Note

HOW NON-PRODUCT-SPECIFIC MANUFACTURING PATENTS BLOCK BIOSIMILARS

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ABSTRACT

A new class of drugs called biologics has potential to finally cure previously untreatable conditions such as cancer and Alzheimer's disease. But there is a catch: these innovative drugs are expensive. On average, prices range from $10,000 to $30,000 per year, and the most expensive ones exceed $500,000. The Biologics Price Competition and Innovation Act ("BPCIA") was passed in 2010 to lower prices by providing a new regulatory pathway in approving biosimilars—copies of brand-name biologics. Yet, the BPCIA's promised regulation of drug prices has not materialized partly due to brand-name companies' vast patent portfolios, also known as patent thickets. This Note analyzed all BPCIA patents disputed in BPCIA litigations and found that over half of the asserted patents are manufacturing method patents, many of which were filed years after FDA approval. Given the non-product-specific nature of these patents and stringent FDA requirements, these inventions are not only unnecessary, but are also unlikely to be practiced when producing brand-name biologics. Regardless of their actual worth, these patents are extremely valuable to brand-name manufacturers because even a patent of marginal improvement can foreclose biosimilar access entirely. This Note proposes that brand-name manufacturers should be required to disclose related patents at the time of the FDA approval and share the FDA license application with biosimilar manufacturers. Further,

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Congress should eliminate the availability of injunctive remedies for these problematic assertions of patents.

INTRODUCTION

In June 2021, the U.S. Food and Drug Administration ("FDA") approved aducanumab, the first new Alzheimer's drug in nearly two decades.[1] Aducanumab is also the first drug that can potentially reverse the progression of the disease by removing "amyloid beta plaques in the brain."[2] Aducanumab is a genetically engineered monoclonal antibody that binds to amyloid molecules.[3] Once the binding occurs, the body's immune system recognizes the amyloid beta plaques as foreign invaders and removes the plaques.[4] Scientists expect that "once the plaques are removed, the brain cells will stop dying."[5] More than six million patients in the United States can finally hope to slow down the devastating effects of memory loss and impaired cognitive functioning.[6]

Aducanumab belongs to a class of drug called biologics, which are at the heart of both new drug innovations and the United States' drug pricing crisis.[7] Biologics, on average, cost about $10,000 to $30,000 per

1. Patrizia Cavazzoni, *FDA's Decision To Approve New Treatment for Alzheimer's Disease*, U.S. FOOD & DRUG ADMIN. (June 7, 2021), https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease [https://perma.cc/U6KY-MMGS].

2. *Id.*

3. Andrew E. Budson, *A New Alzheimer's Drug Has Been Approved. But Should You Take It?*, HARV. HEALTH PUBL'G (July 15, 2021), https://www.health.harvard.edu/blog/a-new-alzheimers-drug-has-been-approved-but-should-you-take-it-202106082483 [https://perma.cc/MT7C-KAJF].

4. *Id.*

5. *Id.*

6. *See id.* ("The hope and expectation are that . . . thinking, memory, function, and behavior will stop deteriorating."); Cavazzoni, *supra* note 1 ("[M]ore than 6 million Americans are living with Alzheimer's disease . . . ."). Despite the FDA's approval, many scientists questioned whether the drug indeed confers clinical benefits due to limited data from clinical trials. Pam Belluck, *Many Alzheimer's Experts Say Use of Aduhelm Should Be Sharply Limited*, N.Y. TIMES, https://www.nytimes.com/2021/06/21/health/aduhelm-alzheimers-drug.html [https://perma.cc/E8AL-XD77] (last updated Sept. 2, 2021); Pam Belluck & Rebecca Robbins, *Alzheimer's Drug Poses a Dilemma for the F.D.A.*, N.Y. TIMES, https://www.nytimes.com/2021/06/05/health/alzheimers-aducanumab-fda.html [https://perma.cc/KD2J-XMAZ] (last updated Oct. 20, 2021).

7. *See* Avik Roy, *Biologic Medicines: The Biggest Driver of Rising Drug Prices*, FORBES (Mar. 8, 2019, 8:20 PM), https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices [https://perma.cc/M4GF-VFGW] ("[O]ne issue that is at the heart of high prices has attracted little attention: the role of biologic drugs in rising drug costs.").

year and the most expensive ones exceed $500,000.[8] In 2017, biologics represented only "2 percent of all U.S. prescriptions, but [accounted for] 37 percent of net drug spending," as well as 93 percent of the overall growth in drug spending since 2014.[9] Aducanumab, priced at nearly $60,000 per patient per year, "could cost upward of $100 billion a year," potentially doubling Medicare's current drug spending budget.[10] In 2020, Medicare spending exceeded $800 billion.[11] The cost of these expensive drugs affects all U.S. patients and taxpayers by raising insurance premiums and taxes.[12]

Biologics[13] refer to large complex molecules produced or extracted from living systems such as microorganisms or living cells.[14] While traditional chemical drugs called small molecules have fixed chemical structures, most biologics have dynamic and complex three-

8. Brian K. Chen, Y. Tony Yang & Charles L. Bennett, *Why Biologics and Biosimilars Remain So Expensive: Despite Two Wins for Biosimilars, the Supreme Court's Recent Rulings Do Not Solve Fundamental Barriers to Competition*, 78 SPRINGER NATURE 1777, 1777 (2018).

