6, at 1975 nn.134–36; *see also* Linfong Tzeng, *Follow-On Biologics, Data Exclusivity, and the FDA*, 25 BERKELEY TECH. L.J. 135, 138, n.23 (2010) (“The complexity of the biologic molecules, production in living organisms, and sensitivity of end-product structure to changes in the manufacturing process render exact [follow-on biologic] replication nearly impossible.”) (emphasis added).

48. *See e.g.*, Hessler Carver et al., *supra* note 10, at 698–99, 698 n.218, 699 nn.218–25, 700 nn.232–37, 701 n.271 (arguing, for example, that FDA reference to biologics manufacturing information submitted in earlier products’ marketing applications raises “insurmountable legal obstacles” and describing the Industry’s efforts to assert and enforce that position; describing Industry’s successful efforts to foreclose FDA utilization of data contained in earlier regulatory filings for the approval of follow-on biologics); *see also supra* note 39 and accompanying text.

on a case-by-case basis.<sup>49</sup> Such robust, product-specific comparisons, in turn, require a lot more time, money, and expertise than those necessary to ascertain bioequivalence under the Hatch-Waxman Act, thus inevitably making the process much less predictable and a lot more expensive.<sup>50</sup> Even at the conclusion of such robust comparisons, without actual replication of manufacturing processes, biological products are not typically found to be *identical* but only *similar* to one another.

All of this, of course, greatly undermines the prospects of success of producing follow-on products sufficiently equivalent to (let alone interchangeable with) the biologics they seek to imitate.<sup>51</sup> It also makes the regulatory and scientific processes necessary to ascertain clinical equivalence long, costly, and complicated, which makes follow-on biologics expensive, and only minimally cheaper than the original products they seek to emulate. This reality is further compounded by the fact that only relatively few, highly technically-sophisticated, and financially well-backed companies are able to partake in the onerous comparisons necessary to establish sufficient similarity under BPCIA.

Furthermore, as recognized by the FDA, under current scientific methods of biologics' characterization, with complex biologics there could be no guarantee that clinical equivalence between an original biologic and its follow-on version could *ever* be achieved.<sup>52</sup> In such cases, if the market for the original product is sufficiently lucrative, a determined follow-on biologics maker may endeavor—at a considerable investment of time and money—to recreate the clinical results of the original biological product by trying different molecular

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49. See *Building a Wall Against Biosimilars*, *supra* note 5, at 264; Interchangeability Draft Guidance, *supra* note 31; see also U.S. FOOD & DRUG ADMIN., SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY WITH A REFERENCE PRODUCT; GUIDANCE FOR INDUSTRY 7, 10–12 (2017) (discussing a case-by-case approach wherein the sponsor of a follow-on biologic uses a “stepwise approach to developing the data and information needed to support a demonstration of biosimilarity,” yet also arguing that the first step should be to compare structural and functional characterization, before beginning in-vitro and animal studies); Hannah Koyfman, *Biosimilarity and Interchangeability in the Biologics Price Competition and Innovation Act of 2009 and FDA’s 2012 Draft Guidance for Industry*, 32 BIOTECHNOLOGY L. REP. 238, 246 (2013) (stating FDA’s stepwise approach does not describe what differences in structure would require heightened animal or clinical studies, and further proposing a step-by-step approach using scientific literature to determine what amount of structural difference might affect the biologic). Notably, such comparisons would need to meet BPCIA’s exacting requirement that the two products “can be expected to produce the same clinical result . . . in any given patient.” 42 U.S.C. § 262(k)(4)(A)(ii).

50. See e.g., U.S. FOOD & DRUG ADMIN., *supra* note 49, at 7, 10–12 (discussing FDA’s guidance on the “stepwise approach”); see also Jordan Paradise, *The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the United States Healthcare System*, 41 AM. J. L. & MED. 49, 68 (2015) (describing the task of determining that two biologic products are similar and the regulatory process thereof as complicated and uncertain).

51. See W. Nicholson Price II & Arti K. Rai, *Are Trade Secrets Delaying Biosimilars*, 348 SCIENCE 188, 189 (2015) (describing attempts of follow-on biologics makers to imitate original products as “rang[ing] from merely expensive to nearly impossible and creat[ing] much of the cost barrier for biosimilar entrants”).

52. At least as late as May 2015, the FDA’s position was that “[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability . . . given the statutory standard for interchangeability and the sequential nature of that assessment.” U.S. FOOD & DRUG ADMIN., BIOSIMILARS: ADDITIONAL QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009: GUIDANCE FOR INDUSTRY 7 (May 2015), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>.

compositions. Yet, without access to the original biologic's manufacturing information (due to it being held as proprietary and confidential) the follow-on product maker would be forced to do so by undertaking a kind of "molecular hide-and-seek," in which it would try to fashion a follow-on product sufficiently akin to the original product so as to produce comparable clinical outcomes in patients.<sup>53</sup> The wastefulness and ethical deficiencies of this outcome are troubling, especially considering the potential need to test the follow-on product on humans more rigorously than would have been necessary had the original product's manufacturing information been available to the follow-on product maker and/or the FDA. Moreover, such an onerous undertaking would not make financial sense in less-lucrative biologics markets, which may well result in such markets remaining bereft of competition and the product inaccessible to patients.

To recapitulate, the Industry's position on the proprietary and confidential nature of earlier regulatory filings, to which the FDA currently subscribes, (1) categorically undermines the clinical equivalence of follow-on biologics, which then (2) undercuts their fungibility with the products whose clinical benefits they seek to emulate, and, as a result, (3) denies follow-on biologics the competitive edge necessary to drive biologics market prices down sufficiently to increase access.<sup>54</sup> In short, the Industry's position on the proprietary and confidential nature of regulatory filings and the FDA's subscribing to that position makes follow-on biologics expensive and difficult (maybe even impossible, in certain cases) to make, thereby rendering them less attractive as a commercial endeavor and, ultimately, as substitutes. This is even more true for interchangeable biologics. That commercial and regulatory reality helps original biologics maintain their strong market positions, sometimes long after their various exclusivities have expired.<sup>55</sup>

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53. See Price & Rai, *supra* note 51, at 189.

54. See also Price, *supra* note 6, at 1770, 1777, 1784–93 (making the observation that, despite BPCIA, biologics are "wildly expensive and look to stay that way" and concluding that the lack of competition in biologics markets is attributable to the combination of trade secrecy and FDA regulation).

