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## A SOLUTION IN SEARCH OF A PROBLEM AT THE BIOLOGICS FRONTIER

Erika Lietzan\*

I am honored to have been asked by the editors of the University of Illinois Law Review to comment on Professor Michael Carrier's new article, *Biologics: The New Antitrust Frontier*.<sup>1</sup> His article—coauthored with Carl Minniti, a recent graduate of his law school—continues a large body of work that considers the application of antitrust law to the pharmaceutical industry. In this body of work, Professor Carrier has consistently identified a variety of actions taken by innovative (and sometimes generic) drug companies as actually or potentially collusive or anticompetitive. These include patent litigation settlements with reverse payments or other terms beneficial to accused infringers (called “pay for delay” by their critics), launch of newer versions of innovative products near the time of generic approval and market launch (“product hopping” by critics), decisions not to provide generic competitors with samples of certain higher-risk products for use in comparative testing unless certain conditions are met (“REMS abuse” by critics), and certain citizen petitions that raise scientific and legal concerns about pending generic drug applications (“sham petitions” by critics).<sup>2</sup>

Professor Carrier's earlier pieces related to conventional drugs (sometimes called “small molecule” drugs) approved under the Federal Food, Drug, and Cosmetic Act (“FDCA”) and their generic equivalents approved under the Hatch-Waxman Amendments to the same statute. In his latest article, Professor Carrier begins the process of extending his analysis to a new marketplace for medicines made possible by a 2010 amendment to the Public Health Service Act (“PHSA”)—the marketplace for biosimilar and interchangeable biologics.<sup>3</sup> Biologics are

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\* Associate Professor of Law, University of Missouri-Columbia. I am grateful to Krista Carver, David Korn, Kristina Lybecker, and Mark Schulz for comments.

1. Michael A. Carrier & Carl J. Minniti, III, *Biologics: The New Antitrust Frontier*, 2018 U. ILL. L. REV. 1 (2018).

2. E.g., Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009 (2010); Michael A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. U. L. REV. 305 (2016); Michael A. Carrier, *Payment After Actavis*, 100 IOWA L. REV. 7 (2014); Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167 (2016).

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

meaningfully different from small-molecule drugs, and the rules and practical considerations that govern the development, FDA approval, reimbursement, promotion, and market uptake of biosimilar and interchangeable biologics may be like nothing antitrust scholars and courts have seen before.<sup>4</sup> Professor Carrier's new article is the first to seriously grapple with application of antitrust law to this new marketplace made possible by the Biologics Price Competition and Innovation Act of 2009 ("BPCIA").

His article proceeds methodically through seven issues that have attracted antitrust scrutiny in the small-molecule setting. With respect to each, Carrier predicts the likelihood that conduct he views as problematic in the small-molecule setting will arise also in the biologics setting, and he offers an antitrust assessment. On the one hand, he predicts fewer reverse-payment settlements, less "product hopping," and fewer of the types of citizen petitions that concern him.<sup>5</sup> On the other hand, he predicts "manipulation" of the patent-litigation scheme by innovators, disparagement of biosimilars by innovators, and price collusion between biosimilar companies and innovators.<sup>6</sup> He also predicts that FDA will continue to require access and distribution restrictions for high-risk biologics and assumes that some innovators will refuse sales of restricted products.<sup>7</sup> As far as antitrust analysis is concerned, he generally argues for "robust" scrutiny in each case "similar to what courts have applied in the small-molecule setting," though he would permit a more deferential analysis of innovator citizen petitions, owing to their likely complexity in this setting.<sup>8</sup>

The article makes a profound initial contribution to a new area of scholarship. But Professor Carrier's article, like my own earlier piece on the marketplace and like this response, is inherently speculative. FDA has approved only a handful of biosimilar biologics, and it has not approved any interchangeable biologics.<sup>9</sup> The new biologics framework is different

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4. See generally Carrier, *Antitrust Frontier*, *supra* note 1, at 4–11, 14–19. Biologics are often manufactured in, composed of, or derived from, living systems. They are usually much larger at the molecular level—as many as 1,000 times larger—than nonbiological drugs. They are also structurally more complex and sometimes not well characterized. A biologic's mechanism of action may not be understood, and the relationship between its structural attributes and clinical performance may not be understood. And, unlike most small-molecule drugs, biological products can stimulate an immune response in the body. This response can affect both product effectiveness and patient safety, in varying and unpredictable ways. As a result of these differences, FDA's regulatory approach to biologics license applications ("BLAs") has always been different from its regulatory approach to small-molecule new drug applications ("NDAs"), and the scientific and regulatory framework for biosimilars is nothing like the scientific and regulatory framework for generic drugs. See generally Erika Lictzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 FLA. ST. L. REV. 1 (2017).

5. Carrier, *Antitrust Frontier*, *supra* note 1, at 25, 30, 58.

6. *Id.* at 39, 69, 72. He uses the phrase "regulatory abuse" as the label for this "manipulation" of the patent provisions.

7. *Id.* at 52.

8. *Id.* at 4, 20.

9. See FDA, *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm> (last visited Nov. 14, 2017)) (showing seven approval biosimilar biologics and no approved interchangeable biologics).

from the Hatch-Waxman framework, uncertain at this early stage, and likely to vary (from one product to another) and evolve (as time passes).<sup>10</sup> We are making our best judgments about the nature of a still emerging marketplace and likely conduct in that marketplace based on our understandings of a new regulatory framework that is itself still emerging, the broader legal landscape that includes reimbursement law and state law (among other things), and intellectual property law. We disagree about the likelihood of particular fact patterns arising in the first instance, and where we agree, our explanations for their emergence are sometimes different. It may be premature to offer antitrust assessments about those fact patterns, particularly when the nature of the marketplace itself remains so profoundly uncertain. There is a substantial risk of minimizing, or even overlooking, factors that will inform business decisions or affect their impact in the marketplace.