9. Roy, *supra* note 7.

10. Dylan Scott, *The New Alzheimer's Drug That Could Break Medicare*, VOX (June 10, 2021, 9:00 AM), https://www.vox.com/policy-and-politics/22524608/new-alzheimers-drug-cost-fda-approval-biogen [https://perma.cc/RKF2-JRWJ]. While this Note was in late-stage editing, the Centers for Medicare & Medicaid Services announced that Medicare will cover Aduhelm, a brand-name for aducanumab, subject to evidence development. This decision likely means that Medicare will not experience as large of an increase in spending, but Medicare still cautioned that "[i]t is not hard to imagine a future scenario where a combination of a high-priced drug and high utilization actually do generate billions of dollars in additional Medicare spending annually." Juliette Cubanski & Tricia Neuman, *Medicare's Coverage Decision for the New Alzheimer's Drug and Why It Matters*, KAISER FAM. FOUND. (Jan. 14, 2022), https://www.kff.org/policy-watch/medicares-coverage-decision-for-the-new-alzheimers-drug-and-why-it-matters [https://perma.cc/U6MY-PSBX].

11. *National Health Spending in 2020 Increases Due to Impact of COVID-19 Pandemic*, CTRS. FOR MEDICARE & MEDICAID SERVS. (Dec. 15, 2021), https://www.cms.gov/newsroom/press-releases/national-health-spending-2020-increases-due-impact-covid-19-pandemic [https://perma.cc/2E8T-74EK].

12. Scott, *supra* note 10.

13. The FDA defines "[b]iological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." 21 C.F.R. § 600.3(h) (2021).

14. *How Do Drugs and Biologics Differ?*, BIOTECHNOLOGY INNOVATION ORG., https://archive.bio.org/articles/how-do-drugs-and-biologics-differ [https://perma.cc/4PZD-7R87]. Recombinant proteins (including insulin), gene therapies, monoclonal antibodies, and vaccines are different types of biologics. Ruth Jessen Hickman, *What Are Biologic Treatments?*, VERYWELL HEALTH, https://www.verywellhealth.com/biologics-or-biological-agents-2615117 [https://perma.cc/9NGS-3W3B] (last updated June 25, 2020).

dimensional structures.[15] If vehicles are used to illustrate the size and complexity of these molecules, "aspirin [would be] a bicycle, a small biologic would be a Toyota Prius, and a large biologic would be an F-16 fighter jet."[16] These complex structures allow fine-tuned interactions with human cells and can improve clinical outcomes for previously untreatable conditions such as cancer and Alzheimer's disease.[17] New gene-editing and cell engineering technologies have the potential to cure genetic diseases and different types of cancer.[18]

When President Barack Obama signed the Biologics Price Competition and Innovation Act ("BPCIA") in 2010,[19] the BPCIA anticipated an opening of the biologics market to competition and a significant drop in prices.[20] The BPCIA finally paved a regulatory pathway for approving biosimilars, which are copies of brand-name

15. *See What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers [https://perma.cc/CZ5J-GUF3] (last updated Feb. 6, 2018) ("In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized."); Huy X. Ngo & Sylvie Garneau-Tsodikova, *What Are the Drugs of the Future?*, 9 MED. CHEM. COMMC'NS 757, 757 (2018) ("Small-molecule drugs include the aspirin, diphenhydramine, and other molecules that we typically have in our medicine cabinets.").

16. W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1026 (2016) [hereinafter Price & Rai, *Manufacturing Barriers*].

17. *See Biologics (Biologic Drug Class)*, MEDICINENET, https://www.medicinenet.com/biologics_biologic_drug_class/article.htm [https://perma.cc/9DPY-NUG8] ("Biologic drugs are . . . the most advanced therapies available . . . . [They] have offered hope for many patients who previously had no effective treatment options for their condition."); Cavazzoni, *supra* note 1 (stating that the biologic aducanumab was approved as a treatment for Alzheimer's disease).

18. *See, e.g.*, *CAR T Cells: Engineering Patients' Immune Cells To Treat Their Cancers*, NAT'L CANCER INST., https://www.cancer.gov/about-cancer/treatment/research/car-t-cells [https://perma.cc/DDU6-N4DH] (last updated July 30, 2019) (describing how CAR-T cells can treat cancer); NCI Staff, *How CRISPR Is Changing Cancer Research and Treatment*, NAT'L CANCER INST. (July 27, 2020), https://www.cancer.gov/news-events/cancer-currents-blog/2020/crispr-cancer-research-treatment [https://perma.cc/QYT3-LJ7M] (describing ways CRISPR technology is changing cancer treatment).

19. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001–03, 124 Stat. 119, 804–21 (2010) (codified as amended at 42 U.S.C. § 262). The BPCIA was passed as part of the Patient Protection and Affordable Care Act. *Id.*

20. Yaniv Heled, *The Biologics Price Competition and Innovation Act at 10—A Stocktaking*, 7 TEX. A&M J. PROP. L. 81, 83 (2021) [hereinafter Heled, *The Biologics Price Competition and Innovation Act*].

biologics.[21] Biosimilars can improve the affordability of older biologics by offering cheaper alternatives.[22] However, as of March 2020, the FDA approved only twenty-six biosimilars against nine brand-name biologics.[23] And as of May 2020, only sixteen of these twenty-six biosimilars were launched in the United States.[24] About 85 percent of biologics that should face biosimilar challenges are not facing any today.[25] The biosimilar entry rate in the United States also lags significantly behind that of Europe. As of January 2022, the European Medicines Agency had approved seventy biosimilars.[26]

