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The Science of Substitution: A Response to Carrier and Minniti

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THE SCIENCE OF SUBSTITUTION: A RESPONSE TO CARRIER AND MINNITI

Jacob S. Sherkow*

In Biologics: The New Antitrust Frontier, Michael A. Carrier and Carl J. Minniti provide an overview of potential antitrust harms in the newly enacted biologic drug approval and litigation regime, the Biologics Price Competition and Innovation Act. Importantly, Carrier and Minniti suggest that the scientific complexity of biologic products has the potential to make some litigation conduct anticompetitive, given uncertainties surrounding regulatory approval and patent infringement. This response advances Carrier and Minniti’s thesis and suggests the authors do not take it far enough when assessing reverse payment settlements, submarine patenting, and citizen petition abuse. This response also makes use of two important court decisions, Sandoz Inc. v. Amgen Inc. and Amgen Inc. v. Sanofi, which were decided after Carrier and Minniti’s article went to press. Regardless of whether Carrier and Minniti’s predictions come to pass, their core insight—that scientific complexity can regulate antitrust harms—provides a key area of future exploration for practitioners, scholars, and policy makers.

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INTRODUCTION

In Biologics: The New Antitrust Frontier, Michael A. Carrier and Carl J. Minniti provide a thoroughly exhaustive overview of all of the possible ways the recent biologic drug approval regime—the Biologics Price Competition and Innovation Act (“BPCIA”)—could be subject to the same anticompetitive con-

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duct found in the small-molecule drug approval regime—the Hatch-Waxman Act.¹ Specifically, they provide assessments of reverse-payment settlements, product hopping, submarine patenting, specious REMS restrictions, citizen-petition abuse, competitor disparagement, and collusion.² This detailed cataloging of the antitrust harms for life-science patent litigation is an achievement and should be of significant practical value to scholars and practitioners.

But Carrier and Minniti’s synthesis goes further: it highlights the *legal* significance of the *scientific* differences between biologics and small molecule drugs. Biologics are inordinately more complex than small-molecule drugs—more difficult to manufacture, protected by more patents, governed by a more complex regulatory regime, and less likely to be interchangeable with their generic rivals, biosimilars.³ These differences undergird the basis for Carrier and Minniti’s conclusions that “conduct like submarine patents, shell licensing, reverse-payment settlements, disparagement, sample denials, and collusion” threaten the BPCIA’s purposes and that “the industry’s science and markets . . . justifies many citizen petitions and makes product hopping and settlements less likely.”⁴

This essay furthers Carrier and Minniti’s insight that the scientific complexity of a product can turn otherwise anticompetitive behavior into procompetitive or neutrally competitive conduct. In the biologics context, the scientific complexity of biologics, in conjunction with a regulatory approval regime that takes such complexity into account, makes many biosimilars not true economic substitutes for their reference biologics.⁵ Without true substitutability, conduct that would initially appear collusive or anti-competitive may be procompetitive

1. Michael A. Carrier & Carl J. Minniti, *Biologics: The New Antitrust Frontier*, 2018 UNIV. ILL. L. REV. 1, 14. It is important to note that the BPCIA is not the first regulatory approval regime for biologics; that honor goes to the 1902 Biologics Control Act, one of the progenitor statutes that eventually led to the creation of the U.S. Food and Drug Administration. Pub. L. No. 57-244, 32 Stat. Ann. 728, ch. 1378 (1902). Rather, the BPCIA is merely a new regulatory regime (albeit, an important one) in a long line of prior regulatory regimes for biologics. 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, 681–88 (2010) (recounting the history of biologics control in the United States).

2. See Carrier & Minniti, *supra* note 1, at 20–73.

3. *Id.* at 7–9; see also Janet Freilich, *Patent Infringement in the Context of Follow-On Biologics*, 16 STAN. TECH. L. REV. 9, 21–22 (2012) (discussing the lack of interchangeability for biologics); W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologic Competition and Innovation*, 101 IOWA L. REV. 1023, 1028 (2016) (“[M]any complex biologic products cannot be fully characterized by current techniques for analyzing the end product. Moreover, slight variations in the manufacturing process can change the quality, safety, or efficacy of the final product.”) (internal citations omitted); W. Nicholson Price II, *Regulating Secrecy*, 91 WASH. L. REV. 1769, 1794–99 (2016) (analyzing trade secrecy for biologics).