To continue the metaphor of the article's title, it may be too soon to send the antitrust sheriffs to the frontier. To illustrate this point, I discuss three factors that may merit greater attention than they receive in Professor Carrier's article: (1) FDA's existing regulatory authorities, (2) the means by which biosimilar companies will compete and achieve market share, and (3) the stacking of the premarket patent-litigation scheme against innovative companies. Disparagement, product hopping, and patent scheme manipulation, respectively, may take on a different light when these factors are considered. In addition, one of the most significant unresolved questions is whether biosimilar companies will choose to market biosimilar biologics or instead interchangeable biologics. Professor Carrier's article sensibly focuses on biosimilar biologics, which are all FDA has approved to date. But a marketplace containing interchangeable biologics may be very different as these products have more expensive marketing applications, receive exclusivity, and may achieve market penetration differently.<sup>11</sup> Surely the competitive landscape will be different in ways we cannot fully imagine at this stage.

Rather than offering antitrust assessments of fact patterns that have not yet materialized in the biologics market, I suggest that we focus on a different issue. The risk in the new world wrought by the BPCIA may not be the lack of competition, but rather a reduction in some types of innovation. We should be closely monitoring innovation in the years ahead.

## I. THE ROLE OF FDA

Federal law gives FDA ample authority to address many of the issues that concern antitrust critics of the innovative industry. In some cases, for instance, the agency may be able to remove or mitigate the impediments

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10. See Lietzan, *The Uncharted Waters*, *supra* note 4 (discussing the variability and dynamic nature of the biologics framework).

11. Lietzan, *Uncharted Waters*, *supra* note 4, at 41–44.

to generic drug approval and market entry that result naturally from a lawful business decision made by an innovator.

For instance, FDA may have untapped flexibility to accommodate generic and biosimilar applicants who are unable to secure samples of the innovative product for purposes of product testing.<sup>12</sup> Innovators whose drugs are subject to use or distribution restrictions due to special safety risks sometimes refuse to provide those drugs to third parties for use in product development, unless their conditions (relating to safety protocols but typically also liability coverage) are met.<sup>13</sup> Professor Carrier believes this is anticompetitive.<sup>14</sup> But FDA may be able to solve the problem—for generic applicants and for biosimilar applicants. As for generic drugs, the agency has repeatedly indicated that it has the flexibility to work with generic applicants where the innovator's drug is no longer available.<sup>15</sup> Indeed, there are approved generic drugs that were *never* tested against a reference product.<sup>16</sup> As for biosimilars, FDA announced three years ago that the bulk of an applicant's comparative testing can be performed with a comparator product purchased outside the United States and thus beyond the scope of any U.S.-imposed use or distribution restrictions.<sup>17</sup> Figuring out a regulatory solution—for both small-molecule generic drugs and biosimilar biologics—may be tricky, but more thinking needs to be done before critics jump to forcing sales through antitrust law or standalone legislation.<sup>18</sup>

12. See Erika Lietzan, *A Second Look at the CREATES Act: What's Not Being Said*, 17 FED. SOC. REV. 28 (2016).

13. See Brief in Support of Defendant Celgene Corporation's Motion to Dismiss, *Mylan Pharmaceuticals, Inc. v. Celgene Corporation*, Case No. 2:14-CV-2094-ESMAH (D.N.J. Apr. 3, 2014) (noting that the company had sold Thalomid to competitors that satisfied its "safety, reputational, business, and liability concerns").

14. Carrier, *Antitrust Frontier*, *supra* note 1, at 50.

15. *E.g.*, 79 Fed. Reg. 60852 (Oct. 8, 2014) (advising that ANDA applicants unable to obtain a particular reference product "should contact the Office of Generic Drugs for a determination of what is necessary to show bioavailability and same therapeutic effect"); 79 Fed. Reg. 49327 (Aug. 20, 2014); 76 Fed. Reg. 7219 (Feb. 9, 2011); 71 Fed. Reg. 2047 (Jan. 12, 2006); 75 Fed. Reg. 36419 (June 25, 2010).

16. Prior to 1997, antibiotics were approved under section 507 of the statute. Generic antibiotics reached the market through a "monograph" procedure; the agency issued a standard of identity in a regulation (also known as a "monograph"), and a generic applicant demonstrated in its abbreviated new drug application ("ANDA") that its product conformed to that monograph. See *generally* 21 C.F.R. part 146 (1996). In 1997 Congress repealed section 507 and deemed antibiotic applications to be approved under section 505. Food and Drug Administration Modernization Act ("FDAMA"), Pub. L. No. 105-115, 111 Stat. 2296 (1997); *id.* at § 125(d) (uncodified). Today, pre-1997 generic antibiotics hold approved ANDAs under section 505(j), but they were never compared with a reference product.

17. FDA, GUIDANCE FOR INDUSTRY: BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 8 (Apr. 2015).

18. It is possible that, when an innovator's product is no longer available, FDA has steered generic applicants towards use of section 505(b)(2) of the FDCA, which provides a more flexible pathway to market than the conventional generic drug application. In connection with innovator drugs under use and distribution restrictions, though, the agency has recently signaled it might permit use of foreign-purchased versions of the reference product. See Brenda Sandburg, *REMS Barriers: US FDA Takes "Foundational Step" to Improve Generic Access*, PINK SHEET (Nov. 8, 2017), <https://pink.pharmaintelligence.informa.com/PS121923/REMS-Barriers-US-FDA-Takes-Foundational-Step-To-Improve-Generic-Access>. Whether this would be consistent with the statute needs to be analyzed.

To give another example,<sup>19</sup> current law does not permit an innovator to raise scientific or regulatory issues that could affect a pending application unless the innovator submits a citizen petition.<sup>20</sup> FDA could mitigate this problem by adopting the European practice of issuing product-class specific guidelines once a few applicants have sought meetings requesting scientific advice.<sup>21</sup> If the agency created a docket for each product class, innovators could present their findings and concerns without having to file formal petitions. Using guidance dockets would also allow the key scientific issues to be vetted in a transparent public process in accordance with the agency's preferred timeline. Biosimilar companies would presumably also benefit if a transparent process about application requirements replaced the current approach of providing scientific guidance in closed door meetings with individual applicants.

