BIOLOGICS IN THE PRACTICE OF LAW

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Biologics have come to occupy an increasingly important role in the medical industry, accounting for well over $200 billion in worldwide sales in 2014. Not surprisingly, biologics also occupy a prominent place in the practice of life-sciences law. Before expanding on how biologics and the law interact, however, it is important to first define "biologics." Most treatments for chemotherapy and autoimmune disorders are biologics. In contrast to a drug, which is a mixture of chemicals according to a set recipe, a biologic comes from a living organism.[1] Rodents, for example, might be a possible source.[2] Because no two biologics will be identical, there can be no "generic" biologic. Rather, a competing biologic may be deemed "biosimilar" or, if heightened requirements are met, "bioequivalent" to a reference biologic. Until recently, the concept of biosimilars was not recognized or approved in the United States. This changed with a little-known provision of the Patient Protection and Affordable Care Act, which is revolutionizing the pharmaceutical industry.

This Essay begins by discussing the recently implemented legislative pathway for marketing biosimilars in the United States, and the intersection of this pathway with the Leahy-Smith America Invents Act's mechanism for *inter partes* challenges to patents. The Essay then explores the competitive strategies at play in, and the initial economic effects arising from, the burgeoning biosimilars market, and ultimately concludes that the societal effect will be beneficial, if less dramatic than proponents of the Patient Protection and Affordable Care Act intended. Strong demand and high prices for biologics

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1. *See* JUDITH A. JOHNSON, CONG. RESEARCH SERV., RL34045, FDA REGULATION OF FOLLOW-ON BIOLOGICS 1 (2010); *see also* 42 U.S.C. § 262(i)(1) (2012) (defining "biological products").

2. *See* Anne Kantardjieff & Weichang Zhou, *Mammalian Cell Cultures for Biologics Manufacturing*, *in* MAMMALIAN CELL CULTURES FOR BIOLOGICS MANUFACTURING 1, 3, 8 (Anne Kantardjieff & Weichang Zhou eds., 2014) (analyzing the biologics market).

have created a robust black market in which smugglers enable physicians to obtain and administer to unknowing patients delicate, temperature-sensitive, non-FDA-approved biologics intended for use on the other side of the world. Drawing in part on the Author's personal experience as a federal prosecutor, the Essay explains why this black market is dangerous for patients who were neither informed of nor consented to treatment with non-FDA-approved biologics. The Essay concludes by exploring how both the legal and illegal markets for biologics are affected by the relationship between doctors and insurance providers, including federal and state governments and formularies, in which patients are merely passive participants.

I. THE LEGISLATIVE PROCESS FOR MARKETING BIOSIMILARS

Historically, the Hatch-Waxman Act[3] provided a legislative pathway to obtain FDA approval of generic drugs.[4] This legislation was enacted in 1984 and signed into law by President Ronald Reagan.[5] However, until the Patient Protection and Affordable Care Act[6] (PPACA) was passed in 2010, no equivalent pathway existed for biologics.[7] This legislative vacuum effectively insulated biologics manufacturers from competition, no doubt contributing to biologics' high prices and profit margins. The PPACA changed this competitive landscape through the Biologics Price Competition and Innovation Act (BPCIA).[8] The BPCIA allows companies that wish to introduce "biosimilar" or "bioequivalent" (per a heightened standard) pharmaceuticals to obtain FDA approval and enter the market.[9]

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3. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified across various provisions of Titles 21 and 35 of the U.S. Code).

4. *See id.* at § 101 (providing for abbreviated approval of new drugs).

5. *See* Remarks on Signing S. 1538 into Law, 20 WEEKLY COMP. PRES. DOC. 1349, 1359–60 (Sept. 24, 1984).

6. Pub. L. 111-148, 124 Stat. 119 (2010) (codified across various provisions of Titles 26 and 42 of the U.S. Code).

7. *See* Julie D. Polovina, Note, *Mutant Biologics: The 2010 Health-Reform Legislation's Potential Impact on Reducing Biologic Research and Development Costs*, 100 GEO. L.J. 2291, 2297 (2012) (explaining that the Hatch-Waxman Act did not apply to biologics).

8. *See* 42 U.S.C. § 262 (2010).

9. Sandoz Inc. v. Amgen Inc., 773 F.3d 1274, 1275 (Fed. Cir. 2014).

These "generic" biologics are aptly called "biosimilars," as they are derived from living organisms and are similar, but not identical, to the biologics for which they will be substituted.[10] This stands in stark contrast to a generic drug, which involves mixing chemicals according to a set recipe.[11] The comparative complexity of biologics makes the process of manufacturing and testing biosimilars much more expensive and time-consuming than the equivalent stages for generic drugs.[12] Yet the vast majority of the most profitable medications in recent years have been biologics, not drugs.[13] As such, everyone from generic drug companies to competing biologics manufacturers is eager to capture a slice of the biosimilars market.[14]

At present, many companies are in the midst of clinical trials for new biosimilars.[15] However, only a few biosimilar applications have been filed with the Food and Drug Administration (FDA), and just one biosimilar has been approved to date.[16] On

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10. *See id*. at 1275 n.2.

11. *See* Laura Lorenzetti, *Biosimilars May One Day Save Your Life. But What Are They?*, FORTUNE (Feb. 6, 2015, 4:35 PM), http://fortune.com/2015/02/06/biosimilars-what-are-they/ [http://perma.cc/8YD9-E8PR] ("Producing generic small-molecule drugs is relatively simple—it's like following a recipe with standard ingredients."); *see also* Kyle Barrett, Note, *Implementing the Biologics Price Competition and Innovation Act: Why Legal Principles Justify a Broad Definition of Biosimilarity*, 85 S. CAL. L. REV. 1597, 1600–01 (2012) (noting the differences between biologic and chemical drugs).