4. Carrier & Minniti, *supra* note 1, at 74.

5. See Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 449 (2007) (noting the imperfect substitutability of a “follow-on protein product”); Henry Grabowski et al., *The Market For Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1298 (2006) (noting that the biosimilars lack perfect substitutability, and this may contribute to price uncertainty); Darren S. Tucker & Gregory F. Wells, *Emerging Competition Issues Involving Follow-on Biologics*, ANTITRUST, Fall 2014, at 102 (“When [biosimilars] are available, less substitution away from the reference biologic is expected than for branded pharmaceuticals.”).

or, at base, within the scope of the patent right.⁶ This essay also makes use of two important court decisions decided after Carrier and Minniti's article went to press: *Sandoz Inc. v. Amgen Inc.*, which limited the availability of injunctions in BPCIA litigation,⁷ and *Amgen Inc. v. Sanofi*, which narrowed the availability of patents covering antibodies, the staple molecule of biologic drugs.⁸ Assessing this connection between biologics' complexity and substitutability may require some more careful thinking about some of Carrier and Minniti's conclusions concerning reverse payment settlements, submarine patenting, and citizen petitions.

I. REVERSE PAYMENT SETTLEMENTS

Carrier is—without equal—the leading scholar on the antitrust concerns raised by reverse-payment settlements, and much of scholars' and practitioners' understanding of these agreements is based on Carrier's work.⁹ In Carrier and Minniti's recent description, “[t]he typical arrangement . . . involves a brand paying a generic to settle patent litigation and delay entering the market.”¹⁰ Since the patent holder otherwise has the right to prohibit infringing conduct during the duration of the patent term, such an arrangement—at first blush—would appear to be *procompetitive*: so long as the generic enters the market prior to the patent's expiration, competition seems to increase.¹¹ But in 2013, the Supreme Court in *FTC v. Actavis, Inc.* concluded that “[b]ecause the settlement requires the patentee to pay the alleged infringer, rather than the other way around, this kind of settlement . . . can sometimes unreasonably diminish competition in violation of the antitrust laws.”¹² The key component to anti-competitive conduct under *Actavis* is “payment” that “payment constituted the anticompetitive harm and that even strong patents were not immune from scrutiny.”¹³

Carrier and Minniti think that such settlements under the BPCIA are unlikely for both economic and legal reasons: Reference biologics' first-mover advantage and the lack of price erosion diminish the value of reverse payment

6. See Charles F. Rule, *The Administration's Views: Antitrust Analysis After the Nine No-No's*, 55 ANTITRUST L.J. 365, 369 (1986) (“The antitrust laws, however, only condemn patent licensing that either restricts competition among technologies that are economic substitutes, or excludes new technologies from the market, or is a sham designed to coordinate the pricing of products only remotely related to the patent.”).

7. 137 S. Ct. 1664, 1674–78 (2017).

8. 872 F.3d 1367, 1381–82 (Fed. Cir. 2017).

9. See, e.g., Michael A. Carrier, *Payment After Actavis*, 100 IOWA L. REV. 7, 13 (2014) (defining “payment” for reverse-payment settlement analysis); Michael A. Carrier, *Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality*, 108 MICH. L. REV. 37, 73–76 (2009) (plotting antitrust analyses for different reverse payment settlements); Michael A. Carrier, *Why the “Scope of the Patent” Test Cannot Solve the Drug Patent Settlement Problem*, 16 STAN. TECH. L. REV. 1, 5–8 (2012) (criticizing earlier courts' “scope of the patent test” for reverse payment settlements).

10. Carrier & Minniti, *supra* note 1, at 21.

11. See *FTC v. Actavis, Inc.*, 133 S. Ct. 2223, 2230 (2013) (describing the reasoning of several Eleventh Circuit cases).

12. *Id.* at 2227.