Just as federal law may give FDA the power to remove impediments to biosimilar approval and market entry, it may give the agency power to regulate conduct of concern to antitrust critics. Consider "disparagement" by way of example. Because biosimilar biologics are not substitutable, competition between biosimilars and innovative biological products will require marketing to differentiate the products. Professor Carrier's concern is that head-to-head marketing increases the chances that innovators will exaggerate the differences between the products, intimidate prescribers by raising the specter of tort liability, or even simply provide false information about biosimilars.<sup>22</sup>

Under FDA's well-established rules governing advertising and promotion of drugs and biologics, however, neither the innovator nor the biosimilar company may claim that there are clinically meaningful differences between the two products. This would be inconsistent with the standard of approval for the biosimilar product.<sup>23</sup> This means FDA would not permit claims that a biosimilar product was less safe or less effective than the innovative product for its approved conditions of use. Even if the trials detected differences between the products that did not preclude approval as a biosimilar, neither company could point to those differences and suggest clinically meaningful differences between the products. Further, FDA regulations require that comparative claims—whether express or implicit—must be supported by "substantial evidence" or "substantial clinical experience."<sup>24</sup> The agency traditionally has required at least one

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19. See, e.g., Krista Carver, Erika Lietzan, & Jeffrey Elikan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 740–42 (2010).

20. 21 U.S.C. § 355(q)(1)(A)(i) (2012).

21. *Id.* at 693; see also Lietzan, *Uncharted Waters*, *supra* note 4, at 21–22 (noting that the European Medicines Agency has been revising the class-specific guidance documents as the science evolves).

22. Carrier, *New Antitrust Frontier*, *supra* note 1, at 59.

23. 21 C.F.R. § 201.100(d)(2) (2017) (requiring that promotional labeling be consistent with the approved package insert); see also Lietzan, *Uncharted Waters*, *supra* note 4, at 30–31; see also 21 U.S.C. § 352(a) (deeming a drug misbranded if its labeling is "false or misleading" in any particular).

24. 21 C.F.R. § 202.1(c)(6)(ii) (deeming advertising false or misleading if it contains a "drug comparison that represents or suggests that a drug is safer or more effective than another drug in some

head-to-head comparative trial establishing the propositions in question.<sup>25</sup>

For these reasons, traditional innovator-style advertising and promotion, focusing on product features and clinical differences, are unlikely to drive biosimilar market penetration.<sup>26</sup> Biosimilars are likely to compete on the basis of price instead.<sup>27</sup>

These are meaningful rules.<sup>28</sup> Despite recent First Amendment decisions and some indication the agency is reevaluating its regulation of truthful and nonmisleading medical product communications,<sup>29</sup> the agency has never been a lackadaisical enforcer of its advertising and promotion rules. Further, FDA will investigate complaints about conduct that are submitted by a company's competitor or member of the public. Misbranding a product can lead to criminal liability as well as civil liability, and enforcement action can sometimes trigger lawsuits and enforcement actions under other federal and state laws.<sup>30</sup> The larger and more established companies that develop innovative biologics (and biosimilars, for that matter) have extensive experience complying with these rules as well as a high level of sensitivity to enforcement action. They are unlikely to risk enforcement action by suggesting clinically meaningful differences between the products or implying that biosimilar biologics in themselves raise safety concerns that innovative products do not raise.

What innovators may do, however, is educate patients and prescribers about the biosimilar regulatory pathway and perhaps even the data that were submitted in a particular biosimilar application. This is appropriate because the labeling will be silent. FDA has decided to require that each biosimilar bear labeling that copies the corresponding innovator product labeling, *i.e.*, that this product be labeled with descriptions of the

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particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience").

25. See Stefanie A. Doebler, *Comparative Claims: Learning from FDA Warning Letters and Untitled Letters*, REGULATORY FOCUS (Nov. 2012), at 2–3 (giving numerous examples where FDA took enforcement action against comparative claims, citing lack of substantial evidence).

26. Lietzan, *Uncharted Waters*, *supra* note 4, at 31; *see id.* at 31–41.

27. This price competition will not look like the price competition between generic small-molecule drugs and innovative small-molecule drugs. Generic drugs are much less expensive because they are comparatively cheap to develop and produce. Biosimilar applications generally require extensive and expensive marketing applications, and as a result biosimilars may not be offered at substantial discounts. *Id.* at 12–21 (discussing contents of application), 31 (discussing cost savings).

28. Moreover, they are not the only considerations. The product disparagement of concern to Professor Carrier is garden variety misrepresentation, for which there are numerous private and public remedies. For instance, the Lanham Act provides a private cause of action for unsupported claims that lead to competitive harm. 15 U.S.C. § 1125(a). Section 5 of the Federal Trade Commission Act, 15 U.S.C. § 45, prohibits "unfair or deceptive acts or practices" in commerce. State unfair competition laws may allow recovery. *E.g.*, California Business and Professions Code §§ 17200–17210 (prohibiting "unfair competition" which includes "any . . . unfair, deceptive, untrue, or misleading advertising").

29. *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012); *Amarin Pharma. Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015); FDA, GUIDANCE FOR INDUSTRY: MEDICAL PRODUCT COMMUNICATIONS THAT ARE CONSISTENT WITH THE FDA-REQUIRED LABELING—QUESTIONS AND ANSWERS (draft) (Jan. 2017).

30. 21 U.S.C. §§ 332, 333 (2012) (authorizing civil injunctions and criminal prosecution).

trials performed by the innovator on the innovator's product.<sup>31</sup> The biosimilar company may have performed extensive clinical testing, with clinical endpoints, but the results of these studies are not described for prescribers. This is relatively unprecedented for medical products, and the fact that the labeling does not describe the studies that were performed on the product may come as a surprise to these prescribers. It is not unreasonable to believe it important to educate physicians about the regulatory pathway for biosimilars and the studies that were actually performed of the products they will prescribe.

