
REVISITING REGULATORY EVASION

*Jordan Paradise, J.D.**

Biologics: The New Antitrust Frontier by Carrier and Minniti is a tremendously insightful contribution to the legal literature at the intersection of drug and biologic law and regulation, antitrust law, and patent law. Typical biologic and biosimilar product development and marketing activities are subject to joint oversight of the Food and Drug Administration, the Federal Trade Commission, and the Patent and Trademark Office, three federal administrative agencies with different missions, authority, and priorities. The article carefully navigates the intersection of these three legal realms and agencies, remaining squarely focused on industry behaviors and the antitrust analysis and ensuing implications throughout. The article highlights the beginning of a complex tangle of legal and regulatory issues facing industry and federal administrative agencies following passage of the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”).¹ Eight years after enactment, and following much activity among the industry and the relevant agencies, many of these issues are just now arriving in front of the courts.

This article expands on fundamental concepts of variability that emerge from drug and biologic development that fuel industry behaviors. It also offers three additional examples of what Carrier and Minniti term “regulatory evasion” that hinder access and innovation to products. Finally, it assesses recent FDA activity to curb regulatory abuses that has occurred following the publication of the Carrier and Minniti article.

But how exactly did we get here? There are two important and intertwined stories of variability framing the Carrier and Minniti article that warrant some unpacking. The first is *scientific variability*. The authors are careful to point out that the “product is the process” with inherently sensitive biological products.² Replicating a “same” biological product is an impossible task owing to the characteristics of these naturally derived products, which are larger and more complex entities than small-molecule drugs and are subject to differences given factors such as manufacturing practices, storage conditions, and individual immunogenic responses. Chemically synthesized drugs, on the other hand,

* Professor of Law, Loyola University Chicago School of Law

1. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001–03, 124 Stat. 119, 804–21 (2010) (codified in scattered sections of 42 U.S.C. and 21 U.S.C.).

2. Michael A. Carrier & Carl J. Minniti, *Biologics: The New Antitrust Frontier*, 2018 ILL. L. REV. 101, 109.

are relatively easy to replicate from lot to lot, and generic versions will conform to the innovator product on measures of bioequivalence (*i.e.*, pharmacokinetics—how the human body absorbs, distributes, metabolizes, and excretes the drug—and pharmacodynamics, the mechanism of drug action and effects on the human body). Generic drugs are therapeutically “the same” as the innovator. Biosimilars are deemed “highly similar” in comparison to the innovator biologic; they are never the same as the innovator biologic. Given this scientific truth, biologics are much more expensive to develop, and intense secrecy regarding manufacturing processes pervades the industry.

The second story is that of *legal and regulatory variability*. At the federal level, this stems largely from two separate statutes: the Federal Food, Drug, & Cosmetic Act (“FDCA”), addressing drugs,³ and the Public Health Service Act (“PHSA”), addressing biological products.⁴ The historical framework is crucial to understanding the current state of affairs. The Biologics Control Act, now a part of the PHSA, was originally enacted in 1902, setting forth safety, purity, and potency standards for biological products and establishing the basis of current enforcement schemes.⁵ Four years later, Congress passed the Pure Food and Drugs Act, which created mechanisms for federal action in the case of adulterated or misbranded drugs already on the market.⁶ Legislation in 1938 required drug sponsors to demonstrate the safety of products;⁷ subsequently, in 1962, Congress implemented requirements for the showing of both safety and efficacy prior to a drug product entering the market.⁸ From that point on, new drug sponsors were required to conduct rigorous clinical trials to establish safety and efficacy and were subject to enforcement actions and civil penalties for violations. Amendments to the FDCA did not apply to biologics despite the similarities in clinical trial requirements and premarket agency assessments of products that developed over time. Recognizing that this statutory bifurcation hindered opportunities to streamline agency efforts, in 1997 Congress passed legislation tasking the FDA with harmonizing the regulatory approval processes for the two types of products to the extent possible given scientific differences.⁹ But it was not until 2010, with the enactment of the BPCIA, that Congress provided an abbreviated route to market for biologics, something in existence for drugs since the Hatch-Waxman Act of 1984.¹⁰

This chronology of legal and regulatory variability between drugs and biologics provides an interesting study of how the industry adapts behaviors to the environment Congress presents it. This is a core theme that the Carrier and Minniti article examines, utilizing a comparative analysis to explore real-time industry behaviors in the drug and biologic realms and offering projections for

3. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (2012).