13. Carrier, *Payment After Actavis*, *supra* note 9, at 19.

settlements, and the increased availability of patent challenges at the U.S. Patent and Trademark Office (“PTO”) in the form of *inter partes* review make such settlements impractical.¹⁴ Nonetheless, Carrier and Minniti caution against certain payments between reference biologics and biosimilars, including “biosimilar’s access to a biologic’s distribution or reimbursement agreements” such as access to group purchasing organizations (“GPOs”) or pharmacy benefit managers (“PBMs”) through which a reference biologic is sold.¹⁵

But the science and regulatory complexity of biologics make it unclear whether such benefits constitute impermissible “payments” under *Actavis*. Under Carrier’s prior helpful distinction between anticompetitive payments and permissible patent exclusion, payments are “a type of consideration not available as a direct consequence of winning the lawsuit.”¹⁶ While it is true that access to a reference biologic’s distribution network would *not* be available as a remedy for a biosimilar’s successful patent lawsuit, it does not appear that such agreements would be anticompetitive. To the contrary, it seems to be the case that access agreements—even when nominally “large payments,” thus raising *Actavis*’s scrutiny—would be *procompetitive*.

Absent access agreements, biosimilars face significant distributional challenges “such as prescriber and patient education, consumer reluctance,” pricing uncertainties, and a lack of interchangeability between the biosimilar and the reference biologic.¹⁷ Indeed, this latter concern—interchangeability—drives much of newly approved biosimilars distributional difficulties.¹⁸ In the small-molecular context, true generics are widely interchangeable with one another and the reference listed drug.¹⁹ This generally creates a unified, competitive market: Given a single prescription, payers can choose, at the point of sale, which manufacturer’s product it will purchase.²⁰

But biosimilars are not automatically interchangeable; the scientific complexity of biologics and the BPCIA’s provisions make it so.²¹ The manufacture

14. Carrier & Minniti, *supra* note 1, at 23–24.

15. *Id.* at 27.

16. Carrier, *Payment After Actavis*, *supra* note 9, at 16.

17. Carrier & Minniti, *supra* note 1, at 23; *see also* Grabowski et al., *supra* note 5, at 1298.

18. *See* Alfred B. Engelberg et al., *Balancing Innovation, Access, and Profits—Market Exclusivity for Biologics*, 361 N. ENG. J. MED. 1917, 1918 (2009) (“If biosimilar products are not similarly interchangeable with the original biologic product, they could not be substituted for the original and would have to be marketed to physicians as therapeutic alternatives. The cost of deploying a promotional program and sales force for this purpose would inevitably limit the number of potential market entrants and increase drug costs.”), <http://www.nejm.org/doi/full/10.1056/NEJMp0908496#t=article>; Ameet Sarpatwari et al., *Progress and Hurdles for Follow-On Biologics*, 372 N. ENG. J. MED. 2380, 2381–82 (2015) (“[H]eightened barriers to substitution are likely to reduce the market penetration of interchangeable biologics.”), <http://www.nejm.org/doi/full/10.1056/NEJMp1504672#t=article>. [CC: these are consecutively paginated journals under R16, I do not believe they need links]

19. Sarpatwari et al., *supra* note 18, at 2381.

20. Greg Perry, *The European Generic Pharmaceutical Market in Review: 2006 and Beyond*, 4 J. GENERIC MED. 1, 13 (2006) (“American generics companies . . . benefit from a large, unified market fortified by a strong legal and commercial environment designed to favour generic medicines competition. . . .”).

21. Paul J. Declerck, *Biotherapeutics in the Era of Biosimilars: What Really Matters is Patient Safety*, 30 DRUG SAFETY 1087, 1089 (2007) (“As a consequence of the complexity of both the biotechnology product and

of biologics is inordinately complex and poses safety and efficacy risks not typically encountered in the small-molecular context.²² The BPCIA therefore requires biosimilars to affirmatively demonstrate interchangeability through low-product complexity, low-immunogenicity risk, or switching studies—none of which a biosimilar applicant has accomplished to date.²³ Even then, because prescriber substitution is a state-law concern, only some states would even allow substitutability.²⁴ Thus, contrary to their name, most biosimilars are not truly substitutes for their reference biologics.