Innovators might also educate patients and prescribers about the differences between biosimilarity and interchangeability and about the concerns that have been raised (by Congress, FDA, and others) regarding immunogenic reactions when patients are switched from one protein to another protein that is similar but not identical.<sup>32</sup> This does involve talking about safety concerns, but these concerns are not associated with the use of a biosimilar *per se*; rather, they relate to switching from one product to the other or alternating between the products. It would be a serious and dangerous mistake for scholars and courts to confuse discussion and warning about immunogenicity, which is a real and terrifying possibility that motivated a special and separate standard for automatic substitution of biologics, with disparagement of the biosimilar. Even seemingly minor manufacturing changes to a product can trigger life-threatening immune reactions. For instance, when Johnson & Johnson made a minor manufacturing change to Eprex (recombinant human erythropoietin) in the late 1990s, patients using the subcutaneous dosage form of the product developed pure red cell aplasia, a condition in which the bone marrow stops producing red blood cells.<sup>33</sup> Educating the healthcare community about the immunogenicity concerns that prompted a special standard for automatically substitutable biologics—and the fact that a particular product is a biosimilar and has not been found interchangeable—is fully consistent with the statutory and regulatory framework, which precludes an interchangeability rating until these safety concerns have been addressed.<sup>34</sup> To the extent this sort of public education campaign prompts prescribers to be cautious about switches, it affects the innovative product as well because the same concerns would counsel against switching any treatment-naïve patients who had started on the biosimilar biologic.

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31. FDA, DRAFT GUIDANCE FOR INDUSTRY, LABELING FOR BIOSIMILAR PRODUCTS (Mar. 2016). The statute does not require this. Compare 42 U.S.C. § 262(a) (2012), with 21 U.S.C. § 355(j)(2) (A)(v).

32. See generally FDA, GUIDANCE FOR INDUSTRY, IMMUNOGENICITY ASSESSMENT FOR THERAPEUTIC PROTEIN PRODUCTS (Aug. 2014); see also FDA, GUIDANCE FOR INDUSTRY, SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 16-18 (Apr. 2015).

33. See Lictzan, *Uncharted Waters*, *supra* note 4, at 9–10 (discussing this experience); see also Johnson & Johnson, Comment Letter on the Passage of the Biologics Price Competition and Innovation Act of 2009, at 2, 3 (Dec. 23, 2010). See generally Katia Boven et al., *Epoetin-Associated Pure Red Cell Aplasia in Patients with Chronic Kidney Disease: Solving the Mystery*, NEPHROLOGY DIALYSIS TRANSPLANTATION, Sept. 2006, at iii33, iii34.

34. 42 U.S.C. § 262(k)(4).



The role of FDA at the new “frontier” should not be overlooked. It should inform predictions about likely fact patterns. It should also inform assessment of those fact patterns. Before antitrust law—or Congress, acting because of perceived deficiencies in antitrust law—steps in to attach liability to company decisions or force changes in company decision-making, the agency needs to explore the flexibility that its current statute and regulations may provide to reduce burdens on applicants and speed products to market. Although the agency may have lacked the inclination or incentive in the past to solve these problems itself, if its policies or practices impede competition—or could be revised to enhance competition—then the first steps at the new frontier should be regulatory.

## II. MEANS OF COMPETING AND ACHIEVING MARKET PENETRATION

Concerns about anticompetitive behavior in the small-molecule drug marketplace generally focus on company decisions and conduct that prevent or delay FDA approval of generic drugs, on the one hand, or block or slow generic drug uptake in the market, on the other hand. The latter theories frequently turn on the generic industry’s business model. A conventional generic drug is, by definition, therapeutically equivalent.<sup>35</sup> When a prescriber specifies an innovative product, state pharmacy law generally leads the dispensing pharmacist to substitute the therapeutically equivalent generic drug.<sup>36</sup> Generic companies generally do not market their products except through the distribution of product and price catalogs.

Professor Carrier and others use the phrase “product hopping” to refer to an innovator’s development and introduction of another version of its approved product—for instance, a new dosage form, a new active ingredient (such as a new salt or ester, in the case of a small-molecule drug), or a new combination product.<sup>37</sup> The term “product hopping” is pejorative, and the complaint is that newer versions of the innovator’s product impede generic drug market penetration. Specifically, after the innovator introduces its new product, physicians prescribe the newer innovative product (without a generic equivalent), rather than the older innovative product (with a generic equivalent). Thus, substitution never happens. Through this incremental innovation (also sometimes called “evergreening” by its detractors), the argument goes, the innovator inappropriately extends its dominant market position past the end of any intellectual property rights on the first version of its product.

35. Compare 21 U.S.C. § 355(j)(2)(A) (containing a required showing in a generic drug application), with FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS vii (37th ed. 2017) (containing standards for a finding of therapeutic equivalence).

36. See *New York v. Actavis*, 787 F.3d 638, 645 (2d Cir. 2015) (describing variation in state substitution laws).

37. E.g., Michael Carrier, *A Real World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1016–1017 (2010).

Professor Carrier advocates here and elsewhere for a “no-economic-sense” test, pursuant to which an innovator would be presumed to have anticompetitive intent if its incremental innovation makes no economic sense except insofar as it impairs competition.<sup>38</sup> Courts and scholars do not, however, universally agree that incremental innovation should give rise to antitrust liability simply because the innovator’s second-generation product wins sales away from the generic copies of the innovator’s first-generation product.<sup>39</sup> The response to critics has always been that: (a) incremental innovation never precludes approval of a generic drug that copies the first innovative product, (b) generic companies choose to rely on automatic substitution but could in fact market their products, and (c) rational payers and physicians will select the generic first-generation product if the innovative second-generation product is not meaningfully better.

Professor Carrier believes that changes to innovative biologics are likely to be based on innovations that make economic sense, in any case, and he therefore sees less potential for antitrust violations in the biologics framework.<sup>40</sup> I share his view about the type of innovation likely in the wake of enactment of biosimilar law, but my reasoning is different. And because my reasoning is different, I have a very different view of the implications. I think the real risk is a decline in important medical innovation.