Moreover, even after biosimilars enter the market, the price of biologics does not decline much when compared to the drop witnessed when generics—identical copies of small molecules—enter the market.[27] For example, the average price of Herceptin biosimilars "remains 26 percent higher than the [original] 2007 price for branded Herceptin," even though five biosimilars have entered the market since then.[28] On average, the price of biosimilars is about 24 to 27 percent

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21. § 7002, 124 Stat. at 805–08 (codified as amended at 42 U.S.C. § 262(k)); *see* Heled, *The Biologics Price Competition and Innovation Act*, *supra* note 20, at 83–84 (discussing how biosimilars entered the market after enactment of the BPCIA). Under the BPCIA,

> The term 'biosimilar' or 'biosimilarity' . . . means . . . that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components . . . and [that] there are no clinically meaningful differences between the biological product and the [original] product in terms of the safety, purity, and potency of the product.

42 U.S.C. § 262(i)(2).

22. Claire Bugos, *Low-Cost Biosimilar Is Set To Disrupt the Drug Market*, VERYWELL HEALTH (Aug. 20, 2021), https://www.verywellhealth.com/biosimilar-lower-drug-cost-5198235 [https://perma.cc/N8UG-W3RG].

23. Heled, *The Biologics Price Competition and Innovation Act*, *supra* note 20, at 84.

24. *Id.* at 85.

25. Peter B. Bach & Mark R. Trusheim, *The Drugs at the Heart of Our Pricing Crisis*, N.Y. TIMES (Mar. 15, 2021), https://www.nytimes.com/2021/03/15/opinion/how-to-control-drug-prices.html [https://perma.cc/55PG-CSX2] ("By our count, 85 percent of biologic drugs that should be squaring off against biosimilar competitors face none."); Nancy Yu, Mark R. Trusheim & Peter B. Bach, *Biosimilars: Market Changes Do Not Equal Policy Success*, DRUG PRICING LAB (Mar. 15, 2021), https://www.drugpricinglab.org/wp-content/uploads/2021/03/Biosimilar-market-update-3_12_21-formatted.pdf [https://perma.cc/35TM-7EPK].

26. *Biosimilars Approved in Europe*, GENERICS & BIOSIMILAR INITIATIVE, https://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe [https://perma.cc/ZRL7-VY2V] (last updated Jan. 28, 2022) (noting that the European Medicines Agency "has recommended the approval of [eighty-four] biosimilars," but fourteen biosimilar approvals have been withdrawn after approval).

27. Bach & Trusheim, *supra* note 25.

28. *Id.* (emphasis omitted).

lower than that of brand-name biologics.[29] This number pales in comparison to the price drop of more than 70 percent typically observed for generics observed after four or five generics have entered the market.[30]

Limited availability and high prices of biosimilars are, at least in part, due to brand-name companies' vast patent portfolios, also known as patent thickets.[31] Only a tiny percentage of the patent portfolio consists of primary patents that protect the key "billion-dollar molecules."[32] The vast majority of the portfolio consists of secondary patents that protect follow-on innovations such as manufacturing methods, new indications, or formulations.[33] While manufacturing patents[34] are rarely disputed in litigations involving small molecules, these patents are at the center of disputes for biologics. The synthesis of traditional chemical drugs is generally well-understood, and generics are essentially identical to the original drug regardless of its chemical synthesis pathway.[35] Manufacturing through living cells is more complex and offers more opportunities for patenting.[36] In biologics,

29. Heled, *The Biologics Price Competition and Innovation Act*, *supra* note 20, at 85.

30. *Id.* at 86 n.21.

31. *See, e.g.*, Stanton R. Mehr, *Can the FTC Clear a Path for Biosimilar Access Through the Patent Thicket?*, BIOSIMILAR DEV. (June 4, 2019), https://www.biosimilardevelopment.com/doc/can-the-ftc-clear-a-path-for-biosimilar-access-through-the-patent-thicket-0001 [https://perma.cc/695B-S8BC] ("The existence of what we now call 'patent thickets' is a threat to the biosimilar industry . . . ."); Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents To Delay Generic Versions*, N.Y. TIMES (July 15, 2016), https://www.nytimes.com/2016/07/16/business/makers-of-humira-and-enbrel-using-new-drug-patents-to-delay-generic-versions.html [https://perma.cc/7Q5F-57HG] (quoting an AbbVie executive's statement that "[a]ny company seeking to market a biosimilar version of Humira will have to contend with this extensive patent estate, which AbbVie intends to enforce vigorously"); Cynthia Koons, *This Shield of Patents Protects the World's Best-Selling Drug*, BLOOMBERG BUSINESSWEEK (Sept. 7, 2017, 6:00 AM), https://www.bloomberg.com/news/articles/2017-09-07/this-shield-of-patents-protects-the-world-s-best-selling-drug [https://perma.cc/37NG-JF6D] ("The more than 100 patents AbbVie has secured over Humira's lifetime make it difficult for another company to replicate the drug . . . ."); Roy, *supra* note 7 (noting that manufacturing costs, clinical trials, and uncertainty created by the patent thickets lead to the high costs of biosimilars).

32. *See infra* Part II. For the terminology "billion-dollar molecules," see generally BARRY WORTH, THE BILLION DOLLAR MOLECULE: ONE COMPANY'S QUEST FOR THE PERFECT DRUG (2014).