On the ground, the markets for biosimilars and their reference biologics are badly balkanized. GPOs and PBMs control access to manufacturer-specific biologic products,²⁵ and consumers are therefore frequently subject to a single choice, independent of typical market levers, such as price, quantity, quality, or preference.²⁶ Further, consumers are unlikely to have any choice in these built-in supply controls. For example, a cancer patient and filgrastim scrip holder who obtains health insurance through an employer-sponsored health insurance plan may be required, through the plan's PBM, to receive Amgen's Neupogen and not Sandoz's biosimilar product—even if the latter is cheaper or more widely distributed through the patient's healthcare provider network. Obtaining the biosimilar may require drastic action: changing health insurers by changing employers.²⁷

This intersection of the scientific and regulatory complexity of biosimilars suggests that patent settlements that allow access to biologics' markets allow competition among manufacturers that would not otherwise exist. Thus, even though such settlements appear to constitute "large payments" under both Carrier and Minniti's framework, as well as *Actavis's* analysis, they are almost certain to be procompetitive. The counterargument is that such agreements should be balanced with the concomitant delay to the biosimilars' entry.²⁸ But, even if a biosimilar won its patent suit against the reference biologic, it would not be

the production process . . . no solid scientific grounds exist to guarantee safe interchangeability between any biologics . . ."); Janet Freilich, *Patent Infringement in the Context of Follow-On Biologics*, 16 STAN. TECH. L. REV. 9, 21–24 (2012) (citing Declerck).

22. Declerck, *supra* note 21, at 1088 (noting differences in manufacturing biologics in cells).

23. 42 U.S.C. § 262(i)(3) (2012); Zachary Brennan, *Interchangeable Biosimilars vs. Biosimilars: Experts Explain Guidance, Discuss Development and Uptake*, REG. FOCUS (Sept. 13, 2017), <http://www.raps.org/Regulatory-Focus/News/2017/09/13/28460/Interchangeable-Biosimilars-vs-Biosimilars-Experts-Explain-Guidance-Discuss-Development-and-Uptake/> ("To date, six biosimilars have been approved in the US, though none are interchangeable biosimilars.")

24. Erika Lietzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 FLA. ST. U. L. REV. 26–27 (forthcoming 2018) (available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2848606).

25. See Andrew W. Mulcahy et al., BIOSIMILAR COST SAVINGS IN THE UNITED STATES, RAND CORP. (2017), https://www.rand.org/content/dam/rand/pubs/perspectives/PE200/PE264/RAND_PE264.pdf ("[O]ne major PBM, Express Scripts, recently listed Zarxio® and Granix®, but not Neupogen® (the reference biologic for Zarxio®), on its 2018 National Preferred Formulary, while another large PBM, CVS Caremark, restricted coverage of Neupogen® in July 2017.")

26. See *id.*

27. See *id.*

28. Carrier & Minniti, *supra* note 1, at 22–28.

clear the biosimilar would have anywhere to sell its product. It is entirely feasible that even a complete biosimilar victory would make *no* difference in the competitive landscape. Carrier and Minniti are right that the science and regulation of biologics raises different concerns over reverse payments than do small-molecule drugs. But they do not appear to go far enough to recognize that these differences mean that *any* agreement that allows biosimilar market access is likely a competitive improvement.

II. SUBMARINE PATENTING

Carrier and Minniti also raise concerns over “submarine patenting,” a patent “applicant’s use of silent delay tactics at the PTO, aimed at obtaining issuance of a patent years after the initial filing, but still with the legal right to surprise a mature market.”²⁹ While Carrier and Minniti rightly note that such tactics have largely disappeared since 1995—when patent terms shifted from seventeen years from issuance to twenty years from the date of filing—they provide areas of the BPCIA that may continue to provide areas of abuse. They note that the BPCIA appears to allow reference biologics to seek preliminary injunctions against their biosimilar competitors on late-issued patents, allowing reference biologics to continually assert new, late-issued patents to stymie the entry of biosimilars.³⁰ This, they conclude, violates the antitrust maxims laid out in *Verizon Communications, Inc. v. Law Offices of Curtis V. Trinko, LLP*, that refusal-to-deal antitrust claims under § 2 of the Sherman Act within a regulated industry should turn on “the existence of a regulatory structure designed to deter and remedy anticompetitive harm.”³¹

The merits of this analogy to *Trinko* notwithstanding,³² Carrier and Minniti’s article went to press prior to two significant court decisions likely to temper the authors’ concerns. The first is *Sandoz Inc. v. Amgen Inc.*, a Supreme Court decision in June 2017 that will likely limit the availability of the injunctions complained of by Carrier and Minniti.³³ In *Sandoz*, the Court confronted two issues in interpreting the BPCIA: (1) whether a biosimilar applicant must provide its application and manufacturing information to the reference biologic;

29. *Id.* at 38.

30. *Id.* at 39–40.