55. Examples of original biologics that have maintained strong market positions long after their launch despite expiration of their exclusivities include Amgen's Neupogen, which was approved by the FDA on Feb. 20, 1991, but has remained without follow-on competition in the United States until the approval of Sandoz's Zarxio, on March 6, 2015, more than 24 years later. *Drugs@FDA: FDA Approved Drug Products – Approval Date(s) and History, Letters, Labels, Reviews for BLA 103353*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103353> (last visited Apr. 3, 2018) (citing the approval date of Neupogen as February 20, 1991) [hereinafter *Neupogen Approval*]; *Drugs@FDA: FDA Approved Drug Products – Approval Date(s) and History, Letters, Labels, Reviews for BLA 125553*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125553> (last visited Apr. 3, 2018) [hereinafter *Zarxio Approval*] (citing the approval date of Zarxio as March 6, 2015). For further discussion of the legal fight over the approval of Zarxio, see *infra* Part D, and Price & Rai, *supra* note 1, at 189 (describing the current FDA approach to follow-on biologics as "potentially creat[ing] very long-lasting monopolies far longer than the explicit, carefully calibrated monopolies provided by patent law and FDA regulatory exclusivity"); Price, *supra* note 6, at 1792, n.122, 1797, nn.149–52, 1798, n.153 (describing the monopoly in the product Premarin, which has lasted for over seventy years); Bronwyn Mixer, *Administration Works on Increasing Rx Competition Due to Spending Concerns*, BLOOMBERG LAW, PHARMACEUTICAL LAW & INDUSTRY REPORT (Apr. 15, 2015) (quoting Richard G. Frank, Assistant Secretary for Planning and Evaluation

Yet, the Industry's position on the proprietary and confidential nature of earlier regulatory filings is not a foregone conclusion.<sup>56</sup> Far from. Indeed, at least once, in the Federal Fungicide, Insecticide and Rodenticide Act ("FIFRA"),<sup>57</sup> Congress rejected a similar position taken by the pesticide industry,<sup>58</sup> and yet the Act passed constitutional muster.<sup>59</sup> It is thus baffling that both the FDA and Congress (including strong proponents of establishing a regulatory pathway for approval of follow-on biologics) have accepted without meaningful debate the Industry's views on the proprietary and confidential nature of regulatory filings with respect to biologics.<sup>60</sup>

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at the Department of Health and Human Services, saying that even after patents covering original biologics have expired, and that "exclusivity was allowed to carry on for longer than one might have expected").

56. See e.g., Hessler Carver et al., *supra* note 10, at 698 n.218 ("The threshold question whether FDA could lawfully approve a biosimilar product on the basis of trade secrets and confidential commercial information owned and submitted by another applicant were explored in submissions to FDA as well as Congress, and discussed in a hearing before the Senate Judiciary Committee. The question was never resolved.")

57. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Pub. L. No. 80-104, ch. 125, 61 Stat. 163 (1947) (codified as amended at 7 U.S.C. §§ 136-136w-8 (2012)).

58. In 1978, Congress amended FIFRA creating a ten-year exclusivity period for data submitted by manufacturers of original pesticide products, which was then followed by an additional five-year mandatory compensation period, during which the administering agency, the Environmental Protection Agency (EPA), may use information from previously submitted applications "if the [follow-on] applicant has made an offer to compensate the original data submitter . . ." 7 U.S.C. §§ 136a(c)(1)(F)(i)-(iv). After expiration of the five-year mandatory licensing/compensation period (which may also be regarded as a compulsory licensing period), the data becomes freely available for use in follow-on applications without any need to receive the permission of the original data submitter or offer compensation for the data. *Id.* Notably, FIFRA further creates an elaborate scheme for resolution of disputes regarding the actual amount of compensation that follow-on applicants would need to pay original data submitters for use of the latter's data without their concession during the five-year mandatory compensation period that follows the initial ten-year data exclusivity period. *Id.* § 136a(c)(1)(F)(iii). Also notably, FIFRA mandates that disagreement between the parties regarding the compensation will not delay registration of the follow-on product by the EPA. *Id.* For further discussion see Yaniv Heled, *When Agencies May Disclose Regulatory Submissions to Third Parties* (temporary title; forthcoming).

59. See *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1006-07 (1984) (holding that EPA's consideration or disclosure of data submitted by an original product developer to the agency did not constitute an unconstitutional taking regardless of whether such data included trade secrets so long as submitters of data were on notice that the agency might do so prior to submitting its data); *Union Carbide Agric. Prods. Co. v. Costle*, 632 F.2d 1014, 1017 (2d Cir. 1980) (reversing a temporary restraining order against the implementation of the 1978 amendments to FIFRA); see also Heled, *supra* note 28, at 334-36.

60. See e.g., Hessler Carver et al., *supra* note 10, at 702 & n.248 (describing FDA's acceptance of the Industry's position that the FDA does not have legal authority to use information from prior regulatory filings in approval of follow-on biologics). A notable exception was an amendment proposed by Sen. Sanders (I-VT), which, had it made it to the final enacted bill, would have created an arrangement akin to the FIFRA mandatory compensation arrangement under which a follow-on applicant would have been able to directly rely on clinical data (but not manufacturing information) submitted by an original product applicant. 155 Cong. Rec. S12164, 12258 (2009) (amendment S.A. 2858 to S.A. 2786 of Sen. Sanders to the Patient Protection and Affordable Care Act, H.R. 3590) (proposing to add an "Ethical Pathway for the Approval and Licensure of Generic Pharmaceutical Products").

Notably, the Industry's position cuts against current transparency trends in Europe and at FDA itself. See e.g., Joshua M. Sharfstein et al., BLUEPRINT FOR TRANSPARENCY AT THE U.S. FOOD AND DRUG ADMINISTRATION: RECOMMENDATIONS TO ADVANCE THE DEVELOPMENT OF SAFE AND EFFECTIVE MEDICAL PRODUCTS, 45 JLME 7 (2017).

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*C. State Laws Making Biologics' Substitution More Onerous*

Increasing access to biologics is inextricably tied to the principle of substitutability, namely the ability to *quickly and efficiently* substitute one (already-approved, expensive) biological product with another (follow-on, cheaper) product. Yet for a quick and efficient substitution to occur, certain preconditions must be met: (1) prescribers must be able to rely on the FDA finding that two biologics are sufficiently clinically equivalent to be substituted for one another (“interchangeable”),<sup>61</sup> and (2) dispensing pharmacists must be allowed to substitute biologics under relevant state laws either automatically or, if substitution is discretionary, without it becoming financially or administratively prohibitive. Undermining any of these preconditions inevitably raises the cost of substitution, thereby making such substitution less appealing to prescribers, dispensers, and patients. The Industry, however, has vehemently rejected the notion that two biologics may be substitutable from the outset.<sup>62</sup>

As discussed earlier, the FDA’s inability to disclose or even rely on earlier-approved biologics’ manufacturing information potentially significantly complicates attempts to find two biologics clinically equivalent. Nonetheless, BPCIA, at least on its face, accepts the idea of biologics’ clinical similarity and equivalence, and thus grants the FDA the authority to find two biologics sufficiently clinically equivalent to deem them “biosimilar” and even “interchangeable.”<sup>63</sup> Since January 2017, the FDA has been engaged in a notice and comment process in order to develop a regulatory pathway to establishing interchangeability in biologics.<sup>64</sup> If and when such a pathway is ultimately established, prescribers will be able to rely on the FDA finding that two biologics are sufficiently clinically equivalent. As discussed above, however, the principle of substitutability requires meeting another precondition, namely that dis-

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61. 42 U.S.C. §§ 262(k)(4).

62. See e.g., Hessler Carver et al., *supra* note 10, at 712, 715 (describing the Industry’s rejection of the “therapeutic equivalence” model for biologics and its position that immunogenicity of a biologic and its follow-on product must be assessed in pre- and post-approval clinical studies); see also BIOTECHNOLOGY INDUS. ORG., THE DIFFERENCE WITH BIOLOGICS: THE SCIENTIFIC, LEGAL, AND REGULATORY CHALLENGES OF ANY FOLLOW-ON BIOLOGICS SCHEME 16 (2007) (discussing BIO’s early stance on therapeutic equivalence and arguing that, since it can be nearly impossible to determine if a biosimilar has the same “active ingredient,” it is nearly impossible to state that a follow-on biological is “therapeutically equivalent to the innovator and thus may not be substituted for the innovator”). Biologics legislation proposed in the 110th Congress varied in the approach to “therapeutic equivalence” and substitutability. Compare Patient Protection and Innovation Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 2(k)(2)(D) (2007) (PPIBMA) (unenacted) (disallowing the FDA to make a determination of “therapeutic equivalence”), with Pathway for Biosimilars Act of 2009, H.R. 5629, 110th Cong. § 101(k)(4)(A)(ii) (2007) (discussing a test seeking to determine the risk of “switching” between two biological products).