The landscape in which biologics innovators choose whether and how to innovate will be fundamentally different from the landscape confronting small-molecule drug innovators. For instance, a biosimilar applicant may not deviate from the innovator’s conditions of use.<sup>41</sup> In contrast, the drug statute allows a generic competitor to file what is known as a “505(b)(2) application” and propose variations of the innovator’s product.<sup>42</sup> In other words, the generic applicant may rely on the innovator’s data and itself propose different features (a new dosage form, a new route of administration) or a modification to the active ingredient (such as a new salt).<sup>43</sup> A drug innovator always faces the risk of competition from a generic company that has beaten it to the punch with a slightly tweaked molecule. But biosimilar companies have no option to introduce modifications to the innovative product using an abbreviated application. A biosimilar company must replicate the innovator’s biologic as it appears in the

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38. E.g., Michael Carrier & Steve Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167 (2017).

39. E.g., *Mylan Pharms. v. Warner Chilcott*, 838 F.3d 421 (3d Cir. 2016) (affirming summary judgment in favor of defendant in case involving three reformulations of Doryx® (doxycycline hyclate) combined with ceasing sales of, and buying back, prior formulations, and promotion of the new formulations); Douglas H. Ginsburg, Koren Wong-Ervin, & Joshua Wright, *Product Hopping and the Limits of Antitrust: The Danger of Micromanaging Innovation*, CPI ANTITRUST CHRONICLE (Dec. 2015) (arguing that product hopping should be *per se* lawful absent objective evidence that the second product is a “sham innovation with zero or negative consumer welfare effects”).

40. Carrier, *Antitrust Frontier*, *supra* note 1, at 33–34.

41. 42 U.S.C. § 262(k)(2)(A)(i)(III) (2012).

42. 21 U.S.C. § 355(b)(2) (2012).

43. *Id.*; see also FDA, GUIDANCE FOR INDUSTRY, APPLICATIONS COVERED BY SECTION 505(B)(2) (Oct. 1999).

marketplace, on the one hand, or file a biologics license application with the full complement of laboratory, animal, and clinical trials, on the other hand.<sup>44</sup> In practice, this means that if there are *any* modified products on the market, they will be the subject of a full-blown application—most likely the innovator’s.

At the same time, the biologics statute does not provide exclusivity for new conditions of use. Whether they are proposed in standalone applications or in supplements to previously approved applications, new indications, routes of administration, dosing schedules, dosage forms, delivery systems, delivery devices, and strengths receive no data exclusivity of their own—even if supported by clinical trials.<sup>45</sup> Put another way, barring patent protection, when the twelve-year exclusivity on the first-generation product expires, a biosimilar applicant may copy not only the first-generation product but any other innovations the innovator has introduced in the intervening years—the new dosage forms, the new routes of administration, any new uses it has discovered, and so forth.<sup>46</sup> This should steer innovators away from engaging in this sort of research and development, even if it would be productive and yield dividends for the public health, particularly towards the end of the exclusivity term on the original product. Structural changes to the active ingredient will be handled differently. A structural change that results in a clinical difference yields an entirely new reference product with its own twelve-year period of exclusivity.<sup>47</sup> The regulatory exclusivity provisions steer innovators to invest in the development of structural modifications that have the potential to be clinically meaningful, instead of new conditions of use that could be clinically meaningful.

This language was enacted in response to concerns about “product hopping.”<sup>48</sup> But we must be candid about the price that has been paid. To prevent supposed “product hopping,” policy-makers abandoned new uses for approved drugs—even though some new uses make profound contributions to the public health.<sup>49</sup> Policy-makers also abandoned other new

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44. 42 U.S.C. § 262(a) (full application), § 262(k) (biosimilar application); Lietzan, *Uncharted Waters*, *supra* note 4, at 58.

45. 42 U.S.C. § 262(k)(7).

46. Where new features of a product—like new dosage forms—are patent-protected, the “must copy” aspect of the biosimilar pathway will protect the innovation. If the innovation is a new use, however, the biosimilar biologic will simply be approved without the new use in its labeling, and it may be prescribed and dispensed “off label,” meaning for the use that was omitted.

47. 42 U.S.C. § 262(k)(7)(C)(ii)(II). There are many open questions about interpretation of this provision, including some relating to the phrase “structure of the product” (instead of “structure of the active ingredient”). FDA’s view is that this phrase means structure of the active ingredient. See FDA, GUIDANCE FOR INDUSTRY, REFERENCE PRODUCT EXCLUSIVITY FOR BIOLOGICAL PRODUCTS FILED UNDER SECTION 351(A) OF THE PHS ACT 5–6 (Aug. 2014) (giving examples that are, exclusively, modifications to active ingredient, such as differences in amino acid sequence and pegylation).

48. *E.g.*, Carver, *supra* note 19, at 764–66, 791–96.

49. *See, e.g.*, Richard N. Spivey et al., *New Indications for Already-Approved Drugs: Time Trends for the New Drug Application Review Phase*, 41 CLIN. PHARM. & THER. 368, 368–69 (1987) (discussing numerous examples of major therapeutic advances realized after a drug has initially been approved, “often for an indication unrelated to the major breakthrough”).

conditions of use, like new dosage forms—even though these, too, can play an important public health role. Consider, for instance, an oral solution of a new drug that was first approved in solid oral dosage form (such as a capsule). The new dosage form may be the only way the new medicine can be made available to additional patient populations, like children, the elderly, and anyone with difficulty swallowing (after a stroke, perhaps). But policy-makers walked away from these innovations because critics of the industry persuaded them that “product hopping” was a concern. Further, the approach taken in the legislation could even discourage important structural modifications. Putting aside pegylation (which reliably increases the half-life of a molecule), it may be impossible to predict the clinical significance of molecular modifications before investing the time and money in clinical trials, and it may be difficult to prove that a structural change “results in” a clinical difference, given how poorly we understand the mechanism of action of some biological products.<sup>50</sup> Some important structural innovations may be left on the shelf.