31. 540 U.S. 398, 412 (2004); *see also* Carrier & Minniti, *supra* note 1, at 44–48.

32. In the section of their article assessing submarine patenting under *Trinko*, Carrier and Minniti do not make clear that the *Trinko* antitrust plaintiff failed in its attempt to lodge a § 2 Sherman Act claim against refusal-to-deal conduct. *Trinko*, 540 U.S. at 411 (“[W]e do not believe that traditional antitrust principles justify adding the present case to the few existing exceptions from the proposition that there is no duty to aid competitors.”). Rather, they argue that *Trinko*’s framework, despite its holding, should compel the opposite conclusion in the BPCIA submarine patenting case. Carrier & Minniti, *supra* note 1, at 44–48. This is not altogether clear—or persuasive—from my reading of *Trinko*. At the same time, in later sections of their article, such as Section III.D on REMS abuses, Carrier and Minniti demonstrate a variety of later, lower court cases doing just that, such as *Actelion Pharmaceuticals Ltd. v. Apotex, Inc.* and *Mylan Pharmaceuticals Inc. v. Celgene Corp.* *Id.* at 50–51. To the extent submarine patenting and REMS abuses are similar, it is analogies to these cases—not *Trinko*—that appear to be more persuasive.

33. 137 S. Ct. 1664 (2017).

and (2) whether a biosimilar applicant can provide its notice of commercial marketing prior to approval by the Food and Drug Administration (“FDA”).³⁴ In assessing the first issue, the Court unanimously answered no: a biosimilar applicant *need not* provide its application and manufacturing information to the reference biologic, despite the BPCIA’s strictures.³⁵ The reason? Because the statute also provides an exclusive remedy to the reference biologic for the biosimilar’s failure: the ability to immediately file a declaratory judgment against the biosimilar for the infringement “of any patent that claims the biological product or a use of the biological product.”³⁶ Regarding the second issue, the Court unanimously answered yes: A biosimilar applicant may provide its notice of commercial marketing to the reference biologic prior to FDA approval—thus similarly triggering a reference biologic’s declaratory judgment suit against the biosimilar applicant.³⁷ This, according to the Court, was dictated by the plain language of the BPCIA.³⁸

The benefit of this ruling is that biosimilars, rather than reference biologics, are now largely in control of the contours of BPCIA litigation against them. Bio-similars can essentially decide whether to engage in the BPCIA’s patent dance at all, with the provision that their failure to do so—either in whole or in part—will almost certainly result in a declaratory judgment by the reference biologic.³⁹ During the course of that litigation, the biosimilar would almost certainly be required to disclose the application and manufacturing information it had previously withheld and, in parallel, obtain through discovery a list of all patents the reference biologic considers infringed by biosimilar’s proposed product.⁴⁰ That discovery would also be sure to include a list of any currently prosecuted or recently transferred patent applications—the submarine patents that concern Carrier and Minniti.⁴¹ Further, because the declaratory judgment action is the *exclusive* remedy for the biosimilar’s failure to initially provide its marketing information under the BPCIA, it does not appear that a reference biologic would be able to obtain a revolving series of preliminary injunctions against the biosimilar based on newly issued patents. Rather, the *Sandoz* Court implied that such injunctions would only be proper under 35 U.S.C.

34. *Id.* at 1669.

35. *Id.*

36. *Id.* at 1672; *see also* 42 U.S.C. § 262(l)(9)(C) (2012).

37. *Sandoz*, 137 S. Ct. at 1672.

38. *See id.* at 1678 (“[Amgen’s] arguments could not overcome the statute’s plain language, which is our ‘primary guide’ to Congress’ preferred policy.”).

39. *See id.* at 1672 (“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.”).

40. *See Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347, 1356 (Fed. Cir. 2015), *rev’d in part and vacated in part*, *Sandoz*, 137 S. Ct. at 1664 (“Once the [reference biologic] brings an infringement suit under those two provisions, it can access the required information through discovery.”). Nonetheless, there appear to be some limitations to discovery in the BPCIA context. *See Amgen Inc. v. Hospira, Inc.*, 866 F.3d 1355, 1361 (Fed. Cir. 2017) (prohibiting discovery concerning the biosimilar’s cell culture techniques given that Amgen did not list its cell culture patents in Phase I litigation and conceded that “the cell-culture manufacturing information is not relevant to the currently asserted claims.”) (quotation marks and citation omitted).