63. 42 U.S.C. §§ 262(k)(2)–(4).

64. See Interchangeability Draft Guidance, *supra* note 31 (announcing the availability of the guidance and calling for the submission of comments); U.S. Food & Drug Admin., Considerations in Demonstrating Interchangeability With a Reference Product; Draft Guidance for Industry; Availability; Extension of Comment Period, 82 Fed. Reg. 13,819 (Mar. 15, 2017) (extending the deadline for comments through May 19, 2017); U.S. Food & Drug Admin., Statistical Approaches to Evaluate Analytical Similarity; Draft Guidance for Industry; Availability, 82 Fed. Reg. 44,425 (Sep. 22, 2017).

persers be allowed to substitute biologics under relevant state laws either automatically or, if substitution is discretionary, without too much financial or administrative burden.

While BPCIA authorizes the FDA to make substitutability determinations, actual substitution of original products with their follow-on versions is governed by state laws (regulating the practice of medicine and dispensation of biomedical products). In the context of small molecule drugs, substitution of an original product with its cheaper generic version is *mandated* in fourteen states and *allowed*, at the discretion of the pharmacist, in the remaining thirty-six.<sup>65</sup> Yet, when it comes to biologics, substitution is not that straightforward. Even before the first biosimilar has been approved by the FDA (and the interchangeability pathway even contemplated), the Industry has engaged in a lobbying effort in the various states that would make the substitution of original biologics with their follow-on products all the more difficult and cumbersome (and, thus, less likely to occur) than the substitution of small molecule drugs.<sup>66</sup>

The Industry, both directly and through its many lackeys (typically, industry-funded patient groups and politicians receiving Industry donations), has successfully pushed for the enactment of statutes that erect hurdles to biologics substitution. Since 2013, thirty-seven states and Puerto Rico have passed legislation addressing biologics substitution, with most of them imposing special pre-requisites for biologics substitution.<sup>67</sup> Virtually all states that have passed biologics substitution legislation only allow for such substitution to take place when the FDA approved the follow-on biologic as *interchangeable* with the original biologic rather than just as biosimilar to it. As a result, since substitution of biosimilars for original biologics may not take place automatically, makers of biosimilars are being forced to invest in marketing their product to physicians to convince them to prescribe their follow-on products.<sup>68</sup> This inevi-

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65. U.S. DEP'T OF HEALTH & HUMAN SERVS., EXPANDING THE USE OF GENERIC DRUGS, Appendix A (2010), <https://aspe.hhs.gov/system/files/pdf/76151/ib.pdf>; see also Jesse C. Vivian, *Generic-Substitution Laws*, 33 U.S. PHARMACIST 30, 32 tbl.2 (2008), <https://www.uspharmacist.com/article/generic-substitution-laws> (noting that the vast majority of states also require patient notification of and/or consent to the substitution).

66. See Paradise, *supra* note 50, at 75, 79; Andrew Pollack, *Battle in States on Generic Copies of Biotech Drugs*, N.Y. TIMES, Jan. 28, 2013, at A1; *Building a Wall Against Biosimilars*, *supra* note 5, at 264 (describing Industry efforts lobby for state legislation that would restrict and hinder substitution by follow-on biologics).

67. Richard Cauchi, *State Laws and Legislation Related to Biologic Medication and Substitution of Biosimilars*, NAT'L CONF. ST. LEGISLATURES, <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx> (last visited Feb. 8, 2018).

68. In industry-familiar terms, biosimilars are relegated to the position of "me-too drugs." According to the former Congressional Office of Technology Assessment,

[m]e-too drugs are introduced after the pioneer and are similar but not identical to pioneer compounds . . . . Many me-too drugs are developed through deliberate imitation of the pioneer compound and have a shorter and more certain discovery period.

. . . .  
The pursuit of "me-too" drugs is an attempt by rival firms to shave off part of the monopoly profits enjoyed by the maker of the pioneer drug in a therapeutic class. The higher the initial monopoly profits, the more incentive rivals have to develop a similar competing drug.

U.S. CONG., OFFICE OF TECH. ASSESSMENT, PHARMACEUTICAL R&D: COSTS, RISKS AND REWARDS, OTA-H-522, 7, 46 (1993), [ota.fas.org/reports/9336.pdf](http://ota.fas.org/reports/9336.pdf).

tably raises the cost of biosimilars, driving up their price for payors and patient-consumers, further diminishing their savings and, thus, their attractiveness as possible substitutes to the original biologics.

Furthermore, even when deemed interchangeable by the FDA, almost all of the states that passed biologics substitution laws now require communication with or notification of the prescribing physician to “alert” him or her to the substitution.<sup>69</sup> Notably, this is despite the fact that BPCIA *defines* interchangeable biologics as “substitut[able] for the reference product without the intervention of the healthcare provider who prescribed the reference product”<sup>70</sup> and despite evidence showing that such notification requirements discourage substitution.<sup>71</sup> A number of states go even further and only allow substitution if the prescriber *explicitly* indicates that substitution is permissible, thereby completely turning the idea of automatic substitution on its head.<sup>72</sup> Many of the laws include additional record-keeping requirements, which do not apply to small-molecule drugs, and which impose added administrative burden on substituting pharmacists and prescribing physicians.<sup>73</sup> Various other hurdles to quick and simple substitution abound, such as a requirement that the state Board of Pharmacy maintains a list of interchangeable products.<sup>74</sup>

The Industry uses safety and “patient choice” arguments as pretexts for advocating for all of these extra-requirements in state biologics substitution laws.<sup>75</sup> Its true goal, however, is to inflict an added administrative burden on prescribers and pharmacists, thereby discouraging them from substituting original biologics with follow-on versions.<sup>76</sup> If and when the FDA approves a follow-on biologic as interchangeable, these requirements are sure to make such substitution less likely.<sup>77</sup>

Having been drafted by the Industry, state biologics substitution laws in general also reflect poorly on follow-on biologics as such.<sup>78</sup> Thus, for example, some statutes explicitly (and unnecessarily) mention prescribers’ right to pro-

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69. See Cauchi, *supra* note 67 (listing about thirty states as requiring some form of communication with the prescribing physician to alert him to the substitution, with about two thirds of these states requiring actual communication and the remaining requiring notification); see also Paradise, *supra* note 50, at 77.

70. 42 U.S.C. § 262(i)(3).

71. See Martha M. Rumore & F. Randy Vogenberg, *Biosimilars: Still Not Quite Ready for Prime Time*, 41 PHARMACY & THERAPEUTICS 366, 372 (2016) (“Notification ultimately serves to discourage pharmacist substitution.”).