33. *See infra* Part II.

34. In this Note, the term "manufacturing patents" refers to a subset of secondary patents that protect manufacturing technologies and methods.

35. Price & Rai, *Manufacturing Barriers*, *supra* note 16, at 1034.

36. *Id.* ("Biologics, as opposed to small-molecule drugs, are typically far more path-dependent entities."); Yaniv Heled, *The Case for Disclosure of Biologics Manufacturing*

"the [manufacturing] process is the product," and any variation in the process could lead to a material change in the product's safety or efficacy.[37] For example, even minor changes in pH during the manufacturing process can impact how proteins fold and ultimately change how drugs interact with cells.[38] In short, biosimilar developers must mimic the originator's manufacturing processes as much as possible to ensure the product's safety and efficacy, while avoiding infringing secondary patents protecting the underlying manufacturing technologies.

This Note documents, for the first time, how patents not practiced in original biologics can be used to delay and block the entry of biosimilars. Suppose a patented mRNA technology leads to the development of a new COVID-19 vaccine. Once the patent and statutory exclusivity periods[39] expire, other companies should theoretically be able to manufacture COVID-19 vaccines using the same mRNA technology, create alternatives for patients, and lower vaccine prices. However, under the current BPCIA framework, manufacturing patents can both delay or block the entry of alternative vaccines and unduly extend the exclusivity period, regardless of whether the manufacturer uses the technology to make the original COVID-19 vaccine.

By analyzing all patents disputed in BPCIA litigations, this Note reveals that over 50 percent of the asserted patents covered manufacturing technologies, and 61 percent were filed more than one

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Information, 47 J.L. MED. & ETHICS 54, 56 (2019) [hereinafter Heled, *The Case for Disclosure*] ("[I]t is broadly accepted that short of meticulously replicating the process of making a biologic under the same conditions and using the same cell line, it would be very difficult and sometimes impossible to guarantee identity or even near identity between an original biologic and its follow-on version(s).").

37. Huub Schellekens, *How Similar Do 'Biosimilars' Need To Be?*, 22 NATURE BIOTECHNOLOGY 1357, 1357 (2004).

38. *See* BPI Contributor, *Buffer Selection in Biologics Manufacturing*, BIOPROCESS INT'L (June 27, 2017, 1:01 PM), https://bioprocessintl.com/sponsored-content/buffer-selection-biologics-manufacturing [https://perma.cc/HZT5-ZFFU] ("The production and purification of these biologic products require the use of different buffers for pH control and stabilization of the reactions in the various steps during manufacture.").

39. *See* 42 U.S.C. § 262(k)(7)(A) (setting a twelve-year statutory exclusivity period). "[M]arket exclusivity" refers to "a period during which potential generic competitors are not allowed to enter the particular product's market, which is typically enforced by a prohibition on the FDA to approve applications for comparable generic products for the duration of the exclusivity period." Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 436 n.67 (2012) [hereinafter Heled, *Patents vs. Statutory Exclusivities*].

year after the FDA approval of original biologics.[40] Further analysis of those postapproval patents covering manufacturing technologies showed that about 53 percent were non-product-specific manufacturing patents.[41]

The Note proposes novel legislative solutions to combat abusive patent practices. First, brand-name manufacturers should be required to disclose product-associated patents at the time of FDA approval so that biosimilar companies can either proactively challenge patents' validity or "design around" the patented technologies early in biosimilar development process. Second, brand-name manufacturers should be required to share their FDA license information with biosimilar companies. With the FDA license in hand, biosimilar companies can assess the asserted patents' relevancy to original biologics. Third, injunctive remedies should be eliminated in disputes around secondary patents. Without injunctive remedies, parties are more likely to negotiate and reach a fair price that matches the actual value of patented technologies.

The Note proceeds as follows. Part I explains the key provisions contained in the BPCIA and its major shortcomings in moderating drug prices. Part II introduces the methodology used to analyze patents disputed in BPCIA litigations and shares the study's key findings. Part III offers several suggestions that can improve transparency and curb abusive patent assertions.

I. INTRODUCTION TO THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT

This Section introduces protections available for drugs in the form of patents and statutory exclusivity periods, and how the BPCIA anticipated an opening of the biologics market to competition once those protections expired. However, biosimilar entry in the United States lags significantly behind that of Europe and Japan due to the impassable patent blockades set up by brand-name biologics.[42]

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40. *See infra* Part II. These postapproval patents, by definition, could not have been used to make products at launch, because practicing the invention for more than a year extinguishes any patent rights. W. Nicholson Price II & Arti K. Rai, *How Logically Impossible Patents Block Biosimilars*, 37 NATURE BIOTECHNOLOGY 862, 862 (2019).

41. *See infra* Part II. Postapproval patents refer to patents that were filed more than one year after the FDA approval of original biologics.