41. *Carrier & Minniti*, *supra* note 1, at 40–41.

§ 271(e)(4)(B), a subsection governing injunctions “to prevent the commercial manufacture, use, offer to sell, or sale . . . [of a] biological product.”⁴² There, too, the *Sandoz* Court noted that biosimilars, not reference biologics, have the power to control the timing of the patent suits against them by allowing biosimilars to file their notices of commercial marketing prior to FDA approval.⁴³ In either of these cases, any submarine patents held by reference biologics’ would be located by biosimilars during discovery, with any preliminary injunctions against the biosimilar occurring prior to FDA approval—when the biosimilar would not have been able to enter the market in any event.

These practical implementations of the BPCIA notwithstanding, the Federal Circuit’s recent decision in *Amgen Inc. v. Sanofi*, also decided after Carrier and Minniti’s article went to press, suggest that submarine patents for biologics are now even more unlikely.⁴⁴ Following a jury trial in favor of Amgen, one aspect of the *Amgen* appeal focused on the court’s jury instructions concerning written description and enablement, two requirements of patentability.⁴⁵ Written description requires patentees to sufficiently describe, in their patents’ specifications, a representative scope of their claimed inventions.⁴⁶ Enablement, meanwhile, requires patentees to claim and describe their inventions in such a way as to enable a “person having ordinary skill in the art” to make and use the inventions without undue experimentation.⁴⁷ These have long been troublesome provisions for patents covering antibodies—the staple molecules of biologics—because antibodies are both chemical complex and *functionally* defined by what molecules they interact with rather than by what they are chemically.⁴⁸ To satisfy written description and enablement, antibody patentees have long resorted to chemically defining the molecule to which the antibody bound, *i.e.*, the antigen, and oftentimes where on the antigen the antibody bound to.⁴⁹ In *Amgen*’s case, for example, it defined its antibody as “anti-PCSK9,” because it bound to certain locations on the protein PCSK9.⁵⁰

42. 35 U.S.C. § 271(e)(4)(B) (2012); *Sandoz*, 137 S. Ct. at 1675 n.2 (“In holding that § 262(l)(9)(C) represents the exclusive remedy for an applicant’s failure to provide its application and manufacturing information, we express no view on whether a district court could take into account an applicant’s violation of § 262(l)(2)(A) (or any other BPCIA procedural requirement) in deciding whether to grant a preliminary injunction under 35 U.S.C. § 271(e)(4)(B) or § 283 against marketing the biosimilar.”).

43. *See Sandoz*, 137 S. Ct. at 1672.

44. 872 F.3d 1367, 1371 (Fed. Cir. 2017).

45. *Id.*

46. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc) (“[S]ufficient description of a genus instead requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.”).

47. *Sanofi*, 872 F.3d at 1375.

48. Hyeongsu Park, Comment, *Written Description Problems of the Monoclonal Antibody Patents after Centocor v. Abbott*, HARV. J.L. & TECH. DIGEST (Mar. 13, 2014), <http://jolt.law.harvard.edu/digest/written-description-problems-of-the-mono-clonal-antibody-patents-after-centocor-v-abbott> (recounting the recent history of these difficulties).

49. *Sanofi*, 872 F.3d at 1375–79 (reviewing cases).

50. *Id.* at 1371–72.

Despite decades of practice, the Federal Circuit concluded this was no longer enough, and jury instructions to that effect were given in error.⁵¹ Rather, the Federal Circuit concluded that defining antibodies by their antigens—even if done with specificity—“ran afoul of what is perhaps the core ruling” of written description.⁵² Adequate written description must contain “a precise definition” of the thing claimed, and where the patent’s claims are directed to a genus of chemicals—as with functionally defined antibodies—the specification must detail “properties . . . of [the] species falling within the genus sufficient to distinguish the genus from other materials.”⁵³ In the biologics context, this means that referencing the antigen to which an antibody binds is not enough: “[I]nstead of ‘analogizing the antibody-antigen relationship to a ‘key in a lock,’ it was more apt to analogize it to a lock and ‘a ring with a million keys on it.’”⁵⁴

The *Amgen* decision means, in all practicality, that antibody patents will be substantially more difficult to obtain. Patent attorneys seeking protection for their clients’ antibodies will now likely be required to disclose the antibodies corresponding DNA sequence—a significant narrowing of the scope of antibody patents to date.⁵⁵ Further, follow-on patents to narrowly claimed antibody patents will also likely to be more difficult to obtain, given narrow claims to a known biologic, variants of that biologic, and new therapeutic uses for it are likely to be obvious and, therefore, unpatentable.⁵⁶ These future restrictions on antibody patents, coupled with robust discovery under the BPCIA after *Sandoz*, should soften Carrier and Minniti’s concerns over the anticompetitive use of submarine patenting in this area.