72. See e.g., IND. CODE ANN. § 16-42-25-4(2)(A) (“[P]harmacist may substitute for a prescribed biological product if . . . The prescribing practitioner has . . . signed on the line under which the words “May substitute” [or] . . . electronically transmitted the instruction “May substitute.”); S.C. CODE ANN. § 39-24-40(A) (2017) (“An oral or written drug prescription must provide an authorization from the practitioner as to whether or not a therapeutically equivalent generic drug or interchangeable biological product may be substituted.”); UTAH CODE ANN. § 58-17b-605.5(6)(a) (2015).

73. Paradise, *supra* note 50, at 77; Cauchi, *supra* note 67.

74. Paradise, *supra* note 50, at 77; Cauchi, *supra* note 67.

75. See also Katherine MacFarlane, *Camouflaging State Biosimilar Laws as Pro-Patient Legislation*, 26 ANNALS OF HEALTH LAW 52, 63–70 (2017).

76. *Id.*

77. See also Paradise, *supra* note 50, at 83 (reaching a similar conclusion).

78. See *id.* at 79.

hibit substitution and patients' right to refuse an interchangeable product; by doing so (as well as by making substitution an administrative pain), these laws undermine physicians, pharmacists, and patients' confidence in follow-on biologics, thereby making the prescription, dispensing, and acceptance of interchangeable biologics even more questionable.<sup>79</sup>

#### *D. Onslaught Against Market Entry by Follow-On Biologics*

Even before the enactment of BPCIA, would-be makers of follow-on biologics had sought FDA approval for such products by asking FDA to rely on other, already-existing regulatory powers.<sup>80</sup> Such attempts, however, were *always* met with strong and—with one exception—ultimately successful Industry opposition, both in and outside of court.<sup>81</sup> The enactment of BPCIA has not changed much in this regard. Virtually any and every attempt to gain FDA approval or launch a follow-on biological product is met with efforts by the Industry to impede such attempts. This is true even, and perhaps especially, when the original biological product has benefitted from long periods of monopoly, often *much longer* than the twelve-year period of market exclusivity afforded under BPCIA, and even when the follow-on product has been long ago approved and tried in other countries.

To illustrate, the biologic filgrastim was first approved in the United States on February 20, 1991 and has since been marketed by the pharmaceutical company Amgen under the name Neupogen.<sup>82</sup> Subsequent to the enactment of BPCIA, on May 8, 2014 the generic pharmaceutical company Sandoz filed

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79. See Pollack, *supra* note 66 (quoting Brynna M. Clark, director of state affairs for the Generic Pharmaceutical Association).

One may view this aspect of the Industry's efforts to hinder the entry of follow-on biologics into the market as part of a much larger public relations campaign by the Industry to convince physicians, pharmacists, and patients that follow-on biologics are unsafe. See *e.g.*, *Building a Wall Against Biosimilars*, *supra* note 5, at 264 (speaking of Industry efforts in Europe and the United States to "cast[] suspicions on the safety and effectiveness of biosimilar competitors. Then, as the market has recognized that biosimilars are not poisons or snake oil, the public relations machine took over from the lobbyists and the message has segued into subtle side-swipes at the 'alien' character of producers of biosimilars that do not make brands"); PUBLIC CITIZEN, COMPETITION INHIBITORS: HOW BIOLOGICS MAKERS ARE LEVERAGING POLITICAL POWER TO MAINTAIN MONOPOLIES AND KEEP PRICES SKY-HIGH 24–26 (2014), <https://www.citizen.org/sites/default/files/report-biologics-industry-leverages-political-power-to-maintain-monopolies-and-inflate-prices.pdf> (stating "BIO has waged a vast campaign at the state level to impose burdensome requirements on pharmacists seeking to substitute FDA-approved interchangeable biosimilars," and that these efforts are to "cast doubt in the minds of doctors and patients on the substitutability of interchangeable biosimilars").

80. See Hessler Carver et al., *supra* note 10, at 684–86 (describing efforts to have certain biologics approved under the FDCA and mentioning that FDA use of FDCA provisions to approve protein products "in virtually every case prompt[ed] controversy and sometimes . . . litigation"); *id.* at 700–02 (describing how Industry pressure has led the FDA to deny an application for approval of a follow-on version of the growth hormone product Omnitrope, despite the fact that the two products were apparently sufficiently clinically equivalent).

81. *Id.* at 686, 699 (discussing the approval of a Omnitrope).

82. See *Neupogen Approval*, *supra* note 55.



an application to have its own version of filgrastim approved by the FDA.<sup>83</sup> Yet, despite Sandoz's filgrastim having been approved in Europe since June 2009;<sup>84</sup> despite its being well characterized, tested, and widely clinically used in other countries;<sup>85</sup> despite the fact that, by the time Sandoz filed its application for its filgrastim product, all patents covering Neupogen have apparently expired; and despite Amgen's monopoly over the filgrastim market in the United States lasting *more than twenty-three years* (almost twice as long as the twelve years of exclusivity under BPCIA), Amgen launched a campaign aimed at delaying the entry of Sandoz's filgrastim into the market. Amgen's suit against Sandoz has, thus far, led to four rounds of litigation (including two before the Court of Appeals for the Federal Circuit and one before the United States Supreme Court),<sup>86</sup> included both state and federal claims, and saw a temporary injunction issued against the launch of Sandoz's filgrastim.<sup>87</sup> Sandoz's filgrastim was eventually launched in September 2015, becoming the first biosimilar to have been approved in the United States.<sup>88</sup> Amgen's actions, however, delayed the launch of Sandoz's filgrastim by another year and four months, which was worth well over \$1 billion for Amgen, and which required Sandoz to spend what was probably many millions of dollars to defend itself against Amgen's attacks.<sup>89</sup>

There are quite a few other examples of such cases. In fact, there has not been a single case in which a follow-on biologic maker/applicant *did not* have to defend itself and its product against an attack by the Industry, including where the follow-on product has been long approved and in continuous clinical

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83. See U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RESEARCH, SUMMARY REVIEW FOR REGULATORY ACTION, APPLICATION NO. 125553ORIG1S000, AT 1 (2015), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/125553Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125553Orig1s000SumR.pdf).

84. European Agency, *Zarxio*, [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000917/human\\_med\\_001170.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000917/human_med_001170.jsp&mid=WC0b01ac058001d124) (last updated Sept. 18, 2017).

85. *Id.*; see also Lisa A. Raedler, *Zarxio (Filgrastim-sndz): First Biosimilar Approved in the United States*, 9 Am. Health Drug Benefits 150, 151–52 (2016) (discussing “[c]omprehensive studies . . . performed to fully characterize and evaluate filgrastim-sndz to meet the FDA’s requirements for its approval as a biosimilar (Table)” and a successful clinical trial that assessed filgrastim-sndz’s clinical comparability with filgrastim).

86. *Amgen, Inc. v. Sandoz, Inc.*, No. 14-cv-04741, 2015 WL 1264756 (N.D. Cal. Mar. 19, 2015); *Amgen, Inc. v. Sandoz, Inc.*, 794 F.3d 1347 (Fed. Cir. 2015) (affirming in part, vacating in part, remanding); *Sandoz, Inc. v. Amgen, Inc.*, 137 S.Ct. 1664 (2017) (reversing in part, vacating in part); *Amgen, Inc. v. Sandoz, Inc.*, 877 F.3d 1315 (Fed. Cir. 2017) (on remand, affirming).