12. *See* Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L.J. 57, 59 (2012).

13. *See* Julia Kollewe, *World's 10 Bestselling Prescription Drugs Made $75bn Last Year*, THE GUARDIAN (Mar. 27, 2014), http://www.theguardian.com/business/2014/mar/27/bestselling-prescription-drugs [http://perma.cc/ZYR6-3PQZ].

14. *See* Cheryl Swanson, *This Market Could Grow 6250% in 10 Years*, THE MOTLEY FOOL (Mar. 23, 2015, 10:15 AM), http://www.fool.com/investing/general/2015/03/23/this-market-could-grow-6250-in-10-years.aspx [http://perma.cc/DW96-ZBS8] (describing the potential for growth and industry investment in the future of biosimilars production).

15. *See, e.g.*, Press Release, Synthetic Biologics, Synthetic Biologics to Initiate Clinical Trials of SYN-004 in 4Q 2014 to Prevent Potentially Deadly *C. Difficile* Infections (Sept. 2, 2014), *available at* http://www.syntheticbiologics.com/2014-09-02-Synthetic-Biologics-to-Initiate-Clinical-Trials-of-SYN-004-in-4Q-2014-to-Prevent-Potentially-Deadly-C-difficile-Infections [http://perma.cc/8D89-G7RJ].

16. *See* U.S. FOOD & DRUG ADMIN., NUMBER OF BIOSIMILAR INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS) RECEIVED IN THE MONTH (2015), *available at* https://web.archive.org/web/20150920160816/http://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cder&status=public&id=CDER-RRDS-

March 6, 2015, the FDA approved Novartis AG subsidiary Sandoz's Zarxio,[17] which is biosimilar to Amgen's Neupogen.[18] Both biologics are approved for use in cancer patients undergoing chemotherapy or bone marrow transplants, among other treatments.[19] On September 3, 2015, Zarxio became the first biosimilar to enter the United States market when Novartis launched the biosimilar at a fifteen-percent discount compared to Neupogen.[20] Just prior to the Zarxio approval, in late February 2015, an FDA advisory committee postponed a scheduled March meeting to discuss Celltrion's application for a biosimilar to Janssen Biotech's Remicade, which is used to treat autoimmune diseases such as rheumatoid arthritis and Crohn's disease.[21] Apotex, a generic drug company, has two biosimilar applications under review for versions of Amgen's Neupogen and Neulasta, both of which are administered to cancer patients to reduce the risk of infection during chemotherapy.[22]

The expected cost savings from biosimilars will not materialize immediately, or perhaps even anytime soon. For starters, there remains a period of exclusivity under the BPCIA.[23] The original biologic manufacturer is guaranteed twelve years of regulatory exclusivity before a biosimilar can be introduced.[24]

Number-of-biosimilar-INDs&fy=All [http://perma.cc/ZW2P-44UL] (reporting nineteen biosimilar investigational new drug applications (INDs) since 2013).

17. *See* Press Release, U.S. Food & Drug Admin., FDA Approves First Biosimilar Product Zarxio (Mar. 6, 2015), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm [http://perma.cc/V7TA-GTZS].

18. *See id.*

19. *See id.*

20. *See* Ben Hirschler & Michael Shields, *Novartis Launches First U.S. 'Biosimilar' Drug at 15 Percent Discount*, REUTERS (Sept. 3, 2015), http://www.reuters.com/article/2015/09/03/us-novartis-drug-idUSKCN0R30C220150903 [http://perma.cc/C62V-LZZ8].

21. *See* Ben Hirschler, *FDA Postpones Key Hearing on Biosimilar Copy of Blockbuster Drug*, REUTERS (Feb. 26, 2015), http://www.reuters.com/article/2015/02/26/health-biosimilars-fda-idUSL5N0W03RI20150226 [http://perma.cc/L2ZC-HCR8].

22. *See FDA Has Accepted Apotex Filgrastim Biosimilar Filing*, BIOSIMILAR NEWS (Feb. 20, 2015, 8:46 AM), http://www.biosimilarnews.com/fda-has-accepted-apotex-filgrastim-biosimilar-filing [http://perma.cc/NE4X-BV3H]; *Apotex Biosimilar of Amgen's Neulasta Under Review by FDA*, BIOSIMILAR NEWS (Dec. 19, 2014, 11:15AM), http://www.biosimilarnews.com/apotex-biosimilar-of-amgens-neulasta-under-review-by-fda [http://perma.cc/5WCE-4C2V].

23. *See* 42 U.S.C. § 262(k)(6)–(7) (2012).

24. *See* 42 U.S.C. § 262(k)(7)(A) (2012).

Indeed, the FDA will not even accept an application for a biosimilar within the first four years after the biologic was approved.[25] Additionally, the first approved biosimilar is granted its own period of regulatory exclusivity—between one and three-and-a-half years—before another biosimilar can enter the market.[26] Thus, a minimum of thirteen years will pass before a truly competitive market—that is, one with three or more players—will exist for any biologic. Neupogen serves as a real-world example. Even if Apotex's pending biosimilar application is approved as a second biosimilar to Neupogen, the Apotex biosimilar will likely not be permitted to launch until 2018, given ongoing litigation between Sandoz and Amgen.