III. CITIZEN PETITION ABUSE

Carrier and Minniti also examine the potential of reference biologics to stave off market competition through the use of FDA citizen petitions, which are requests that FDA revoke a drug’s approval over concerns about the drug’s safety or efficacy.⁵⁷ The topic is one Carrier and Minniti previously explored, empirically and at length, in the small-molecule context.⁵⁸ There, Carrier and Minniti found that brand pharmaceuticals filed 92% of a subset of these petitions—even though the FDA granted only 8% of them.⁵⁹ This low success rate—combined with increasing page lengths and brands’ filing multiple peti-

51. *Id.* at 1379.

52. *Id.* at 1378.

53. *Id.* (quoting *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc)).

54. *Id.*

55. *See id.* at 1372 (noting the narrowness of antibody claims that recite specific sequences).

56. *See* Timothy R. Holbrook, *Patent Anticipation and Obviousness as Possession*, 65 EMORY L.J. 987, 1035–38 (2016) (discussing the obvious-to-try standard in the context of antibodies).

57. Carrier & Minniti, *supra* note 1, at 55–57.

58. Michal A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. U. L. REV. 305 (2017).

59. *Id.* at 308.

tions against the same generic rival—strongly flagged brands’ citizen petition filings as anticompetitive acts.⁶⁰

In *Biologics: The New Antitrust Frontier*, Carrier and Minniti extend these findings to biologics to assess—given the differences in regulatory schemes—whether similar conduct is likely to occur.⁶¹ They “predict that in the biologics setting, the proportion of frivolous, anticompetitive [citizen] petitions will decrease while those raising legitimate scientific concerns will increase.”⁶² Carrier and Minniti ground their prediction in the reality that “biologics are complex and unpredictable, implicating legitimate safety and efficacy concerns. . . . magnified because biosimilars will, at most, be similar (rather than identical) to the biologic.”⁶³ As an analogy, Carrier and Minniti use Mylan N.V.’s petitions over its EpiPen product, a combination drug-device autoinjector consisting of an epinephrine preloaded-syringe, and used to treat the onset of potentially fatal anaphylaxis.⁶⁴ After competitors produced generic versions of EpiPen, Mylan filed several citizen petitions with the FDA raising, what turned out to be, legitimate safety and efficacy concerns over their rivals’ products.⁶⁵ The generic EpiPens complained of by Mylan had difficulty, routinely and without accident, deploying the product’s autoinjector and delivering the correct quantity of the epinephrine payload.⁶⁶ By Carrier and Minniti’s account, these safety and efficacy troubles concerns stemmed from EpiPen’s complexity—an analogous concern to biosimilars writ large.⁶⁷

Outside of the U.S. regulatory regime, it is unclear whether biosimilars really *do* pose the safety concerns so feared by the FDA. Rather, there is evidence in Europe to the contrary, that European biosimilars are just as safe as their biologic-branded counterparts. Europe, unlike the U.S., does not have separate “interchangeability” requirements for biosimilar approval: a biosimilar may be dispensed upon prescription for a reference biologic, just like generic medicines for brand products in the small-molecule context in the U.S.⁶⁸ As a result, Europe has witnessed over the past decade a number of natural experiments concerning the interchangeability of biosimilars with their reference products.⁶⁹ A recent landscape review of these interchangeability studies found that, for biosimilar-biologic switches in 11,000 patients, “[m]ost . . . did not re-

60. *Id.* at 341 (“Such a finding raises a question as to whether the petitions were related to safety concerns or whether they were just another tool in the toolkit of ‘lifecycle management,’ less charitably known as potentially anticompetitive behavior.”).

61. Carrier & Minniti, *supra* note 1, at 55–63.

62. *Id.* at 61.