87. *Amgen, Inc. v. Sandoz, Inc.*, No. 15-1499 (Fed. Cir. May 5, 2015) (order granting injunction).

88. Sandoz's filgrastim was approved by the FDA on March 6, 2015. See Letter from Ann T. Farrell, Dir. Div. of Hematology Prods., Office of Hematology & Oncology Prods., Ctr. for Drug Evaluation & Research, Food & Drug Admin., to Sandoz, Inc. (Mar. 6, 2015). It was launched on Sep. 3, 2015. Press Release, Novartis, Sandoz Launches Zarxio™ (filgrastim-sndz), the First Biosimilar in the United States, Sep. 3, 2015, <https://www.novartis.com/news/media-releases/sandoz-launches-zarxiotm-filgrastim-sndz-first-biosimilar-united-states>.

89. Amgen's reported profits from the sales of Neupogen in the United States in 2014 (prior to the approval of Sandoz's filgrastim product) were \$839 million. See *Amgen's 2014 Revenues Increased 7 Percent To \$20.1 Billion And Adjusted Earnings Per Share (EPS) Increased 14 Percent To \$8.70*, CISION PR NEWSWIRE (Jan. 27, 2015) <https://www.prnewswire.com/news-releases/amgens-2014-revenues-increased-7-percent-to-201-billion-and-adjusted-earnings-per-share-eps-increased-14-percent-to-870-300026586.html>.

use outside of the United States.<sup>90</sup> On their face, such attacks are legal, at least to the extent that they seem to fall under the Knorr-Pennington doctrine.<sup>91</sup> They are also not outside the general norm in the pharmaceutical industry, in which players are accustomed to suing and being sued as part of doing business. BPCIA is different from the Hatch-Waxman Act, however, in that it does not require or directly incentivize parties to sue one another. So, the emerging reality in which follow-on biologics makers are being subject to inevitable, substantial legal attacks—no matter how long the monopoly in the original product has been and how good of a substitute is the follow-on biologic—is unfortunate. This reality is also telling of the structure of incentives in biologics markets as well as of the formidable (if not daunting) financial undertaking for which would-be entrants must be prepared. Legal or not, business-as-usual or not, this reality is wasteful and further inhibits the prospects of there ever being robust competition in biologics markets.

Furthermore, in accord with Carrier and Minniti's warnings, the Industry's attacks against approval and market-entry of follow-on biologics, thus far, has also included some of the Industry's bad old anti-competitive practices. Indeed, as observed by commentators, with the sales of many biologic products being worth many billions of dollars annually,<sup>92</sup> the Industry seems to be pre-

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90. See e.g., *Janssen Biotech, Inc. v. Celtrion Healthcare Co. Inc.*, 210 F. Supp. 3d 244 (D. Mass. 2016). Janssen sued Celtrion for patent infringement under 35 U.S.C. § 271(e)(2)(C) for seeking FDA approval of a follow-on version of infliximab, which has already been approved and in use in Europe since October 2013 and in 47 other countries at that time. See Kurt R. Karst, *A Second Lawsuit Tests the BPCIA Biosimilars "Patent Dance" Waters*, FDA LAW BLOG (Apr. 1, 2014), <http://www.fdalawblog.net/2014/04/a-second-lawsuit-tests-the-bpcia-biosimilars-patent-dance-waters/>. Janssen's infliximab product, Remicade, has been approved in the United States since August 24, 1998; Celtrion's infliximab product, Infectra, has been approved in Europe since 2013). *Amgen Inc. et al v. Hospira, Inc.*, No. 1:15CV00839 (D. Del. Sep. 18, 2015) (Amgen sued Hospira for patent infringement for seeking FDA approval of a follow-on version of Amgen's epoetin product, Epogen/Procrit; Amgen's product has been approved in the United States since 1989; Hospira's epoetin product, Retacrit, has been approved in Europe since 2007); *Amgen, Inc. v. Apotex Inc.*, No. 15-61631-CIV, 2015 WL 11198250 (S.D. Fla. Dec. 9, 2015), *aff'd*, 827 F.3d 1052 (Fed. Cir. 2016) (Amgen sued Apotex for seeking to market a follow-on version of Amgen's pegfilgrastim product, Neulasta, which has been approved in the United States since 2002); *Amgen, Inc. v. Sandoz, Inc.*, No. 3:16-cv-02581 (N.D. Cal. May 12, 2016); *Immunex Corp. et al. v. Sandoz Inc. et al.*, No. 3:16CV01118 (D.N.J. Feb. 26, 2016) (Immunex and two other biotech companies sued Sandoz for patent infringement for seeking FDA approval of a follow-on version of Immunex's etanercept product, Enbrel; Immunex's product has been approved in the United States since 1998; Sandoz's etanercept product, Erelzi, has been approved in Europe since June 2017); *Amgen, Inc. v. Sandoz, Inc.*, No. 3:16-CV-01276 (D.N.J. Mar. 4, 2016); *AbbVie Inc. et al. v. Amgen Inc. et al.*, No. 1:16CV00666 (D. Del. Aug. 4, 2016) (AbbVie sued Amgen for seeking approval for a follow-on version of AbbVie's adalimumab product, Humira; AbbVie's Humira has been approved in the United States since 2002; Amgen's adalimumab product, Amgevita, has been approved in Europe since March 2017); *Genentech, Inc. et al. v. Pfizer, Inc.*, No. 1:17CV01672 (D. Del. Nov. 17, 2017) (Genentech sued Pfizer for seeking approval for a follow-on version of Genentech's trastuzumab product, Herceptin; Genentech's Herceptin has been approved in the United States since 1998).

91. Under the Noerr-Pennington doctrine, private parties are immune from antitrust liability for trying to enforce laws even if the result of their actions may have an anti-competitive effect. *United Mine Workers v. Pennington*, 381 U.S. 657, 670 (1965); *Eastern R.R. Presidents Conference v. Noerr Motor Freight, Inc.*, 365 U.S. 127, 135 (1961).

92. For example, the annual sales of AbbVie's Humira and Amgen's Enbrel are \$14B and \$9B respectively. See Jayne O'Donnell, *Biologic Drugmakers Use Patents, Suits to Thwart Generic Competition*, USA TODAY (Aug. 4, 2016), <https://www.usatoday.com/story/news/politics/2016/08/04/biologic-drugmakers-patents-suits-generic-competition/87915734/>.

pared to do whatever it takes to keep competition out of the market. The scope of this Comment does not allow for a full discussion of the different types and specific instances of Industry anti-competitive conduct that is already taking place and that is aimed at purposely thwarting the entry of follow-on competition into biologics markets. Some examples, however, are illustrative.