4. Public Health Service Act, 42 U.S.C. § 201 et seq. (2012).

5. Biologics Control Act of 1902, Pub. L. 57-244, 32 Stat. 728.

6. Pure Food and Drug Act of 1906, Pub. L. 59-384, 34 Stat. 768.

7. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (2012).

8. Drug Amendments of 1962, Pub. L. 87-781, 76 Stat. 780.

9. Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115, 111 Stat. 2296.

10. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585.

the future. The two statutes dictate several aspects that the authors touch upon explicitly in the article as significant contributors to nuances in industry bad behavior: differences in the patent disclosure and litigation process and related notice mechanisms; differences in market and data exclusivity; and differences in the ability to substitute products.¹¹ Aside from the substitution issue, these statutory differences are not clearly linked to the scientific variability between drugs and biologics. Many commentators urge that Congress deliberately created a different patent and disclosure process because the Hatch-Waxman Acts provisions were not working for drugs, not because the science dictated a new process. Likewise, the debate about biologic exclusivity involved heated discussions largely focused on development costs and available patent protections.

Carrier and Minniti enumerate the factors they view as responsible for the “different biologics context” in the antitrust realm specifically, including more complex products, fewer competitors, the nonidentical relationship between the original and follow-on product, less notice of patents that could be infringed, and a regulatory regime addressing patents through a private information exchange rather than a public listing.¹² They then identify seven types of anticompetitive conduct the pharmaceutical industry commits as a result of the statutory and regulatory landscape, many of which Carrier has written extensively about in other venues: product hopping, reverse payment settlements, disparagement, collusion, strategic filing of citizens petitions, regulatory abuses, and denial of product samples (as a well-defined type of regulatory abuse). They then embark on assessing the likelihood of those same or similar behaviors arising in the biologics space, concluding that instances of the last five behaviors will be more likely with biologics, while instances of product hopping and reverse payment settlements will be less likely.

I offer several additional examples that lend credence to the authors’ discussion of regulatory abuses and disparagement behaviors. The first relates to regulatory abuses resulting from Risk Evaluation and Mitigation Strategies (“REMS”) established in the Food and Drug Administration Amendments Act of 2007.¹³ Over half of the REMS required by the FDA include elements to assure safe use (“ETASU”) that take the form of restrictions on distribution, recordkeeping requirements, and training requirements for pharmacists and prescribers, as well as limits on prescribing and administration.¹⁴ In addition to the use of REMS to refuse samples to follow-on products as the authors detail, innovators are also patenting their ETASU and threatening patent infringement

11. At the state level, legislation defining the scope of substitution of biologic products is dependent on a biosimilar product first achieving interchangeable status by the FDA, a heightened threshold within the statute. Carrier and Minniti noted that, to date, no biosimilar has received interchangeable status. Carrier & Minniti, *supra* note 2, at 129 n.191.

12. *Id.* at 125.

13. Food and Drug Administration Amendments Act of 2007, Pub. L. 110-85, 121 Stat. 823 (codified in scattered sections of 21 U.S.C.).

14. See *Approved Risk Evaluation and Mitigation Strategies (REMS)*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsData.page> (last visited Feb. 24, 2018).

where a manufacturer attempts to use aspects of the patented ETASU in its own label.¹⁵ This has created a serious problem for generic drugs, which are required to have the same label as the innovator product.¹⁶ Where the generic cannot acquire permission from the innovator to use the ETASU, and the FDA does not grant a waiver,¹⁷ the generic will be violating the law when marketing and selling that product. It is yet unclear how this is playing out in the biosimilar realm, but it merits study.