Moreover, obtaining regulatory approval to market a biosimilar is just the initial hurdle in a long and expensive path to reaching market. Biologics, like drugs, are usually protected by a portfolio of patents covering all unique aspects of the manufacturing process and each method of use.[27] Patent protection, which is independent of FDA approval, extends for twenty years from the date of the patent application.[28] The BPCIA therefore also envisions an elaborate set of exchanges between a biosimilar applicant and the "reference product sponsor" (the manufacturer of the branded biologic), culminating in two rounds of patent litigation.[29] The BPCIA "patent dance,"[30] as it is colloquially referred to by patent lawyers, differs greatly from the Abbreviated New Drug Application (ANDA) litigation for generic drugs prescribed by the Hatch-Waxman Act.[31] As just one example, the Hatch-Waxman Act requires a manufacturer to identify publicly the numbers and expiration dates

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25. *See* 42 U.S.C. § 262(k)(7)(B) (2012).

26. *See* 42 U.S.C. § 262(k)(6) (2012).

27. *See* Prachi V. Mehta, Note, *Expanding the Doctrine of Innovator Liability: Using Tort Liability to Create a Viable Follow-On Biologic Regime*, 2014 U. ILL. J.L. TECH. & POL'Y 531, 546 (2014) (citing Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVS. DRUG DISCOVERY 479, 480 (2008)).

28. *See* Richard A. Epstein, *Can Technological Innovation Survive Government Regulation?*, 36 HARV. J.L. & PUB. POL'Y 87, 92 n.23 (2012) ("Under 35 U.S.C. § 154(a)(2) (2006), patents are protected for twenty years from the date on which the patent application was filed.").

29. *See* 42 U.S.C. § 262(l) (2012).

30. *See* 21 U.S.C. § 355(j) (2010).

31. *See id*.

of the patents that cover its branded drug;[32] the FDA publishes this information in what is known as the "Orange Book."[33] Under the BPCIA, the reference product sponsor identifies its covered patents privately to the biosimilar applicant as part of the "patent dance."[34] Because the biosimilars industry is still in its early stages in the United States and the contours of the BPCIA are only beginning to be defined through litigation, this is the ideal moment to give some thought to this momentous development in the medical industry.

In the first-ever BPCIA litigation, *Sandoz Inc. v. Amgen Inc.*,[35] Sandoz sought declaratory judgment that two patents exclusively licensed to Amgen covering Amgen's Enbrel biologic were invalid and unenforceable, and would not be infringed by a Sandoz biosimilar.[36] When it filed suit, however, Sandoz had not yet filed a biosimilar application with the FDA.[37] For this reason, the district court dismissed the case for lack of an Article III controversy[38] and the U.S. Court of Appeals for the Federal Circuit affirmed.[39]

The next BPCIA litigation was also between Sandoz and Amgen, though the parties' roles were reversed. In *Amgen Inc. v. Sandoz Inc.*, Amgen as plaintiff sought—ultimately unsuccessfully—to force Sandoz to comply with the disclosure provisions of the "patent dance." Specifically, when Sandoz filed its biosimilar application for Zarxio, Sandoz refused to provide Amgen with information regarding its manufacturing process. Though its biosimilar application had not yet been approved, Sandoz also purported to provide Amgen with the statutorily-required 180-day notice of commercial launch.

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32. *See* Jacob S. Wharton, *"Orange Book" Listing of Patents Under the Hatch-Waxman Act*, 47 ST. LOUIS U. L.J. 1027, 1032 (2003).

33. *See id.* at 1030.

34. *See id.* ("[T]he BPCIA enumerates a strict process for the resolution of patent disputes. Here, once a biosimilar application has been accepted, the RPS and biosimilar maker are required to exchange information—known informally as the 'Patent Dance.'"); *see also* 42 U.S.C. § 262(l)(3)(A) (2012).

35. 773 F.3d 1274 (Fed. Cir. 2014).

36. *See id.* at 1275.

37. *See id*.

38. *See* Sandoz Inc. v. Amgen Inc., No. C-13-2904 MMC, 2013 WL 6000069 at *3 (N.D. Cal. Nov. 12, 2013).

39. 773 F.3d at 1278.

In response, Amgen sought regulatory and judicial relief. Amgen filed a Citizen Petition asking the FDA to require a biosimilar applicant to certify, as part of the biosimilar application process, that it will timely disclose its application and manufacturing processes to the reference product sponsor.[40] Amgen asked the district court for a preliminary injunction barring Sandoz from marketing Zarxio pending a court ruling on whether the "patent dance" is mandatory. Notwithstanding the pending Citizen Petition, the FDA approved Zarxio as a biosimilar on March 6, 2015.[41] Less than two weeks later, on March 19, 2015, the district court denied Amgen's request for a preliminary injunction,[42] thereby opening the door for Zarxio's commercial launch. The district court held that Sandoz was *not* required to provide Amgen with a copy of its biosimilar application or details of its manufacturing process. The district court further held that Sandoz properly provided Amgen with its 180-day notice of intent to launch Zarxio *before* the FDA approved Zarxio.[43] Six days later, the FDA denied Amgen's Citizen Petition,[44] reasoning that the BPCIA did not *mandate* the FDA to require biosimilar applicants to disclose to reference product sponsors the application and manufacturing processes.[45] The agency thus further declined to exercise discretion to regulate under that statutory provision while litigation was pending.[46]

The U.S. Court of Appeals for the Federal Circuit, which has exclusive jurisdiction over all patent appeals, granted a temporary injunction pending appeal. On July 21, 2015, in a fractured

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40. *See* Amgen Citizens Petition, *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2014-P-1771-0001 [http://perma.cc/JFY5-QJ8E] (last visited on Sept. 19, 2015).

41. *See* Amgen Inc. v. Sandoz Inc., 794 F.3d 1347, 1352 (Fed Cir. 2015).