First, as per Carrier and Minniti's predictions, the Industry has been persistently campaigning the FDA, using the citizen petition procedure, to adopt rules that would make more difficult the evaluation, approval, and marketing of follow-on biologics. Examples include Abbott Laboratories' 2012 petition to have the "FDA confirm that it will not accept for filing, file, approve, or discuss . . . any application . . . for biosimilar that cites [an original product] submitted to FDA . . . prior to the date on which BPCIA was signed into law,"<sup>93</sup> AbbVie Inc.'s 2015 petitions,<sup>94</sup> numerous petitions submitted pertaining to the naming of follow-on biologics,<sup>95</sup> and Amgen's petition to have the FDA force Sandoz to follow BPCIA's Patent Dance procedures.<sup>96</sup> Notably, Carrier and Minniti predict that anti-competitive use of citizen petitions may be less prevalent with respect to biologics.<sup>97</sup> It may also be too early to evaluate the use of citizen petitions as an anti-competitive instrument in the context of biologics, as Carrier and Minniti have done with respect to small-molecule drugs.<sup>98</sup> Yet, as noted by other commentators, "[t]he science of biologics—and the stakes involved for competitors—provides some caution to Carrier and Minniti's otherwise hopeful conclusions about citizen petitions."<sup>99</sup>

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93. See Letter from Covington & Burling, on behalf of Abbott Laboratories, to Div. of Dockets Mgmt., Food & Drug Admin. (Apr. 2, 2012), <https://www.regulations.gov/document?D=FDA-2012-P-0317-0001> (citizen petition).

94. Letter from AbbVie Inc., to Div. of Dockets Mgmt., Food & Drug Admin. (June 2, 2015) <http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001> (citizen petition) (asking FDA to require the labeling of biosimilar products include statements and descriptions that would differentiate them from the original biologics they seek to emulate); Letter from AbbVie Inc., to Div. of Dockets Mgmt., Food & Drug Admin. (Dec. 16, 2015), <https://www.regulations.gov/document?D=FDA-2015-P-4935-0001> (citizen petition) (asking FDA to require that follow-on biologics would only be deemed interchangeable if they are held as such for every approved clinical use of the original product).

95. See e.g., Letter from AbbVie Inc., to Div. of Dockets Mgmt., Food & Drug Admin. (June 2, 2015), <http://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001> (citizen petition) (arguing the name filgrastim after Zarxio "could easily mislead prescribers into thinking that Zarxio either is filgrastim or can be substituted for it interchangeably, neither of which is true"); Letter from Jay P. Siegel, Chief Biotechnology Officer, Johnson & Johnson, to Div. of Dockets Mgmt., Food & Drug Admin. (Jan. 7, 2014), <https://www.regulations.gov/document?D=FDA-2014-P-0077-0001> (citizen petition) (asking FDA to "require biosimilars to bear nonproprietary names that are similar to, but not the same as, those of their reference products").

96. Letter from Jeffrey P. Kushan, Partner, Sidley Austin LLP, on behalf of Amgen, Inc., to Div. of Dockets Mgmt., Food & Drug Admin. (Oct. 29, 2014), <https://www.regulations.gov/contentStreamer?documentId=FDA-2014-P-1771-0001&attachmentNumber=1&contentType=pdf>.

97. See Carrier and Minniti, *supra* note 1, at 62; see also Jacob S. Sherkow, *The Science of Substitution: A Response to Carrier & Minniti*, 2018 U. ILL. L. REV. ONLINE 11 (forthcoming 2018).

98. See generally Michael A. Carrier and Carl J. Minniti, *Citizen Petitions: Long, Late-Filed, and At Last Denied*, 66 AM. U. L. REV. 305 (2016).

99. See Sherkow, *supra* note 97, at 11.

Second, in what appears, at least on its face, to be violations of antitrust laws—both in the United States and abroad—the Industry has been, reportedly, using its current market power to force follow-on biologics makers out of the market. In one recently filed suit, the pharmaceutical company Johnson & Johnson (J&J) is being accused of using its power in the market for the biologic product infliximab to “impos[e] a web of exclusionary contracts on both health insurers and healthcare providers” in order to drive the biosimilar product Inflectra out of the market.<sup>100</sup> According to another recent lawsuit, the pharmaceutical company Roche lowered the price of Herceptin in Russia to below-cost levels (while raising its price in the United States) in order to drive a local competitor, the Russian company Biocad, out of the market and prevent it from ever launching its follow-on version of trastuzumab in the United States.<sup>101</sup> These claims portray a concerning picture of a set of anti-competitive practices which, if allowed to persist, will likely “become the playbook for biologic originator firms seeking to preserve their dominance in the face of biosimilar competition” by all means necessary.<sup>102</sup>

Third, subsequent to BPCIA, makers of original biologics have been amassing patents<sup>103</sup> with the apparent intention of asserting these patents en masse against follow-on product makers in order to further delay their entry into the market.<sup>104</sup> For example, in anticipation of the expiration of the patents on its best-selling biologic, Humira (adalimumab), the pharmaceutical company AbbVie has pursued and secured many dozens of secondary patents.<sup>105</sup> AbbVie seems to hope that its newly acquired patent thicket would help it secure an additional five more years to its fourteen years of monopoly in the market for ada-

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100. Complaint at 1, *Pfizer Inc. v. Johnson & Johnson et al.*, 2:17-cv-4180, 1 (E.D. Pa. Sept. 20, 2017). Notably, according to the Complaint, Johnson & Johnson’s (J&J) anti-competitive actions are part of a pre-conceived “Biosimilar Readiness Plan” aimed at foreclosing follow-on makers’ access to the infliximab market. *Id.* at 2. Interestingly, the lawsuit was filed by the pharmaceutical giant Pfizer, which is typically associated with the Industry.

101. See generally *Biocad, JSC v. F. Hoffman-La-Roche, Ltd.*, No. 16 CIV. 4226 (RJS), 2017 WL 4402564 (S.D.N.Y. Sept. 30, 2017) (*appeal pending in Biocad, JSC v. F. Hoffman-La-Roche, Ltd.*, No. 17-3486 (2d Cir. Oct. 27, 2017)).

102. See Complaint, *supra* note 100, at 9.

103. Biomedical products are typically covered by relatively early “primary patents” on the therapeutic compound (a.k.a. active pharmaceutical ingredient (API)). They may also be covered by later patent on modified forms of the API, additional medical uses of the API, combinations of known APIs, formulations of the API (e.g., tablets, injections), dosage regimens, etc. See generally Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of “Secondary” Pharmaceutical Patents*, 7 PLOS ONE, e49470 (2012). Secondary patents are usually associated with practices aimed at prolonging an original product’s market power as part of what the Industry calls “life cycle management” and critics of such practices call “evergreening.” See e.g., Tahir Amin & Aaron S. Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study of How Patents on Two HIV Drugs Could Be Extended for Decades*, 31 HEALTH AFFAIRS 2286, 2286 (2012).

104. See e.g., Carrier and Minniti, *supra* note 1, at 37.

105. See Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions*, N.Y. TIMES, Jul. 15, 2016, at B1 (quoting an AbbVie executive saying “[a]ny company seeking to market a biosimilar version of Humira will have to contend with this extensive patent estate, which AbbVie intends to enforce vigorously”). As noted above, AbbVie is already asserting these patents against follow-on biologics makers seeking to enter the market for adalimumab. See *AbbVie Inc. et al. v. Amgen Inc. et al.*, No. 1:16CV00666 (D. Del. Aug. 4, 2016).

limumab.<sup>106</sup> Similarly, as reported by Carrier and Minniti, the pharmaceutical company Amgen was able to obtain two “submarine patents”<sup>107</sup> on its product Enbrel (Etanercept), which are expected to extend Enbrel’s monopoly by another fifteen years to a total of thirty-one years.<sup>108</sup> In another example, according to two lawsuits filed by follow-on biologics makers, which attempted to follow the Patent Dance procedure, subsequent to sharing their products’ manufacturing information with the manufacturer of the original products, they received back a list of no less than *forty patents*, which the original product manufacturer, Genentech, asserts may be infringed by the proposed follow-on products.<sup>109</sup> The complaints further allege that Genentech is insisting on maintaining a “panoply of vague allegations” and refuses to narrow down its claims to a subset of those patents that are realistically implicated by the follow-on products.<sup>110</sup> As a side, the amassing of patents as well as their use to perpetrate anti-competitive abuses reaffirms and reinforces calls to make original biologics makers choose between the twelve-year exclusivity and enforcing patents covering their products against follow-on applicants.<sup>111</sup>