The second example relating to regulatory abuses deals with the “patent dance” in the BPCIA, particularly the implications of the June 2017 Supreme Court decision and a Federal Circuit follow up in December 2017. Although the BPCIA contemplates “good faith negotiations” and Carrier and Minniti state that the law aims to “expeditiously” resolve litigation, the case law tells a different story. Innovator and follow-on sponsors are viciously contesting the language of the statute, chiefly regarding whether certain provisions are mandatory and when the clock begins to run. In *Sandoz v. Amgen*, the Supreme Court held that the BPCIA¹⁸ was not enforceable by injunction, and thus there were no “artificial infringement” triggering remedies available in the generic drug context.¹⁹ Rather, the exclusive remedy was an action for declaratory judgment.²⁰ The Court also held that the statute allows a biosimilar applicant to give notice of first commercial marketing prior to obtaining a license from the FDA.²¹ A brief concurrence seems to nudge the FDA to act to interpret the notice provisions within the statute.²² The Supreme Court remanded to the Federal Circuit the issues of whether the BCPIA preempts state-law remedies²³ and whether California unfair competition law provides a separate remedy.²⁴ On December 14, 2017, a unanimous Federal Circuit panel ruled that the BPCIA “fully occupied” the field of patent litigation for biosimilars, meaning that state laws cannot compel disclosure of manufacturing information.²⁵ This outcome seems to exacerbate the problems of secrecy, and it ties directly into themes of regulatory abuses enabled by the current state of the law.

15. For a detailed discussion of the REMS provisions and the associated patent problems, see Jordan Paradise, *REMS as a Competitive Tactic: Is Big Pharma Hijacking Drug Access and Patient Safety?*, 15 HOUS. J. HEALTH L. & POL'Y 43 (2015). One example is Celgene's patented distribution system for thalidomide. U.S. Patent No. 7,141,018 B2 (filed Nov. 28, 2006).

16. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j)(A)(v) (2012).

17. The FDA has the authority to waive the use of a single, shared REMS system. A waiver is possible where the innovator reference listed drug REMS is subject to patent protection and the generic could not obtain a license. The generic sponsor must certify to the FDA that they attempted to obtain a license and were refused. *Id.* § 355-1(i)(1)(B); Use of a Drug Master File for Shared System Risk Evaluation and Mitigation Strategy Submissions, 82 Fed. Reg. 52,058 (Nov. 9, 2017) [hereinafter Use of a Drug Master File].

18. Specifically, 42 U.S.C. § 262(l)(2)(A) (2012).

19. See 35 U.S.C. § 271(e)(4) (2012); *Sandoz, Inc. v. Amgen, Inc.*, 137 S. Ct. 1664, 1673–76 (2017).

20. *Sandoz*, 137 S. Ct. at 1674–75 (citing 42 U.S.C. § 262(l)(9)(C)).

21. *Id.* at 1668 (citing 42 U.S.C. § 262(l)(8)(A)).

22. *Id.* at 1678 (Breyer, J., concurring).

23. *Id.* at 1678.

24. *Id.*

25. *Amgen, Inc. v. Sandoz, Inc.*, 794 F.3d 1347 (Fed. Cir. 2017).

The third example relates to the role of the FDA in resolving uncertainty within the statutory language as a means to curb regulatory abuses. Notably, the FDA has taken two assertive actions within the last year that address aspects of relevant industry behavior worthy of attention. The FDA recently published draft guidance establishing a two-prong approach to address issues involved in single, shared REMS systems that the statute and industry behaviors raised.²⁶ The guidance is an incremental step, though it fails to address instances where an innovator threatens patent infringement or denies a license to use the ETASU.