63. *Id.*

64. *Id.* at 64.

65. See Carrier & Minniti, *supra* note 58, at 350–51.

66. See Carlos A. Camargo et al., *Auvi-Q versus EpiPen: Preferences of Adults, Caregivers, and Children*, 1 J. ALLERGY & CLINICAL IMMUNOLOGY 266, 267 (2013) (discussing some of the practical difficulties in an equally responsive generic EpiPen).

67. Carrier & Minniti, *supra* note 1, at 63.

68. Pekka Kurki et al., *Interchangeability of Biosimilars: A European Perspective*, 31 BIODRUGS 83, 83 (2017).

69. *Id.* at 84.

port any switch-related adverse effects.”⁷⁰ Tracking such effects through European Public Assessment Reports (EPARs), the authors found serious switching events in only two cases: coagulation factor VIII (FVIII) and interferon (IFN)- β .⁷¹ And in both cases, the safety problems arising from switching were scientifically idiosyncratic. Regarding FVIII, patients generally lack tolerance to the protein, increasing the likelihood that patients will reject “switched” FVIII biosimilars due to a natural build-up of an immune response against both the reference and biosimilar version of the drug.⁷² Even then, however, some “recent clinical studies suggest that the risk of [this response] is not significantly increased upon switching between different coagulation factor products.”⁷³ Regarding IFN- β , the biosimilar product was ultimately not comparable to the reference product: the biosimilar consisted of IFN- β -1a while the reference product was IFN- β -1b, “two proteins [with] different amino acid sequences, post-translational modification profiles, and administration routes.”⁷⁴ The lack of adverse events from biosimilars led the authors to conclude that “the potential risks [of switches] have been exaggerated.”⁷⁵

Given this scientific reality—and manufacturers’ past behavior in the small-molecule context—there is little reason to believe that citizen petitions in the biologics context would *not* be anticompetitive. To the contrary, reference biologics may use the specter of scientific complexity to exaggerate the safety or efficacy concerns of competing biosimilars. Also, given the market for biologics, developers would have every incentive to do so. At the same time, safety concerns surrounding biosimilars cannot be completely discounted as evinced by the FVIII and IFN- β . But given their particularity, validating such claims would be extraordinarily difficult. This is likely to require FDA to devote even more of its dwindling resources to assessing such claims, separating legitimate risks from merely perceived ones due to the products’ complexity. These perceived risks raise concerns that citizen petitions, even in the biologics context, may decrease legitimate market competition.

At the same time, Carrier and Minniti’s prior work on citizen petitions provides some guidance as to what are likely to be anticompetitive uses of such petitions, at least at a surface level. Carrier and Minniti note that the filing of multiple citizen petitions soon before patent expiration raises a serious likelihood of anticompetitive conduct.⁷⁶ Given reference biologics’ robust patent portfolios covering their products, the analogy is an imperfect one. But it can nonetheless be extended to patents covering the biologic drug product itself—the antibody composition, for example—rather than methods of use or manufacture. Oppositely, reference biologic-filed citizen petitions grounded in adverse event data from elsewhere—like EPARs—should be afforded more

70. *Id.* at 86.

71. *Id.*

72. *Id.*

73. *Id.*

74. *Id.*

75. *Id.* at 89.

76. See Carrier & Minniti, *supra* note 58, at 332 Table 4.

weight because such studies were not performed with the purpose of stymying competition in the U.S.

The science of biologics—and the stakes involved for competitors—provides some caution to Carrier and Minniti's otherwise hopeful conclusions about citizen petitions. But the authors also provide a roadmap for assessing our own skepticism. One can hope the authors are right about the latter and wrong about the former.

CONCLUSION

Carrier and Minniti's article, *Biologics: The New Antitrust Frontier*, provides an extensive and useful discussion of extending the variety of antitrust concerns in small-molecule drug litigation to biologics. But its most interesting contribution is its linkage of antitrust law to the scientific complexity of the underlying products—that biologics' *complexity* makes conduct anticompetitive in some instances but not others. In their article, Carrier and Minniti may not take this insight far enough, at least as concerning reverse payment settlements, submarine patents, and citizen petitions. Only future litigation will tell. For now, Carrier and Minniti's excellent work will likely require practitioners, scholars, and policy-makers to confront the intersection of antitrust and scientific complexity—the science of substitution.