All of these are but early examples of potentially anti-competitive behaviors, as none of them has yet been recognized as such by a court. Still, the fact that there are so many, so early after the approval of the first biosimilars (and before any interchangeable biosimilar has even been approved) does not bode well for the future of follow-on biologics and, more generally, for competition in biologics markets. At the very least, these examples confirm that Carrier and Minniti’s warnings and predictions regarding risks of anti-competitive practices in biologics markets were not unjustified.<sup>112</sup>

### III. THE RESULTING HINDERED FOLLOW-ON BIOLOGICS MARKETS: PRESENT

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106. See Pollack, *supra* note 105; see also Nicholas Mitrokostas & Elaine Blais, *End of a Humira Battle: Observations from the AbbVie-Amgen Armistice*, BIOSIMILAR DEV. (Oct. 31, 2017), <https://www.biosimilardevelopment.com/doc/end-of-a-humira-battle-observations-from-the-abbvie-amgen-armistice-0001>.

107. See Carrier and Minniti, *supra* note 1 at 43 & nn. 327–28.

108. *Id.* at 44; see also Pollack, *supra* note 105.

109. See Complaint for Declaratory Judgment, Celltrion, Inc. et al. v. Genentech, Inc. et al., No. 3:18-cv-274-LB, at 2 (N.D. Cal. Jan. 11, 2018); Complaint for Declaratory Judgment, Celltrion, Inc. et al. v. Genentech, Inc. et al., No. 5:18-cv-276-HRL, at 2 (N.D. Cal. Jan. 11, 2018); see also Greg Langlois, *Celltrion, Teva Suit Says Biosimilar Patent Claims Over-the-Top*, BLOOMBERGLAW BIOTECH WATCH, Jan. 17, 2018 (describing Genentech’s tactic as including “everything but the kitchen sink”).

110. See Complaint for Declaratory Judgment, *supra* note 109, at 2. Notably, in so doing, Genentech seems to breach its obligations under BPCIA, including the obligation to partake in “good faith negotiations to agree on which, if any, [of these] patents. . . shall be the subject of an action for patent infringement.” 42 U.S.C. § 262(l)(4)(A) (2017).

111. See Heled, *supra* note 29, at 462–70 (proposing to make developers of original biologics choose between the ability to enforce patents covering their products against follow-on biologics makers or the twelve-year exclusivity. Although the proposal excepts secondary patents, experience with BPCIA and the grim state of competition in biologics may nonetheless require that secondary patents be made part of the proposed choice of original biologics developers between the two forms of exclusivity).

112. *But see* Lietzan, *supra* note 32, at 20, 34 (describing Carrier and Minniti’s predictions as “speculative” and a “solution in search of a problem,” warning that BPCIA might result in too little incentives for innovation, and generally disagreeing with Carrier and Minniti’s descriptions and assessments).

## AND FUTURE

The current picture of competition in biologics markets is grim. The first biosimilar product approval in the United States took place in 2015, almost a full decade after the approval of the first biosimilar in Europe and nearly twenty years—a full generation—after the initiation of the debate regarding follow-on biologics.<sup>113</sup> Since then, a total of only nine biosimilar products have been approved in the United States<sup>114</sup> (as compared with Europe’s thirty-seven<sup>115</sup>), with only three of these products actually clearing all hurdles to make it to the market (while others languish in legal battles),<sup>116</sup> and with none of these products approved as interchangeable.<sup>117</sup>

113. See *Zarxio Approval*, *supra* note 55.

114. The eight biosimilars approved since Zarxio are: (1) Inflectra (Infliximab-dyyb) approved April 2016; (2) Erelzi (Etanercept-szszs) approved August 2016; (3) Amjevita (Adalimumab -atta) approved September 2016; (4) Renflexis (Infliximab-abda) approved May 2017; (5) Cyltezo (Adalimumab-adbm) approved August 2017; (6) Mvasi (Bevacizumab-awwb) approved September 2017; (7) Ogivri (trastuzumab-dkst) approved December 2017; and (8) Ixifi (infliximab-qbtbx) approved December 2017. *Biosimilar Product Information*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm> (last visited Apr. 3, 2018).

115. An additional five biosimilar market authorization applications were either rejected or withdrawn post-approval. *European Public Assessment Reports: Biosimilars*, EUROPEAN MEDS. AGENCY, [http://www.ema.europa.eu/ema/index.jsp?mid=WC0b01ac058001d124&searchType=name&taxonomyPath=&genericsKeywordSearched=Submit&searchGenericType=biosimilars&keyword=Enter+keywords&alreadyLoaded=true&curl=pages%2Fmedicines%2Flanding%2Fepar\\_search.jsp&status=Authorised&treeNumber=&searchTab=searchByAuthType&pageNo=1](http://www.ema.europa.eu/ema/index.jsp?mid=WC0b01ac058001d124&searchType=name&taxonomyPath=&genericsKeywordSearched=Submit&searchGenericType=biosimilars&keyword=Enter+keywords&alreadyLoaded=true&curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&status=Authorised&treeNumber=&searchTab=searchByAuthType&pageNo=1) (last visited Apr. 3, 2018).

116. Besides Zarxio, only Renflexis (Infliximab-abda) and Inflectra (Infliximab-dyyb) are currently marketed. Zachary Brennan, *FDA Approves 6th Biosimilar in US, Second for Humira*, REG. AFFS. PROFS. SOC’Y (Aug. 28, 2017), <https://www.raps.org/news-articles/news-articles/2017/8/fda-approves-6th-biosimilar-in-us,-second-for-humira> (stating Cyltezo (adalimumab biosimilar) is not expected “for at least another couple of years because of patent litigation”); *Court Battle Will Delay Launch of Enbrel Biosimilar Until at Least 2018*, Managed Care (Jan. 25, 2017), <https://www.managedcaremag.com/news/court-battle-will-delay-launch-enbrel-biosimilar-until-at-least-2018> (stating Erelzi (etanercept biosimilar) is held up by patent litigation with Amgen, the maker of Enbrel (etanercept), who claims it has a valid patent until 2029); Jeff Evans, *Launch of adalimumab biosimilar Amjevita postponed*, RHEUMATOLOGY NEWS (Sept. 29, 2017), <https://www.mdedge.com/rheumatologynews/article/148375/rheumatoid-arthritis/launch-adalimumab-biosimilar-amjevita-postponed> (stating an agreement with AbbVie, the maker of Humira (adalimumab), will keep Amjevita (adalimumab biosimilar) off the market until 2023); *Genentech’s Complaint Against Amgen Regarding MVASI® (bevacizumab-awwb)*, GOODWIN: BIG MOLECULE WATCH (Oct. 18, 2017), <https://www.bigmoleculerwatch.com/2017/10/18/genentechs-complaint-amgen-regarding-mvasi-bevacizumab-awwb/> (stating the launch of Mvasi is held up by litigation); Manas Mishra, *FDA OKs Mylan’s biosimilar of Roche cancer drug Herceptin*, REUTERS (Dec. 1, 2017, 11:07 AM), <https://www.reuters.com/article/us-mylan-l-fda/fda-oks-mylans-biosimilar-of-roche-cancer-drug-herceptin-idUSKBN1DV5BI> (stating an agreement with Roche, the maker of Herceptin (trastuzumab), will keep Ogivri off the market until 2019); Nicolle Rychlick, *Biosimilars for Rheumatoid Arthritis: Don’t Count Them Out Quite Yet*, Managed Care (Jan. 1, 2018), <https://www.managedcaremag.com/archives/2018/1/biosimilars-rheumatoid-arthritis-don-t-count-them-out-quite-yet> (stating Renflexis and Inflectra are currently battling for market share against Remicade, the originator infliximab).