42. *See* Amgen Inc. v. Sandoz Inc., No. 14-cv-04741-RS, 2015 WL 1264756, at *10 (N.D. Cal. Mar. 19, 2015).

43. *See id*.

44. *See* Dave Cotta, *FDA Denies Request to Make "Patent Dance" a Prerequisite for Biosimilar Approval*, GLOBAL IP MATTERS (Apr. 3, 2015), http://www.globalipmatters.com/2015/04/03/fda-denies-request-to-make-patent-dance-a-prerequisite-for-biosimilar-approval [http://perma.cc/S652-YQ3Z].

45. *See* Citizen Petition Denial Response, *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2014-P-1771-0004 [http://perma.cc/8H3W-NCFB] (last visited on Sept. 19, 2015).

46. *See id*.

opinion in which all three judges issued separate opinions,[47] the Federal Circuit agreed with the district court that the "patent dance" provisions are optional.[48] However, the Federal Circuit reversed the district court on the second issue, holding that a biosimilar manufacturer must obtain FDA approval before it can give the reference product sponsor its 180-day notice of Zarxio's commercial launch.[49] The Federal Circuit's ruling effectively extends a biologic's period of exclusivity for another 180 days.

The Amgen and Sandoz litigations have answered some, but by no means all, questions regarding the meaning of the BPCIA and implementing regulations. But even outside the Article III courts, the BPCIA has proven a boon for patent lawyers. This is because the Leahy-Smith America Invents Act (AIA)[50] creates an adversary process in the United States Patent and Trademark Office (USPTO) in which any petitioner can seek to invalidate patents quickly and efficiently.[51] It has become standard practice for aspiring biosimilar applicants to file petitions for *inter partes* review (IPR petitions) with the USPTO, in an attempt to preemptively invalidate key patents covering reference biologics.[52] The number of IPR petitions is booming.[53] Indeed, the USPTO has opened satellite offices across the United States[54] and Adminis-

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47. *See* Amgen Inc. v. Sandoz Inc., 794 F.3d 1347, 1350 (Fed. Cir. 2015); *id*. at 1362 (Newman, J., concurring in part, dissenting in part.); *id*. at 1366 (Chen, J., dissenting in part).

48. *Id*. at 1355–56.

49. *See id.* at 1358.

50. *See* 35 U.S.C. § 311–18 (2011).

51. *See* Changes to Implement Inter Partes Review Proceedings, Post-Grant Review Proceedings, and Transitional Program for Covered Business Method Patents, 77 Fed. Reg. 48,680 (Aug. 14, 2012). *See* 37 C.F.R. pt. 42 (2012) for the relevant procedural mechanisms.

52. *See* Jacob Sherkow, *Administering Patent Litigation,* 90 WASH. L. REV. 205, 218 (2015) ("Because the PTO engages in reexaminations *de novo*, and because reexamination proceedings tend to be more adversarial in nature than original prosecutions, re-exam has become a potent weapon-of-choice for accused infringers seeking to invalidate the asserted patents.") (emphasis added) (citations omitted).

53. *See* Yasser El-Gamal, Ehab M. Samuel & Peter D. Siddoway, *The New Battlefield: One Year of Inter Partes Review Under the America Invents Act*, 42 AIPLA Q.J. 39, 41 (2014) ("[T]he number of IPR filings in the first year alone exceeds the aggregate number of filings for the first nine years of *inter partes* reexamination.").

54. *See* U.S. Patent & Trademark Office (USPTO), *USPTO Satellite Offices Bring Resources to Innovators*, http://www.uspto.gov/blog/director/

trative Patent Judges are being hired prolifically[55] to ensure that the USPTO is able to meet the strict AIA timelines—180 days to decide whether to institute review of a patent and twelve months thereafter to issue a ruling on patentability.[56]

Since the AIA process began in 2012, most petitions have been instituted for review, and patents—particularly pharmaceutical patents—have been invalidated at an incredible rate.[57] As such, biologics manufacturers must fight to protect their valuable monopolies on two fronts. Given the billions of dollars at stake, and the complexity and ambiguity present in this area of the law, there is no doubt that biosimilar litigation will keep patent lawyers busy for years to come.

II. ECONOMIC EFFECTS OF BIOSIMILARS

Thus far, biologics manufacturers appear to be adapting effectively to the new environment. To illustrate, Pfizer recently purchased Hospira for $17 billion, in large part because of Hospira's robust biosimilars portfolio.[58] Indeed, Hospira has two biosimi-

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entry/uspto_satellite_offices_bring_resources [http://perma.cc/MBB5-UTBB] (last visited on Sept. 18, 2015).

55. *See* Dennis Crouch, *Notes from the Patent Public Advisory Committee Meeting*, PATENTLYO (Nov. 20, 2014), http://patentlyo.com/patent/2014/11/advisory-committee-meeting.html [http://perma.cc/5AEV-ZV65].

56. *See* 35 U.S.C. § 314(b)(1–2); § 318(a) (2012).

57. *See*, *e.g.*, Arlene Chow & Ernest Yakob, Commentary, *Novel AIA Adversarial Procedures for Challenging Validity of Pharmaceutical Patents*, 21 WL J. INTELL. PROP. 1, 1–2 (2015) (discussing how the number of IPR petitions filed against pharmaceutical patents has doubled since the AIA became effective); USPTO, Inter Partes *Review Petitions Terminated to Date* (Apr. 30, 2015), *available at* http://www.uspto.gov/sites/default/files/documents/inter_partes_review_petitions_%2004%2030%202015_0.pdf [http://perma.cc/BV5P-QV47] (showing the number of claims challenged through *inter partes* review); Eugene Perez, Birch, Stewart, Kolasch & Birch, LLP, *January 1, 2015 PTAB Trial Statistics* (Jan. 1, 2015), *available at* http://www.postgrantproceedings.com/statistics/January12015PTABTrialStatistics.html [http://perma.cc/8CH8-LEUH] (showing the significant increase in the number of IPR petitions filed since September 2012).