42. Chen et al., *supra* note 8, at 1777–78.

Patent rights "have the attributes of personal property."[43] A patent grants a time-limited monopoly "to exclude others from making, using, offering for sale, or selling the invention."[44] Under current law, patent protections last twenty years from the date on which the application for the patent was filed with the U.S. Patent and Trademark Office ("PTO").[45] Granting patent rights dates to the fifteenth century[46] and appears in the U.S. Constitution: "The Congress shall have Power . . . [t]o promote the Progress of Science and useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their respective . . . Discoveries."[47] Patents promote innovation in two ways. First, patents provide financial incentives to invest in and invent intangible ideas.[48] Second, patents compel disclosure of the inventions in exchange for an exclusive right to practice that innovation.[49] Such disclosure fosters the industry's growth as a whole by ensuring that up-to-date technical information becomes publicly accessible.[50]

In addition to patents, statutory exclusivity periods following the approval of original drugs protect small molecules and biologics.[51] During statutory exclusivity periods, the FDA is barred from approving follow-on products such as generics or biosimilars.[52] Although both patents and statutory exclusivity periods offer time-limited monopolies, patents are enforced by filing infringement suits in courts, while statutory exclusivity periods are enforced by the FDA's rejection of follow-on product applications.[53]

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43. *See* 35 U.S.C. § 261 ("[P]atents shall have the attributes of personal property.").

44. *Id.* § 154(a)(1)–(2).

45. *Id.* § 154(a)(2).

46. Giulio Mandich, *Venetian Patents (1450-1550)*, 30 J. PAT. OFF. SOC'Y 166, 168–69 (1948).

47. U.S. CONST. art. I, § 8, cl. 1, 8.

48. STAFF OF SUBCOMM. ON PATS., TRADEMARKS, & COPYRIGHTS OF THE S. COMM. ON THE JUDICIARY, 85TH CONG., AN ECONOMIC REVIEW OF THE PATENT SYSTEM 21 (Comm. Print 1958).

49. ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 247 (7th ed. 2017) ("[T]he prevailing [notion of the] 'contract' metaphor . . . [dictates] that disclosure of an invention . . . [is] the price the inventor pa[ys] for the reward of a patent.").

50. Heled, *Patents vs. Statutory Exclusivities*, *supra* note 39, at 426 ("An underlying premise of this theory is that the required disclosure of the invention by the inventor, once made, will enable the public to build upon the disclosed technology to further innovation.").

51. 42 U.S.C. § 262(k)(7)(A); 21 U.S.C. § 355(c)(3)(E)(ii).

52. 42 U.S.C. § 262(k)(7)(A); *supra* note 39.

53. Heled, *Patents vs. Statutory Exclusivities*, *supra* note 39, at 430–31.

To introduce a biologic into interstate commerce, the manufacturer must first obtain a license from the FDA.[54] The manufacturer must demonstrate safety, efficacy, and purity to obtain a license,[55] which entails extensive research and development and regulatory approval processes.[56] To reduce costs and spur competition, the BPCIA created an abbreviated regulatory pathway for the FDA to approve biologics that are "biosimilar" to[57] or "interchangeable" with an already approved biologic.[58] Unlike small molecules, biologics cannot be fully replicated, and the FDA defines biosimilars as being "highly similar to" original biologics with "no clinically meaningful differences."[59] In addition, the BPCIA set up an intricate scheme called the "patent dance" to resolve potential patent disputes against biosimilars.[60] The patent dance begins when a biosimilar applicant sends a copy of the FDA application to the brand-name manufacturer.[61] It then leads to the exchange of the "list of patents for

54. 42 U.S.C. § 262(a)(1) ("No person shall introduce or deliver for introduction into interstate commerce any biological product unless . . . a biologics license . . . is in effect for the biological product . . . .").

55. *Id.* § 262(a)(2)(C)(i)(I); 21 C.F.R. § 600.2 (2021).

56. *See, e.g.*, 21 C.F.R. §§ 601.2(a), 601.20, 601.25, 601.27, 601.70 (2021) (specifying various FDA approval requirements).

57. 42 U.S.C. § 262(k), (i)(2).

58. *Id.* § 262(k), (i)(3). The original biologic is called a "reference product" under the BPCIA. *Id.* § 262(i)(4).

59. 42 U.S.C. § 262(i)(2); *Biosimilar and Interchangeable Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products [https://perma.cc/CGP7-PYWT] (last updated Oct. 23, 2017) ("[S]light differences . . . are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product.").

60. A biosimilar applicant may choose not to engage in the patent dance. Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664, 1674–75 (2017) (holding that an applicant seeking approval of a biosimilar cannot be forced to engage in the patent dance by an injunction under federal law); *see also* Jon Tanaka, *"Shall" We Dance? Interpreting the BPCIA's Patent Provisions*, 31 BERKELEY TECH. L.J. 659, 659 (2016) ("The patent dispute resolution process [in the BCPIA] included an exchange of information—the biosimilar maker's application and manufacturing information for the reference product sponsor's list of potentially infringed patents—termed the 'patent dance.'").

61. 42 U.S.C. § 262(*l*)(2). For simplicity and consistent terminology, "brand-name manufacturer" refers to what the BPCIA calls the "reference product sponsor." *See id.* § 262(*l*)(1)(a) (describing "the sponsor of the application for the reference product . . . as the 'reference product sponsor'"). A biosimilar applicant can submit an abbreviated Biologics License Application four years (or more) after FDA approval of the reference drug. *Id.* § 262(k)(7)(B). Although a biosimilar applicant need not submit the same safety and efficacy data, it needs to submit "analytical studies that demonstrate . . . similar[ity] to the reference product," animal studies, and "conditions of use" clinical studies. *See id.* § 262(k)(2)(A)(i)(I)

which the [brand-name manufacturer] believes a claim of patent infringement could reasonably be asserted" against the biosimilar applicant.[62] Once both parties agree on the list, the brand-name manufacturer must file a patent infringement complaint within thirty days.[63]

The BPCIA was modeled after the Hatch-Waxman Act,[64] which harbingered a gold rush of generic applications.[65] Under the Hatch-Waxman Act, generic manufacturers can leverage the safety and efficacy data of the original drug to forgo costly and lengthy clinical studies.[66] Various studies estimate that pharmaceutical companies spend about $1 billion to bring a new drug to market, with most of the development costs arising from clinical trials.[67] Generics often enter the market as soon as original drug patents expire and replace as much as 90 percent of the original drug's market share within three months of launch.[68] Today, "[n]early 90 [percent] of prescriptions in the United

(listing the sources from which data on biosimilarity must be obtained and reported in the application). Other required information is listed in *id.* § 262(k)(2)(A)(i)(II)–(V).