117. See U.S. FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RESEARCH, LIST OF LICENSED BIOLOGICAL PRODUCTS WITH (1) REFERENCE PRODUCT EXCLUSIVITY AND (2) BIOSIMILARITY OR INTERCHANGEABILITY EVALUATIONS TO DATE (Feb. 1, 2018) (“Purple Book”), <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf>.

Part of the responsibility for this record is, to be sure, the FDA's, which has taken very long to create an actual pathway for approval of biosimilars and is taking even longer to create a pathway for approval of interchangeable follow-on biologics. Yet, much of the responsibility for these delays rests with the Industry, whose actions in every step of the way have contributed greatly to delays and made it difficult and daunting for potential competitors to enter the market. Indeed, given all of the above, entry into the business of follow-on biologics is not for the faint of heart or risk-averse. From the outset, follow-on biologics markets have been predicted to yield levels of competition significantly below those in generic drug markets. Yet, the success of Industry efforts to curtail competition in these markets has made things all the more so, resulting in potential follow-on biologics makers becoming even more reluctant to enter these markets.<sup>118</sup> The result, as predicted by some commentators, is that biologics markets are inhabited by only a handful of pharmaceutical giants which, protected by high entry barriers, only minimally compete with one another.<sup>119</sup>

As for the future, there is little reason to believe competition in biologics markets in the United States is going to become significantly better. Since biologics markets are highly lucrative, it is expected that incentives for follow-on entry will be sufficiently high for a limited number of sophisticated and financially well-backed players to attempt to enter these markets.<sup>120</sup> This, in turn, might give out the impression that follow-on biologics markets are thriving and achieve their object of increasing access to biologics. Yet, from a public health standpoint, follow-on biologics will, in all likelihood, continue to be a highly limited phenomenon, providing few, expensive, and mostly non-interchangeable options for payors, prescribers, and patients.

#### CONCLUSION

Between BPCIA, confidentiality of regulatory filings, state substitution legislation, and the extraordinary legal and regulatory cost of launching follow-

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118. See e.g., Paradise, *supra* note 50, at 82–83 (“[T]here appears to be a hesitation to enter the market due to both uncertainties regarding regulation and increasing state activity to place restrictions on substitution . . . restrictions imposed on substitution may serve as barriers to market entry by potential applicants.”).

119. As poignantly stated in a Nature Biotechnology editorial:

. . . only a few subsidiaries of big pharma, a handful of established multinational generic manufacturers and the dominant large-cap biotech companies are likely to make the biosimilars business a success. The tables are currently tilted so far in favor of these few companies, it is difficult to see how sufficient new entrants can come into the market and drive down pricing, especially when originator companies are playing the game from both sides—betting on brands and biosimilars at the same time.

See *Building a Wall Against Biosimilars*, *supra* note 5, at 264; see also EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, *supra* note 28, at iii–iv (making similar predictions).

120. See EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, *supra* note 28, at iii–iv.

on biologics, the legal ecosystem of biologics is itself anti-competitive.<sup>121</sup> One must not be overly heartened by the number of biosimilar applications pending at the FDA and the likely possibility that some biologics markets will see the entry of some competition in the next few years.<sup>122</sup> One also should not take the mere emergence of such competition to be a sign that BPCIA is working properly nor be impressed by sales figures—high as they may be—of a few approved follow-on biologics, as sales figures are poor indicators of competition and are more indicative of medical need (and desperation of patients). The goal has never been merely to have *some* competition in biologics markets. Rather, it is to have *sufficient competition to drive biologics prices down significantly*.

Without a sea change (*e.g.*, in the science of analyzing and comparing biologics) or paradigm shift in the way follow-on biologics are evaluated and approved, competition in biologics markets in the United States will remain more akin to the kind of competition that exists in markets in which a few large companies promote their “me too” versions of certain drugs<sup>123</sup> than markets that have seen the entry of true generics.<sup>124</sup> Like in Europe, a few exceptions may exist where competition does end up driving the price of some biologics below the typical 15-30% decrease upon the entry of a biosimilar product, but the prices of most biologics will remain high, to the detriment of patients and payors. In all likelihood, another generation will have passed before we acquire sufficient data to decidedly establish that biologics markets are—to put it plainly—rigged; that BPCIA and follow-on biologics markets have failed to significantly lower biologics prices and increase access to biologics; that barring a paradigm shift in how we develop and approve follow-on biologics, competition in biologics will remain stunted and biologics’ prices high.

At this point and in this political landscape, the prospect of change is bleak. However, if and when policymakers and regulators become interested in fostering robust competition in biologics markets and/or in making biologics affordable, they should look to solutions outside of BPCIA, or even outside of markets.

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121. See also *Building a Wall Against Biosimilars*, *supra* note 5, at 264 (making the similar argument that biosimilars markets are not “molded” to foster a reality where “better products do better, and equivalent products compete on price”).

122. As of January 2018, eleven biosimilars are pending approval at FDA. These include: Retacrit (epoetin alpha biosimilar), Lapelga (pegfilgrastim biosimilar), Gastrofil (filgrastim biosimilar), LA-EP2006 (pegfilgrastim biosimilar), CHS-1701 (pegfilgrastim biosimilar), MYL-1401H (pegfilgrastim biosimilar), CT-P6 (trastuzumab biosimilar), ABP 980 (trastuzumab biosimilar), Adello Biologics’ unnamed filgrastim biosimilar, Rixathon/GP2013 (rituximab biosimilar), and SB3 (trastuzumab biosimilar). *Status of Biosimilar Applications: January 2018*, MINTZ LEVIN, [https://www.mintz.com/newsletter/2018/Documents/Status-of-Biosimilar-Applications\\_January-2018.pdf](https://www.mintz.com/newsletter/2018/Documents/Status-of-Biosimilar-Applications_January-2018.pdf) (last visited Apr. 3, 2018).

123. See PHARMACEUTICAL R&D: COSTS, RISKS AND REWARDS, *supra* note 68, at 7.

124. The Federal Trade Commission had reached a similar conclusion as early as 2009 (pre-BPCIA). See EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, *supra* note 28, at iii (“[C]ompetition from FOB drug entry is likely to resemble brand-to-brand competition, rather than brand-to-generic drug competition.”); see also Trevor Woodage, *Blinded by (a Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-On Biologics and Barriers to Their Approval and Commercialization*, 2012 STAN. TECH. L. REV. 9 (2012) (predicting that “as currently structured, BPCIA is not likely to result in the dramatic reductions in healthcare costs”).



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SET UP TO FAIL

137

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