58. *See* Press Release, Pfizer, Pfizer to Acquire Hospira (Feb. 5, 2015), *available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer_to_acquire_hospira [http://perma.cc/CQN8-9XP5] (explaining that Pfizer moved to acquire Hospira partly because it was a "global leader in biosimilars" and Pfizer wanted to broaden its biosimilar portfolio); *see also* David Risser, *Pfizer to Buy Hospira in Deal Valued at About $17 Billion*, BLOOMBERG (Feb. 5, 2015, 9:13 AM), http://www.bloomberg.com/news/articles/2015-02-05/pfizer-agrees-to-buy-hospira-in-deal-valued-at-about-17-billion [http://perma.cc/PA54-LPJZ] (noting

lars applications pending before the FDA.[59] At the same time it is fighting to ward off competition from Sandoz, Amgen is running its own clinical trials on biosimilar versions of its competitors' blockbuster biologics. As of October 2014, Amgen had at least nine biosimilars in development.[60]

These pharmaceutical companies are generating prolific economic activity on the front end. There is a true race between companies to become the first approved biosimilar for any number of blockbuster biologics. As discussed earlier, the winner of this race will enjoy its own period of regulatory exclusivity, meaning that there will be just two players in the market for some period of time.[61] Despite the risks and enormous expenses associated with pharmaceutical development and clinical trials generally,[62] and the significant up-front legal activity

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that patent expirations partially motivated Pfizer to seek "its next blockbuster" via acquisition).

59. *See* Dan Stanton, *Hospira's Remicade Copycat Up for FDA Review as US Biosimilars March On*, BIOPHARMA-REPORTER.COM (Feb. 16, 2015, 9:52 AM), http://www.biopharma-reporter.com/Markets-Regulations/Hospira-s-Remicade-copycat-up-for-review-as-US-biosimilars-March-on [http://perma.cc/6VL9-LBY4] (discussing pending FDA review of Hospira's version of Remicade); Dan Stanton, *US Biosimilar Advancement: Next Up, Hospira's Epoetin Alfa*, BIOPHARMA-REPORTER.COM (Jan. 14, 2015, 9:44 AM), http://www.biopharma-reporter.com/Markets-Regulations/US-biosimilar-advancement-Next-up-Hospira-s-epoetin-alfa [http://perma.cc/2V3E-XTKU] (describing Hospira's application for Epoetin Alfa).

60. *See* Press Release, Amgen, Amgen Outlines Strategy, Growth Objectives And Capital Allocation Plans (Oct. 18, 2014), *available at* http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1982411 [http://perma.cc/778V-P99Y] (listing the biologics Amgen has under development and how they "represent a major growth opportunity" for Amgen).

61. *See* 42 U.S.C. § 262(k)(7)(A); *see also* Randi Hernandez, *Patent Exclusivity for Biologics: Seven or Twelve Years?*, BIOPHARM INTERNATIONAL (Jan. 30, 2015), http://www.biopharminternational.com/patent-exclusivity-biologics-seven-or-twelve-years?rel=canonical [http://perma.cc/P7ZM-PP9W] (discussing confusion and politics surrounding exclusivity time frame for biosimilars).

62. *See* FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 14–15 (2009), *available at* https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf [https://perma.cc/DZ68-NENZ] (noting that the barriers to entry are high because biosimilars usually take eight to ten years to develop, at costs ranging between $100 to $200 million); *see also id.* at 17–18 (explaining that an oligopolistic market will likely develop because most biologics are delivered as treatments in hospitals or doctors' offices, which are reluctant to incur restocking expenses by switching to new biologics and, because they are not

and uncertainty with biosimilars specifically, scores of companies have decided that the potential rewards justify the risks.

The implicit corollary to this emerging legal framework is one of duopolistic competition: the price decline to insurers and patients will be only as steep as needed to capture a healthy market share. Stated more plainly, we are unlikely to see prices fall steeply once a biosimilar enters the market. Indeed, when Zarxio launched on September 3, 2015, it was offered at only a fifteen percent discount from Neupogen.[63] The period of regulatory duopoly allows the biosimilar manufacturer flexibility to lower prices just enough to be placed on formularies—the list of medications that health insurance plans will cover.[64] Consequently, while some patient savings is likely—the RAND Corporation projects a thirty-five percent price decrease between 2014 and 2024[65]—biologics will remain a highly lucrative business. Furthermore, as both Amgen's active participation in biosimilar development and Pfizer's purchase of Hospira illustrate, the BPCIA may result in the largest biologics manufacturers simply spreading the wealth from their respective blockbuster drugs amongst themselves, albeit sooner than they would prefer.[66]

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obtained by patients through pharmacies involving copays, cost-lowering incentives do not apply).

63. *See* Ben Hirschler & Michael Shields, *Novartis launches first U.S. 'biosimilar' drug at 15 percent discount*, REUTERS (Sept. 3, 2015), http://www.reuters.com/article/2015/09/03/us-novartis-drug-idUSKCN0R30C220150903 [http://perma.cc/6DXW-J9ZB].

64. *See, e.g.*, Henry Grabowski et al., *Implementation of a Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 538–39 (2011) (discussing how the small market and lack of competition will not lead to a significant reduction in prices for biosimilars); *see also id.* at 529, 556 (noting that lower cost biosimilars better qualify under various formulary structures).