Assuming the engine of incremental innovation does not grind to a halt, it is hard to see how any changes could be exclusionary in the biologics framework. Again, the heart of the complaint against “product hopping” has always been that incremental changes to the innovator’s product interfere with generic drug market penetration, because physicians switch to use of the newer innovative product, which defeats the generic business model of relying on automatic substitution for the older innovative product. Regardless of whether one agrees that this should give rise to antitrust liability in the small-molecule-drug setting, the factual foundation for the complaint evaporates without the generic entry model. Unlike generic drugs, biosimilar biological products do not receive market share through automatic substitution.<sup>51</sup> A biosimilar must be prescribed by the treating physician.<sup>52</sup> Moreover, in the biologics marketplace, payers will play a key role in the choice of medicine for any particular patient.<sup>53</sup> This is why most people expect biosimilar companies will brand and market their products to payers.

The result is brand-to-brand competition. As compared to the innovator’s first-generation product, the biosimilar company can offer modest cost savings.<sup>54</sup> As compared to the innovator’s second-generation product, however, the biosimilar company may have the option to argue that the

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50. 42 U.S.C. § 262(k)(7)(C)(ii)(II).

51. The PHSA deems “interchangeable” biologics—not biosimilar biologics—substitutable. 42 U.S.C. § 262(i). State pharmacy laws, in turn, authorize substitution of interchangeable biologics, not biosimilars. See, e.g., DEL. CODE ANN. tit. 24, § 2549A (2017); FLA. STA. § 465.0252 (2016); IND. CODE § 16-42-25-4 (2016); MASS. GEN. LAWS. ch. 112, § 12EE (2016); N.D. CENT. CODE § 19-02.1-14.3 (2013); OR. REV. STAT. § 689.522 (2015); UTAH CODE ANN. § 58-17b-605.5 (2015); VA. CODE ANN. § 54.1-3408.04 (2013).

52. Lietzan, *Uncharted Waters*, *supra* note 4, at 25.

53. *Id.* at 25–26.

54. See Kristina Lybecker, *Essay: When Patents Aren’t Enough: Why Biologics Necessitate Date Exclusivity Protection*, 40 WILLIAM MITCHELL L. REV. 1427, 1436 (2014).

new innovative product is not the cost-effective choice—that its biosimilar version of the first-generation product is the better choice—given the nature of the changes that the innovator made. A rational payer should push physicians and patients to biosimilars of the first-generation product unless the second-generation product is not only clinically superior but also comparatively cost-effective. This would be true even if the innovator removed its own first-generation product from the marketplace. Removing the first-generation product should have no impact on the biosimilar uptake, because substitution plays no role in this marketplace. But because biosimilar applicants seem inclined to provide only modest discounts in the immediate term,<sup>55</sup> and because biosimilar market share will depend on competition rather than automatic substitution, innovators may continue marketing their first-generation products even after biosimilar market entry. In this case, the introduction of a second-generation innovative product will simply give physicians and payers a third product in the class from which to select.

It is not clear if any of this depends on when the innovator introduces its second-generation product. To be sure, some physicians who switch their patients to the second-generation innovative product will be hesitant to switch those patients to the biosimilar of the first-generation product, due to the heightened risk of immunogenicity from repeat switches. This will depend on the biological product—including the incidence and type of immunogenicity it is thought to trigger and the impact of that immunogenicity—as well as the nature of the differences between the first and second-generation products. But if the immunogenicity profile of a product gives rise to switching concerns in the first instance, it is less likely physicians will migrate those patients from the innovative first product to the innovative second product in the first instance. In these situations, innovators are especially unlikely to withdraw the first-generation products from the market.

### III. STACKED PATENT-LITIGATION PROVISIONS

Finally, commentators have not fully grappled with the bias in the premarket patent-litigation provisions of the 2010 legislation. The patent scheme is fundamentally, and by design, stacked against the innovating industry. Decades of allegations that small-molecule innovators misuse the Hatch-Waxman patent-litigation provisions prompt Professor Carrier and others to predict that biologics innovators will find a way to “manipulate” the premarket patent process for biologics. But these concerns make no sense once the true nature of the scheme is laid bare. The dice are loaded

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55. E.g., Nicholas Florko, *Remicade Biosimilar to Launch in November, 15% Cheaper Than Innovator*, INSIDE HEALTH POLICY (Oct. 17, 2016); Ben Hirschler, *Novartis Launches First U.S. ‘Biosimilar’ Drug at 15 Percent Discount*, REUTERS (Sept. 3, 2015).

in favor of biosimilar applicants. Patent owners could not manipulate the scheme to their advantage, even if they wanted to.

The issues in the Hatch-Waxman setting ultimately stem from its stay provision. Section 505 of the FDCA precludes the agency from approving a generic drug application for thirty months, if the patent owner or NDA holder brings a suit against the generic applicant within forty-five days of receiving notice of a patent challenge.<sup>56</sup> For nearly twenty years after the scheme was enacted, the statute imposed a stay every time suit was brought following notice of a patent challenge, even if the challenge related to a patent issued by the Patent and Trademark Office (“PTO”) while the generic application was pending before FDA.<sup>57</sup> This meant that a generic application could be stayed more than once, which was controversial. Some argued that innovators delayed the issuance of their patents at PTO to make sequential stays possible, and some argued that innovators improperly listed patents that were not eligible for listing.<sup>58</sup> The statute has since been amended to mostly eliminate sequential stays,<sup>59</sup> but the history prompts Professor Carrier to speculate about potential abuse of the biologics patent-litigation provisions by biologics innovators.<sup>60</sup>

These possibilities are remote. It will not be possible, for instance, for an innovator to assign its patents to a third party (so as not to disclose the patents during the “patent dance”) and later secure reassignment to bring a surprise lawsuit.<sup>61</sup> During the legislative negotiations that led to enactment of the BPCIA, stakeholders spent a great deal of time worrying about third-party patent owners, who were thought to be more common for biologics than small-molecule drugs.<sup>62</sup> The final statute addresses them directly. After a biosimilar company files its application, there is an exchange of information between the biosimilar applicant and the innovator, during which the latter must identify not only relevant patents it owns but *also* relevant patents for which it holds an exclusive license.<sup>63</sup> To ensure that third-party patents were listed at this time, Congress also amended the Patent Act to provide that the owner of a patent that (a) should have been included in this list and (b) was not in fact included in the list may *not* bring an infringement action with respect to the biosimilar biologic in question.<sup>64</sup> As a result, assignment to a third party prior to the

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56. 21 U.S.C. § 355(j)(5)(B)(iii) (2012).