62. *Id.* § 262(*l*)(3)(A)(i). A reference drug sponsor cannot sue for infringement of patents not included on this list. 35 U.S.C. § 271(e)(6)(C).

63. 42 U.S.C. § 262(*l*)(4)(A), (6)(A). If the reference drug sponsor does not file a complaint within thirty days, it cannot seek an injunction in court and will be entitled only to a reasonable royalty that is an estimation of damages. 35 U.S.C. § 271(e)(6)(A)–(B). In addition, the BPCIA provides a mechanism for additional exchanges of patent lists in case the parties cannot agree on a final patent list. 42 U.S.C. § 262(*l*)(5)(B).

64. *See* Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 15, 21, 28, and 35 U.S.C.) (modifying the system for regulation and approval of generic pharmaceutical drugs). For differences between small molecule and biologics drugs, see generally BIOTECHNOLOGY INDUS. ORG., THE DIFFERENCE WITH BIOLOGICS: THE SCIENTIFIC, LEGAL, AND REGULATORY CHALLENGES OF ANY FOLLOW-ON BIOLOGICS SCHEME 6–8 (Apr. 25, 2007), http://www.bio.org/sites/default/files/WhitePaper.pdf [https://perma.cc/Y888-2UXS].

65. *What Is Hatch-Waxman?*, PHRMA, https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/D-F/Fact-Sheet_What-is-Hatch-Waxman_June-2018.pdf [https://perma.cc/UUB9-Y9JQ].

66. 21 U.S.C. § 355(j)(2); *see also* Heled, *The Case for Disclosure*, *supra* note 36 ("[T]he Hatch-Waxman Act gives the FDA the authority to approve a follow-on product based on the assumption that if the original product was proven clinically safe and effective, and the two products are the same, then the follow-on product is expected to be *equally* safe and effective.").

67. *See, e.g.*, Olivier J. Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed To Bring a New Medicine to Market, 2009-2018*, 323 J. AM. MED. ASS'N 844, 849, 851 (2020) ("Based on data for 63 therapeutic agents developed by 47 companies between 2009 and 2018, the median research and development investment required to bring a new drug to market was estimated to be $985 million, and the mean was estimated to be $1336 million.").

68. PHRMA, *supra* note 65.

States are filled with generics," and "[m]ore than 80 [percent] of approved pharmaceuticals have generic versions available."[69]

Although almost a decade has passed since its enactment, the BPCIA's promised regulation of drug prices has not materialized.[70] In some ways, this is unsurprising. Economists generally predicted that the impact of biosimilar entry under the BPCIA would be much less drastic than was the case for generics.[71] Unlike small molecules, biologics cannot be easily replicated, and most of the technology is protected by trade secrets.[72] Biologics manufacturing begins with "a highly specific (and potentially proprietary) . . . cell line," and subsequent steps involve "many standards and techniques [often] developed in-house."[73] For FDA licensure, brand-name manufacturers must submit the Biologics License Application, which includes detailed manufacturing information under the Chemistry and Manufacturing Controls ("CMC") section.[74] However, FDA regulation prohibits the FDA from disclosing any manufacturing information, even after product exclusivity and associated patents have expired.[75]

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69. *Id.*

70. *See supra* notes 23–30 and accompanying text.

71. *See, e.g.*, Henry Grabowski, Rahul Guha & Maria Salgado, *Biosimilar Competition: Lessons from Europe*, 13 NATURE REVS. 99, 100 (2014) ("[B]iosimilar price discounts are likely to be modest compared to generics, reflecting much greater costs of development, fewer competitors and the absence of interchangeability for the foreseeable future.").

72. Lisa Diependaele, Julian Cockbain & Sigrid Sterckx, *Similar or the Same? Why Biosimilars Are Not the Solution*, 46 J.L., MED. & ETHICS 776, 777 (2018); W. Nicholson Price II & Arti K. Rai, *Are Trade Secrets Delaying Biosimilars?*, 348 SCIENCE 188, 188 (2015) ("The key hurdle to competitive entry by biosimilar manufacturers, and thus to price reduction, is trade secrecy in the biologics manufacturing process."). For the definition of trade secrets, see *Trade Secrets / Regulatory Data Protection*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/ip-policy/trade-secret-policy [https://perma.cc/U7ZX-U4KZ] (last updated Oct. 7, 2021, 1:45 PM).

73. Heled, *The Case for Disclosure*, *supra* note 36.

74. 21 C.F.R. § 601.2 (2021). The CMC section is updated throughout the product's lifecycle, as required by 21 C.F.R. § 601.12 (2021). The FDA also provides guidance documents to aid manufacturers to fulfill the CMC requirements. *CMC and GMP Guidances*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/cmc-and-gmp-guidances [https://perma.cc/DS6R-7H9H] (last updated Dec. 16, 2021).