65. *See* ANDREW W. MULCAHY ET AL., RAND CORP., THE COST SAVINGS POTENTIAL OF BIOSIMILAR DRUGS IN THE UNITED STATES 1, 7 (2014), *available at* http://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf [http://perma.cc/H9JH-SWH5]. This projection may be optimistic. In Europe, where Zarxio has been competing with Neupogen since 2009, Zarxio is now offered at a price twenty to thirty percent lower than Neupogen. *See* Hirschler & Shields, *supra* note 63.

66. *See* Grabowski et al., *supra* note 64, at 529 (discussing how the expense of biologic treatments encourages the use of lower priced biosimilars despite institutional reluctance to change treatments of serious illnesses, such as cancer).

III. ECONOMIC EFFECTS OF THE U.S. SYSTEM FOR BIOLOGIC PRICING AND DISTRIBUTION

Another complicating factor is how the United States' regulatory scheme, pricing practices, and distribution networks affect the global market for biologics. These concerns manifest themselves in a robust black market of smuggling and illegal sales, which federal prosecutors are working diligently to curb.[67] The Cybercrime Unit of the United States Attorney's Office for the Eastern District of Virginia ("Cybercrime Unit"), in particular, has become a leader in prosecuting these illegal smuggling rings and doctors who facilitate them.[68]

One such prosecution involved Gallant Pharma International, Inc. ("Gallant Pharma"), an unlicensed wholesale pharmaceutical distributor headquartered in Northern Virginia.[69] Gallant Pharma smuggled non-FDA-approved pharmaceuticals intended for sale in countries throughout Asia and the Middle East into the United States via nondescript packages addressed and delivered to a "med spa" in the upscale Washington, D.C.,

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67. *See*, *e.g.*, 42 U.S.C. § 262(a) (2010) (requiring a license before selling biologics); 21 C.F.R. § 601.15 (2010) (providing for random sampling of imported biologics); *id.* at § 601.20 (establishing the requirements for the issuing of a biologics license); 1 FOOD & DRUG ADMIN. § 13:126 (2015) (noting the unique safety considerations for biologics); Memorandum from Interagency Working Group on Import Safety to President Bush (Sept. 10, 2007) (discussing how the FDA screens imported biologics); *see also* Parker Tresemer, Note, *Interests in the Balance: FDA Regulations Under the Biologics Price Competition and Innovation Act*, 16 UCLA J.L. & TECH. 46–47 (2012) (noting Congress's intent to limit the ability to obtain biosimilar approval); John A. Littleton, Jr., *Taking from Trailblazers: Learning from Those Who Have Gone Before When Approving Biosimilars*, 44 GA. L. REV. 1097, 1102–03, 1125–29 (2010) (arguing that allowing the FDA more discretion would increase the efficiency the approval process without compromising safety).

68. *See*, *e.g.*, Press Release, U.S. Dep't of Justice, Illegal Drug Company Gallant Pharma And Co-Founder Sentenced (Mar. 18, 2015), *available at* http://www.justice.gov/usao-edva/pr/illegal-drug-company-gallant-pharma-and-co-founder-sentenced [http://perma.cc/FQ3K-J5E8] (describing how Gallant Pharma was prosecuted for smuggling misbranded and non-FDA approved drugs into the United States).

69. *See id*. The Author previously served in the Cybercrime Unit of the U.S. Attorney's Office for the Eastern District of Virginia and was lead prosecutor for the *Gallant Pharma* case.

suburb of McLean, Virginia.[70] Gallant Pharma primarily sold intravenous chemotherapy drugs and injectable Botox—the most dangerous neurotoxin known to man.[71] Another case successfully prosecuted by the Cybercrime Unit involved TC Medical, a group based in Canada and Barbados that smuggled its non-FDA-approved biologics and Botox in nondescript packages to several drop-shippers in the United States.[72] Both Gallant Pharma and TC Medical purported to be "Canadian" companies,[73] perhaps to play into many Americans' mistaken belief that pharmaceuticals from Canada are legal. In fact, there is only a narrow exception that allows individuals (not companies) to import into the United States a ninety-day supply of prescription drugs for personal use (not commercial sale).[74] Of course, "personal use" is only possible with a medication that can be self-administered—not a biologic that must be injected intravenously by a physician. Most importantly, however, none of the biologics or Botox sold by Gallant Pharma or TC Medical were "Canadian."[75] Rather, the biologics and Botox were intended for sale in countries such as Pakistan, India, and Tur-

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70. *See* Stipulated Statement of Facts at 2, United States v. Gallant Pharma Int'l Inc., No. 1:13-CR-130-1 (E.D. Va. Dec. 6, 2013), ECF No. 169 [hereinafter Statement of Facts].

71. *See id.*

72. *See* Stipulated Statement of Facts at 1–2, United States v. TC Medical Grp., No. 1:14-CR-397-1 (E.D. Va. May 7, 2015), ECF No. 111 [hereinafter Stipulated Statement of Facts]; *see also* Press Release, U.S. Dep't of Justice, Canadian Company and Drop Shipper Plead Guilty to Conspiracy to Smuggle and Sell Misbranded Prescription Pharmaceuticals (May 7, 2015), *available at* http://www.justice.gov/usao-edva/pr/canadian-company-and-drop-shipper-plead-guilty-conspiracy-smuggle-and-sell-misbranded [http://perma.cc/4Q5F-ZT8A].