57. 21 U.S.C. § 355(j)(5)(B)(iii).

58. *E.g.*, Federal Trade Commission, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY* (July 2002) [hereafter *FTC STUDY*].

59. In 2003, Congress amended the law to provide that generic applicants would not be blocked by multiple (successive) thirty-month stays through the listing of additional patents while their applications were pending. Pub. L. No. 108-173, § 1101, 117 Stat. at 2449.

60. Carrier, *Antitrust Frontier*, *supra* note 1, at 39–44.

61. *Id.* at 43.

62. *E.g.*, Carver, *supra* note 19, at 760 n.755, 763, 765, 771–23, 782, 791–99, 801, 803.

63. 42 U.S.C. § 262(l)(3)(A)(i). The legislation even provides for third party patent owner access to the biosimilar marketing application and manufacturing information. *Id.* § 262(l)(1)(B)(iii).

64. 35 U.S.C. § 271(e)(6)(C).

information exchange will have no effect. The patent must be listed if it is to be enforced.

Nor is it likely that innovators will assert “submarine” patents—a pejorative term that refers to patents filed before June 7, 1995 (sometimes known as “pre-GATT” patents), which have a seventeen-year patent term from their date of eventual issuance.<sup>65</sup> By the third quarter of 2016, there were only twenty pre-GATT applications pending that might cover an approved biological product, and it is not clear how many (if any) actually do.<sup>66</sup> Surely even fewer are pending now, a full year later. It is conceivable that a few pre-GATT applications for biological products remain in the queue at the PTO, but this simply cannot be viewed as a significant issue going forward.

The problem with taking lessons from the Hatch-Waxman experience is that the patent schemes are fundamentally different. The real concern about the biologics patent provisions should be that they are inherently hostile to patent owners. Indeed, these were the patent-litigation provisions favored by the generic industry.<sup>67</sup> Consider the listing process, which has already been described. If an innovator does not place a patent on the master list during the private exchange of information, the patent cannot be enforced against the biosimilar.<sup>68</sup> This “list it or lose it” provision has no precedent in any other federal law.<sup>69</sup> Consider also the process

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65. A patent that issues today on an application filed before June 8, 1995, has a term that is the greater of twenty years from its application date (or the date of an earlier filed application to which it refers) or seventeen years from the patent grant. 35 U.S.C. § 154(c). This is the result of the Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994), which implemented the General Agreement on Tariffs and Trade (“GATT”). Today, in every case, seventeen years from patent grant will be the greater and therefore applicable patent term.

66. *Oversight of the U.S. Patent and Trademark Office, Hearing before the Subcomm. on Courts, Intellectual Prop., & the Internet, of the H. Comm. on the Judiciary*, 114th Cong. 2d Sess. (Sept. 13, 2016), at 25 (testimony of Michelle K. Lee, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office) (“With regard to a certain category of the pre-GATT applications that are not the subject—not belonging to one particular applicant, we have reduced the number of pre-GATT applications by 80 percent, from 100 to 20.”); Dennis Crouch, *Pre-Gatt Applications*, PATENTLYO (Sept. 15, 2016) (“One small aspect of Director Michelle Lee’s testimony to Congress was that the number of pending pre-GATT applications still pending has been reduced to only 20—not counting those owned by Gill Hyatt.”).

67. The House bill contained the patent provisions from Representative Eshoo’s second biosimilar bill, which the innovative industry had urged. The Senate bill contained the patent provisions from the Kennedy biosimilar bill, which the generic industry preferred. Although the bills were not conferred, the Senate language was adopted. *See generally* Carver, *supra* note 19, at 798–806.

68. 35 U.S.C. § 271(c)(6)(C).

69. The list-it-or-lose-it rule pushes innovators to err on the side of including patents that *might* be implicated. A recent ruling from the Federal Circuit amplifies this. Hospira submitted an application seeking approval of a biosimilar of Amgen’s Epogen (epoetin alfa). Hospira declined to provide information about the cell culture medium used in manufacturing its biosimilar. Amgen listed three patents, but it did not cite its patents claiming processes for culturing cells, explaining that it could not “assess the reasonableness of asserting claims for infringement,” which is the statutory standard for listing. The trial court denied discovery on the composition of Hospira’s cell culture medium, on the theory that it was not relevant to the patents in dispute, and the Federal Circuit declined to reverse. *Amgen v. Hospira*, 866 F.3d 1355 (Fed. Cir. 2017). The upshot of the ruling is that innovators will need to take an even more expansive approach to listing. In brief, then, over-inclusion of patents prompted criticism in the drug framework, *see* FTC STUDY, *supra* note 58, but it is baked into the biologics scheme.

for identifying a short list of patents for the first phase of litigation. If negotiations fail, the parties construct the list by simultaneously swapping their choices.<sup>70</sup> But this blind swap is controlled entirely by the biosimilar applicant, which can dictate how many patents the innovator may propose.<sup>71</sup> Consider the initiation of patent litigation on the basis of patents listed for the first phase of litigation. Where the drug statute provides a carrot, the biologics statute wields a club. A drug innovator that brings timely suit secures a thirty-month stay of generic approval.<sup>72</sup> In contrast, the biologics innovator must sue within thirty days to preserve its patent rights. If it misses the deadline, it loses the ability to secure an injunction, even if the patent is valid and infringed.<sup>73</sup> At best it will receive reasonable royalties.<sup>74</sup>

Consider, finally, the second phase of litigation, which involves any patents not short-listed for the first phase of litigation. The biosimilar applicant has almost complete control over which patents are placed in that litigation because (as noted) it may select any patents that it wishes for the first phase. The biosimilar applicant has almost complete control over the timing of that litigation because it triggers the opportunity for this litigation when it files a notice of commercial marketing at the time of its choosing.<sup>75</sup> The biosimilar applicant may also have some influence on the venue of this litigation because once it provides the notice of commercial marketing it may seek a declaratory judgment of non-infringement and invalidity.<sup>76</sup> Finally, and most importantly, suit does not trigger an automatic stay of FDA approval, so the innovator has no power to delay biosimilar market entry. The biosimilar applicant's control of the patent-litigation process makes it highly implausible that the innovator could somehow manipulate the second phase to its advantage.