More generally, the FDA has also been assessing ongoing challenges in the generic realm. In July 2017, the FDA solicited public comments on ways in which the agency should utilize its authority to address challenges faced by generic companies to reach agreements for shared REMS systems; what actions the FDA should take to address difficulties acquiring sufficient samples for testing; and what marketplace dynamics exist that may be disincentivizing the marketing of generics.²⁷ FDA Commissioner Scott Gottlieb issued a statement in November 2017 announcing means to improve the review of shared REMS programs, noting the “need to make sure that REMS programs maintain their role in serving public health and don’t become a tool companies can use to delay or block competition from generic products entering the market.”²⁸ Gottlieb stated that the FDA “will explore new steps . . . to reduce the likelihood that branded drug companies can use the existence of REMS as a way to slow the entry of generic competition.”²⁹ Gottlieb has also publicly stated that agency communications to brand companies informing them that providing or selling samples to a generic sponsor for testing is acceptable under a REMS may be made public.³⁰ Such a move may serve to increase transparency and impact the ability of the innovator company to claim that FDA regulations prevent them from allowing access.

Two final points are research questions for the authors. Regarding disparagement, the authors state, “[u]nlike in the case of small molecules, where automatic substitution brings about instant price erosion, a biologic name’s strength, coupled with confidence in the original product, will play a more prominent role in forestalling competition.”³¹ They state that analysis of disparagement will be trickier in the biologic space, with a key role for state

26. Use of a Drug Master File, *supra* note 16.

27. Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access, 82 Fed. Reg. 28,493, 28,495 (June 22, 2017).

28. Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on New Steps to Improve FDA Review of Shared Risk Evaluation and Mitigation Strategies to Improve Generic Drug Access (Nov. 8, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584259.htm>.

29. *Id.*

30. Derrick Gingery, *FDA Exploring Whether Public Shaming Can Stop REMS Abuses*, PINK SHEET (July 18, 2017), <https://pink.pharmaintelligence.informa.com/PS121134/FDA-Exploring-Whether-Public-Shaming-Can-Stop-REMS-Abuses>.

31. Carrier & Minniti, *supra* note 2, at 129–30.

common law and the courts. “More than any other category, disparagement will present challenges that have not been confronted in the small molecule setting.”³² Furthermore, “[u]nlike the relationship between brands and generics, competition between biologics and biosimilars will require marketing and advertising to differentiate products, which increases the likelihood of disparagement.”³³ Manufacturers, in head-to-head advertising battles, “may seek to influence, or even intimidate, prescribers by exaggerating the differences with biosimilars and highlighting potential tort liability.”³⁴ These are all powerful observations, and I am left wondering whether and how the FDA’s January 2017 biologic naming guidance has impacted this landscape³⁵ and whether there are new off-label promotion issues that accompany the alleged promotional behavior.

Finally, the authors contend that biologics are the “new frontier” in anti-trust litigation. Yet, prior to the BPCIA, biologics sponsors routinely achieved regulatory approval through the full biologics license application (“BLA”) process, conducting full-scale clinical trials for a biologic product and achieving approval for products that would likely now be amenable to the biosimilar pathway. In fact, early coverage of industry reactions to the BPCIA emphasized that biologic sponsors were hesitant to proceed through the new biosimilar pathway and instead were taking the BLA route to market.³⁶ Are the antitrust issues truly an entirely new frontier with biologics? Are there lessons from those products or resulting legal challenges that can be written into this analysis?

32. *Id.* at 191.

33. *Id.* at 188.

34. *Id.*

35. U.S. DEP’T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., NONPROPRIETARY NAMING OF BIOLOGICAL PRODUCTS: GUIDANCE FOR INDUSTRY (2017).

36. *See, e.g.,* Claudia Wiatr, *U.S. Biosimilar Pathway Unlikely to Be Used*, 25 *BIODRUGS* 63 (2011).