73. *See* Press Release, U.S. Dep't of Justice, Eleven Charged In Alleged Illegal Pharmacological Import and Distribution Scheme (Aug. 7, 2014), http://www.justice.gov/usao-edva/pr/eleven-charged-alleged-illegal-pharmacological-import-and-distribution-scheme [http://perma.cc/3U2G-GHM5]; Press Release, U.S. Dep't of Justice, Canadian Company and Drop Shipper Plead Guilty to Conspiracy to Smuggle and Sell Misbranded Prescription Pharmaceuticals (May 7, 2015), http://www.justice.gov/usao-edva/pr/canadian-company-and-drop-shipper-plead-guilty-conspiracy-smuggle-and-sell-misbranded [http://perma.cc/Q44V-7936].

74. *See* U.S. FOOD & DRUG ADMIN., INFORMATION ON THE IMPORTATION OF DRUGS PREPARED BY THE DIVISION OF IMPORT OPERATIONS AND POLICY, FDA (1998).

75. *See* Statement of Facts, *supra* note 70, at 2; Stipulated Statement of Facts, *supra* note 72, at 6–7.

key—which was often obvious from, for example, Farsi script on the packaging.[76]

Companies involved in this type of smuggling employ several strategies to avoid detection and seizure by U.S. Customs and Border Protection. First, large shipments are broken down into multiple, smaller sub-shipments.[77] Second, customs forms attached to shipments are completed with false information—dramatically understating the value of the contents, and using vague and misleading language to describe shipment contents.[78] Third, packages are addressed to benign locations[79]—a "med spa" in the case of Gallant Pharma, and several drop-shipping locations in the case of TC Medical. Smugglers might also take advantage of the U.S. Postal Service's direct connection to Canada Post and the United Kingdom's Royal Mail by "trans-shipping" biologics through Canada or the United Kingdom, rather than having the biologics sent directly from the Middle East or Asia to the United States. Once inside the United States, representatives of companies like Gallant Pharma and TC Medical repackage the biologics for shipment to the physician end users, ensuring that the doctor's office receives the biologics from a U.S. shipping address, which is less likely to arouse suspicion.

Trans-shipping through the United Kingdom or Canada, although attractive to smugglers, significantly increases transport time to the United States, with potentially devastating consequences. Botox and biologics are highly unstable molecules and are often "cold chain" products, which must be kept under strict temperature controls—generally just above freezing—

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76. *See* Statement of Facts, *supra* note 70, at 2; Stipulated Statement of Facts, *supra* note 72, at 6–7.

77. For an analogy with narcotics and other unlawful substances, see BUREAU OF INT'L NARCOTICS AND LAW ENFORCEMENT AFF., U.S. DEP'T OF STATE, INTERNATIONAL NARCOTICS CONTROL STRATEGY REPORT (Mar. 2004), *available at* http://www.state.gov/j/inl/rls/nrcrpt/2003/vol1/html/29839.htm [http://perma.cc/ZUL4-TJRW].

78. *Enforcing America's Trade Laws in the Face of Customs Fraud and Duty Evasion, Hearing Before the Subcommittee on International Trade, Customs, and Global Competitiveness of the S. Comm. on Finance*, 112th Cong. (2011) (statement of Allen Gina, U.S. Customs and Border Protection), *available at* http://www.dhs.gov/news/2011/05/04/statement-allen-gina-us-customs-and-border-protection-senate-finance-committee [http://perma.cc/XL8U-C26A].

79. *See id*.

from the time of manufacture to the time of injection into a patient.[80] Biologics manufacturers employ, and the FDA requires, strict shipping, monitoring, and storage protocols to ensure that these temperature controls are met at all stages of the biologic's journey. If an "excursion" occurs, which is the term used when a biologic leaves the narrow temperature window,[81] the biologic manufacturer segregates and likely destroys the biologic.[82] In contrast, illegal smuggling rings—if they do anything at all—employ stop-gap measures such as placing a Styrofoam cooler with an ice pack inside a cardboard box.[83]

Such stop-gap measures are far from sufficient. Neither U.S. Postal Service delivery trucks nor other widely-used means of transportation are air-conditioned.[84] At trial, a Gallant Pharma executive testified that the company had no knowledge of how the biologics were stored in their countries of origin and no knowledge of the transport conditions from those countries to the United Kingdom.[85] What the evidence did show was not promising.

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80. *See FDA Posts Warning about Illegally Imported Botox—Another Breach of Pharmaceutical Distribution Security*, PHARMACEUTICAL COMMERCE (Dec. 20, 2012), http://pharmaceuticalcommerce.com/latest_news?articleid=26711 [http://perma.cc/Z7EC-B8PL] ("Botox is a cold-chain pharmaceutical that requires 2–8°C storage and shipping."); *Cold Chain Focus*, PHARMACEUTICAL COMMERCE (Jan. 13, 2015), http://pharmaceuticalcommerce.com/top_news?articleid=27439 [http://perma.cc/7PG5-SKR7].

81. For an example of the phenomenon using vaccines, *see* Def. Health Agency Public Health Div., U.S. Dep't of Def., *Vaccine Storage and Handling Guidelines* 11, https://www.vaccines.mil/documents/1788_IHB_SH_Guidelines.pdf [http://perma.cc/FB5J-L6JG].

82. *See id.*

83. *See* Statement of Facts, *supra* note 70, at 10.

84. *See* Aaron M. Kessler, *Reinventing the Mail Truck*, N.Y. TIMES (Mar. 5, 2015), http://www.nytimes.com/2015/03/06/automobiles/the-mail-truck-is-a-classic-and-thats-a-problem-for-a-modern-post-office.html?_r=0 [http://perma.cc/N6NK-ARGY]; *Q&A: How Do I Keep Mailed Item Cold or Refrigerated?*, U.S. POSTAL SERV., https://prdfaq-f2.usps.com/ [http://perma.cc/LS9K-D5F9] (last visited on Oct. 4, 2015); *Security & Temperature Control in the Cold Chain*, FEDEX, http://images.fedex.com/us/healthcare/pdf/Security_Temp_Control_Cold_Chain.pdf [http://perma.cc/RE6M-G8NF] (last visited Oct. 3, 2015).