75. *See* 21 C.F.R. § 601.51(f) (2021) ("The following data and information in a biological product file are not available for public disclosure unless . . . they no longer represent a trade secret . . . (1) Manufacturing methods or processes, including quality control procedures. . . . (3) Quantitative or semiquantitative formulas."); 21 C.F.R. § 20.61(c) (2021) ("Data and information submitted or divulged to the Food and Drug Administration which fall within the definitions of a trade secret or confidential commercial or financial information are not available for public disclosure."). The FDA is also prohibited from comparing manufacturing processes of biosimilar and reference drugs during the internal review. Heled, *The Case for Disclosure*, *supra* note 36.

Since biosimilars cannot be fully characterized in laboratories, biosimilar applicants must conduct clinical studies to establish comparability to original biologics.[76] Animal and human clinical studies must show that biosimilars have the same safety and efficacy profile as the original drug.[77] Due to clinical trial requirements and manufacturing challenges, commercialization of a biosimilar takes about eight to ten years and costs somewhere between $100 and $250 million.[78] In comparison, generics take three to five years to develop and cost only about $1 to 5 million.[79] The exorbitant cost of developing a biosimilar limits the competition and affordability of biosimilars.[80]

Finally, brand-name biologics "built impassable patent blockades," also known as patent thickets.[81] The primary patents protecting the key molecules of a drug generally expire before or

76. *See* 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc) (requiring that applications for marketing approval of follow-on biologics include "a clinical study or studies . . . that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the [original] product is licensed and intended to be used"). This clinical study requirement has been criticized for being wasteful and unethical. *See, e.g.*, Heled, *The Case for Disclosure*, *supra* note 36, at 57 ("Especially problematic in this respect is . . . [that clinical studies] potentially expose human subjects to the risk of significant harm only to confirm that a follow-on product is not more dangerous or less efficacious than an already-approved product.").

77. 42 U.S.C. § 262(k)(2)(A)(i)(I); *see also* Diependaele et al., *supra* note 72, at 777–78 ("[T]he biosimilar applicant is required to prove that the differences between the candidate-biosimilar and the reference product are not clinically significant."). For the "interchangeability" designation, a biosimilar applicant must conduct an additional clinical study called the "switching study." *See, e.g.*, Heled, *The Case for Disclosure*, *supra* note 36, at 57 (explaining that the intent of switching study is to show that the biosimilar is expected to produce the same clinical result as the original biologic and there is no risk of alternating between them). The interchangeability is established when "the risk . . . of alternating or switching between use of the [biosimilar] product and the [original] product is not greater than the risk of using the [original] product without such alternation or switch." 42 U.S.C. § 262(k)(4)(B). However, no interchangeable biologic has been approved to date. *See Biosimilar Product Information*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-product-information [https://perma.cc/F4KZ-8AYQ] (last updated Sept. 20, 2021) (listing approved biosimilars to date, but none is interchangeable).

78. Heled, *The Case for Disclosure*, *supra* note 36, at 57.

79. *Id.*

80. *See, e.g.*, *id.* at 55 ("[T]he prices of most biologics will likely remain high. Therefore, from a public health standpoint, follow-on biologics are . . . a limited phenomenon, providing only few, expensive options for payors, prescribers, and patients."); Sarah Sorscher, *A Longer Monopoly for Biologics?: Considering the Implications of Data Exclusivity as a Tool for Innovation Policy*, 23 HARV. J.L. & TECH. 285, 304–05 (2009) (discussing the high barriers to entry in the generic biologics market, especially as compared to the barriers faced by manufacturers of generic small-molecule drugs).

81. Bach & Trusheim, *supra* note 25; *see, e.g.*, Mehr, *supra* note 31 (discussing "patent thickets").

shortly after the statutory exclusivity period, during which the law prohibits the FDA from approving biosimilars.[82] The vast majority of the patent thicket consists of secondary patents, which protect follow-on innovations such as manufacturing methods, new indications, or formulations.[83] For example, AbbVie, the manufacturer of Humira, filed 247 patent applications for Humira, and 132 of the patents were issued.[84] The Biosimilars Council, an industry group for biosimilar manufacturers, claimed that 75 of these patents were filed three years prior to when biosimilar competition was set to begin.[85] Shortly prior to the FDA approval of Boehringer's biosimilar, AbbVie filed a lawsuit alleging that the biosimilar infringed 1,600 inventions across 74 Humira patents.[86] Boehringer settled with AbbVie, citing "the inherent unpredictability of litigation, [and] the substantial costs of what would have been a long and complicated legal process and ongoing distraction to our business."[87] Although the primary patent on Humira expired in 2016,[88] and the FDA has already approved six biosimilars, the

82. *See* Price & Rai, *Manufacturing Barriers*, *supra* note 16, at 1027 ("[U]nder the Hatch-Waxman Act of 1984, the originator firms' small molecules are protected by patents and by a short (five-year) period of exclusivity over the clinical trial data . . . ."); 42 U.S.C. § 262(k)(7)(A) (setting a twelve-year statutory exclusivity period). For a description of market exclusivity, see *supra* note 39.

83. Amy Kapczynski, Chan Park & Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PLOS ONE, Dec. 2012, at 1, 6 ("[Drugs] may also be covered by [secondary] patents covering modified forms of that base compound, medical uses of a known chemical compound, combinations of known chemical compounds, particular formulations (tablets, topical forms), dosage regimens, and processes, among others.").