#### IV. CONCLUSION

I would be remiss if I failed to mention perhaps the most significant open question about the new marketplace: whether companies will seek approval of interchangeable biologics, instead of biosimilar biologics, and how these products will affect both incentives to innovate and competition in the marketplace. Interchangeable biologics are subject to a different and higher standard of approval than biosimilar biologics.<sup>77</sup> Numerous

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70. 42 U.S.C. § 262(l)(5).

71. *Id.* See *Sandoz Inc. v. Amgen*, \_\_ U.S. \_\_, \_\_ (2017) (“This process gives the applicant substantial control over the scope of the first phase of litigation.”).

72. 21 U.S.C. § 355(j)(5)(B)(iii).

73. 35 U.S.C. § 271(c)(6).

74. *Id.*

75. 42 U.S.C. § 262(l)(8); see *Sandoz*, \_\_ U.S. at \_\_ (“Because the applicant (subject to certain constraints) chooses when to begin commercial marketing and when to give notice, it wields substantial control over the timing of the second phase of litigation.”).

76. *Id.* § 262(l)(9)(A). Nothing in the statute precludes the biosimilar applicant from providing the notice and a complaint at the same time.

77. Compare 42 U.S.C. § 262(k)(4), with 42 U.S.C. § 262(k)(3).



companies are conducting the trials necessary for interchangeability determinations, suggesting that we may see an influx of these products in the medium term. An interchangeability rating indicates that the biologic is substitutable for the innovator's product,<sup>78</sup> so an interchangeable biologic—not a biosimilar biologic—is analogous to a generic drug. But we do not know whether interchangeability determinations will drive market penetration the way small molecule therapeutic equivalence determinations drive generic drug market penetration. Interchangeability ratings could be expensive; current FDA guidance suggests that they will require clinical switching trials.<sup>79</sup> And, they may not be necessary. Most biological products are administered in physician offices or hospitals, which makes automatic pharmacy substitution less important.<sup>80</sup> Moreover, payers may dictate the therapy through their formularies, pushing patients to the biosimilar even when it lacks an interchangeability rating.<sup>81</sup>

Complaints about anticompetitive behavior undertaken by small-molecule drug innovators have focused on actions that have the effect of either delaying generic drug approval or slowing generic drug market penetration. But in the biologics context, the impediments to approval have so far been scientific challenges and manufacturing problems.<sup>82</sup> There is very little information on market penetration, and there have been no findings that any innovator has taken any unlawful step to inhibit the market penetration of an approved biosimilar.<sup>83</sup> Further, we do not even know what types of product will be in the marketplace or how they will achieve market penetration. At this point, the biosimilar scheme is so new that any antitrust analysis necessarily operates in a fact-free zone. It is a solution in search of a problem.

78. 42 U.S.C. § 262(i).

79. FDA, GUIDANCE FOR INDUSTRY, CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT 9–16 (draft) (2017).

80. Lictzan, *Uncharted Waters*, *supra* note 4, at 43.

81. *Id.* Payers may require treatment-naïve patients to begin with the less expensive biosimilar biologic. Indeed, they might even require patients stabilized on the reference product to switch to the less expensive biosimilar. Some biosimilar applicants now include a single switch from the innovative product to the biosimilar product in their premarket clinical trials. *Id.* at 39 n.159. If that switch rules out any significant immunogenic reactions from a single transition, payers might require stabilized patients to switch. In these situations, an interchangeability rating would offer the biosimilar applicant no incremental benefit.

82. *E.g.*, Joanne Eglovitch, *Celltrion Biosimilar Is Latest to Run Into GMP Compliance Concerns*, PINK SHEET (Sept. 11, 2017), <https://pink.pharmaintelligence.informa.com/PS121507/Celltrion-Biosimilar-Is-Latest-To-Run-Into-GMP-Compliance-Concerns>; Sue Sutter, *Pfizer's EPO Biosimilar Stalls in US On Hospira Compliance Woes*, PINK SHEET (June 22, 2017), <https://pink.pharmaintelligence.informabi.com/articles/2015/10/27/biosimilar-denied-hospiras-retacrit-could-head-back-to-fda-in-first-half-2016>; Sue Sutter, *US FDA's Inaugural Biosimilar Review Bumpier Than First Appeared*, PINK SHEET (June 15, 2015), <https://pink.pharmaintelligence.informa.com/PS118268/US-FDAs-inaugural-biosimilar-review-bumpier-than-first-appeared>.

83. In the only antitrust action to date involving biosimilars, Pfizer sued Johnson & Johnson in September 2017, arguing that the latter's "exclusionary contracts" for Remicade (infliximab) with health insurers, hospitals, and clinics effectively prevent Pfizer from offering its biosimilar to those customers. *Pfizer Inc. v. Johnson & Johnson*, Civ. No. 2:17-cv-04180-JCJ (complaint filed Sept. 20, 2017).

Those planning antitrust scrutiny of hypothetical business decisions that may or may not affect competition in the biologics framework may well be missing the bigger picture. In addition to increasing competition, the BPCIA was meant to preserve incentives to innovate. With its failure to incentivize incremental innovation and its punitive patent provisions, the scheme is more hostile to innovators and incentives for innovation than policy-makers and the public realize. If innovation slows as a result, we will have traded long term social welfare for short term cost savings.