85. *See* Trial Trans. at 183–84, United States v. Huda, No. 1:13-cr-00130-CMH (E.D. Va. June 17, 2014), ECF No. 457 (demonstrating that the direct testimony is from Syed Huda, an executive and owner of Gallant Pharma); *id*. at 189 (Huda explaining that he did not know of the conditions of transport for some of the pharmaceuticals sent to him).

At the Gallant Pharma trial, an FDA protein chemist testified about the potential consequences of failing to transport and store biologics properly, using an actual Gallant Pharma shipment as an example. That shipment took more than two weeks to arrive in Virginia from the United Kingdom, during a July heat wave in which temperatures rarely fell below ninety degrees.[86] The FDA expert testified that when strict temperature controls are not followed, the delicate proteins that comprise biologics unfold and, once unfolded, will never regain their initial shape.[87] Because of the small size of these proteins, there is no way to determine with the naked eye if the biologic has been distorted, and thus no way to indicate to a physician or nurse that the biologic should *not* be injected into the cancer patient.

Under the best-case scenario, such biologics are simply ineffective. In the worst case, the patient develops an antibody against the biologic, which causes the patient's body to *fight against* the biologic during subsequent chemotherapy infusions. Because the effect of chemotherapy is cumulative, there is no way to know whether a patient failed to improve because the cancer was truly unresponsive to the chemotherapy or because the patient received ineffective or detrimental "treatments" from improperly transported and stored biologics. What *is* clear is that these smugglers, and the doctors and nurses who knowingly inject unknowing cancer patients with such biologics, demonstrate a morally shocking indifference to one of the most vulnerable populations in the United States—an indifference that few would dispute is criminal.

Indeed, a doctor *was* prosecuted as part of the Gallant Pharma group of defendants.[88] Not only was this doctor injecting smuggled cold-chain products into his patients, but he was also, as noted above, allowing his med spa to serve as the drop-

86. *See id.* at 147–48 (introducing witness and demonstrating witness' status as an expert); *id*. at 153–57 (Timothy Pohlhaus, an FDA chemist, testifying regarding the effects of temperatures on proteins).

87. *See id.*

88. *See* Indictment at 6, United States v. Gallant Pharma Int'l, Inc. (E.D. Va. Mar 27, 2013), No. 1:13-cr-00130; Press Release, U.S. Dep't of Justice, Gallant Pharma Company And Co-Owner Plead Guilty to Sixteen Charges of Prescription Drug Fraud, (Dec. 2, 2013), *available at* http://www.justice.gov/usao-edva/pr/gallant-pharma-company-and-co-owner-plead-guilty-sixteen-charges-prescription-drug [http://perma.cc/AVK6-D34N].

shipper for *all* Gallant Pharma medications, in exchange for free or deeply discounted product.[89] Following a jury trial, the doctor was convicted of thirteen felony counts, and his office manager was convicted of one felony count.[90]

Unfortunately, this was not an isolated incident. A surprisingly large number of doctors in the United States are willing to buy compromised biologics and inject them into patients.[91] One common justification, which the Author has heard from more than one defense lawyer, is to blame the arbitrage opportunities available between countries with and without price controls and to suggest that price controls in the United States would eliminate the black market. To be sure, the higher the biologics prices in the United States, the more profitable it is for smugglers to transport biologics around the world and the more risks smugglers are willing to take to enjoy such profits. But the current insurance programs provide an independent incentive for doctors to inject patients with these low-priced, illegal alternatives. As insurers, particularly Medicare and Medicaid, continue to squeeze doctors' ability to charge a fair price for services rendered, doctors must look for alternative ways to remain profitable. Doctors can cut only so many minutes from a patient visit to try to maximize the number of visits, and thus payments, each day. Like patient visits, biologics are reimbursed by insurers at a set price, generally based on a rolling average price in the U.S. market, *not* on the price the individual doctor actually paid.[92] As such, if a doctor can obtain biologics for a price far below the reimbursement rate, the doctor can go a long way toward making up for reduced compensation elsewhere.

Would biologic price controls eliminate the black market for these medications? Probably not, as any control price in the

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89. *See id*.

90. *See* Jury Verdict for Sarraf at 1, United States v. Gallant Pharma Int'l, Inc., No. 1:13-cr-00130 (E.D. Va. Mar. 27, 2013).

91. *See* U.S. FOOD & DRUG ADMIN., FDA LAW ENFORCERS CRACK DOWN ON ILLEGAL BOTOX SCAMMERS 1–2 (2009), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM143721.pdf [http://perma.cc/9JLP-JB7H] (giving examples of doctors investigated for illegal Botox injections).

92. *See* 42 C.F.R. § 414.707 (discussing current reimbursement calculations); *see also* 42 C.F.R. § 405.517(a)(2) (stating that the current reimbursement calculation is effective Jan. 1, 2004).

United States is still likely to exceed control prices in many countries around the world. Will the biosimilars market solve the problem? Unlikely, given the long period of duopoly and the moderate savings projections by entities like the RAND Corporation. What *would* help is for insurers to adopt a cost-based reimbursement system for biologics, in which doctors submit proof of purchase price and pharmaceutical lot numbers as proof of FDA approval. But then we must face the larger problem: doctors are being forced to leave the medical profession, or at least limit treatment of patients dependent on taxpayer-funded health care, because doctors increasingly struggle to make a decent living under our current health system. That is a topic of discussion for another day.