84. I-MAK, OVERPATENTED, OVERPRICED: HOW EXCESSIVE PHARMACEUTICAL PATENTING IS EXTENDING MONOPOLIES AND DRIVING UP DRUG PRICES 7 (2018), https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf [https://perma.cc/YP3Q-Y55X].

85. BIOSIMILARS COUNCIL, FAILURE TO LAUNCH: PATENT ABUSE BLOCKS ACCESS TO BIOSIMILARS FOR AMERICA'S PATIENTS 8 (2019), https://www.biosimilarscouncil.org/wp-content/uploads/2019/06/Biosimilars-Council-White-Paper-Failure-to-Launch-June-2019.pdf [https://perma.cc/K2F4-PVYQ]; *About*, BIOSIMILARS COUNCIL, https://biosimilarscouncil.org/about-us [https://perma.cc/FKR9-A3AD].

86. Complaint at 1, 8, 15, AbbVie Inc. v. Boehringer Ingelheim Int'l GmbH, No. 1:17-cv-01065-UNA (D. Del. Aug. 2, 2017) (stating that Humira "has resulted in more than 100 issued United States patents . . . 74 of which AbbVie has identified as infringed").

87. Andrew Dunn, *With Boehringer Settlement, AbbVie Completes Humira Sweep*, BIOPHARMA DIVE (May 14, 2019), https://www.biopharmadive.com/news/abbvie-boehringer-ingelheim-settle-humira-patent-biosimilar/554729 [https://perma.cc/RQ2G-6HMZ].

88. Human Antibodies That Bind Human TNF , U.S. Patent No. 6,090,382 (filed Feb. 9, 1996) (expiring Feb. 9, 2016).

biosimilars will likely not be available in the U.S. market until at least 2023.[89]

In the next section, the Note will show how the patent dance, which was originally intended to facilitate resolving patent disputes, is being used to block biosimilar entries.

II. EMPIRICAL FINDINGS AND DISCUSSION

The analysis of all patents disputed during BPCIA litigations revealed that 71 percent of manufacturing patents were filed a year after the FDA's approval of original biologics. Because the FDA imposes stringent regulatory requirements for manufacturing changes implemented after its approval, these inventions are not only unnecessary but also unlikely to be practiced in manufacturing original biologics. These unnecessary and unrelated manufacturing patents can create a windfall for brand-name manufacturers by entirely forestalling biosimilar access, even if the inventions confer only a marginal benefit to the manufacturing process.

A. Assertion of Non-Product-Specific Manufacturing Patents to Block Biosimilars

I conducted the empirical analysis of all patents disputed in BPCIA litigations filed between 2014 and May 2021.[90] The first goal was to identify manufacturing patents filed more than one year after their FDA approval. These postapproval patents, by definition, could not have been used to make products at launch, because practicing the invention for more than a year without seeking a patent extinguishes any patent rights.[91] A long line of cases, now codified in 35 U.S.C. § 102, establishes that the inventor forfeits the right to obtain patents after the inventions have been in use for more than one year.[92] Since these

89. Christine Blank, *When Humira Finally Faces Biosimilar Competition, Losses for AbbVie May Not Be as Steep as Expected, Say Analysts*, MANAGED HEALTHCARE (July 14, 2021), https://www.managedhealthcareexecutive.com/view/when-humira-finally-faces-biosimilar-competition-losses-to-abbvie-may-not-be-as-steep-as-expected-says-analyst-report [https://perma.cc/X9ZF-XLAC].

90. For a list of the BPCIA litigations, see *infra* Appendix A.

91. *See supra* note 40 and accompanying text.

92. *See* 35 U.S.C. § 102 ("A person shall be entitled to a patent unless . . . the claimed invention was . . . in public use . . . before the effective filing date . . . [unless] disclosure [was] made 1 year or less before the effective filing date of a claimed invention . . . ."). This "forfeiture rule" applies regardless of whether the process or product was used in secret.

patents were not practiced prior to launch, these technologies are deemed nonessential to make the product.

The second goal was to determine whether these post-approval manufacturing patents were in any way related to original biologics. Since manufacturing processes of original biologics are not publicly available, the relationship was determined based on whether the patents' titles, abstracts, backgrounds, summaries of the invention, and claims contained any references to original biologics.

A list of a total twenty-eight BPCIA litigations came from the Big Molecule Watch website.[93] The patents in dispute were collected from individual complaints downloaded from Bloomberg Law.[94] Patents' filing, priority,[95] and issuance dates were accessed from Google Patent,[96] and FDA approval dates were verified through the Drugs@FDA database.[97]

> [I]t is a condition upon an inventor's right to a patent that he shall not exploit his discovery competitively after it is ready for patenting; he must content himself with either secrecy, or legal monopoly. . . . [I]f he goes beyond that [one year], he forfeits his right regardless of how little the public may have learned about the invention; just as he can forfeit it by too long concealment, even without exploiting the invention at all.

Metallizing Eng'g Co. v. Kenyon Bearing & Auto Parts Co., 153 F.2d 516, 520 (2d Cir. 1946); *see also* Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc., 139 S. Ct. 628, 630, 634 (2019) (holding that the Leahy-Smith America Invents Act did not later modify the meaning of "on sale," and hence the inventor's sale of an invention to a third party barred the investor from receiving a patent).

93. *Big Molecule Watch: BPCIA Litigations*, GOODWIN, https://www.bigmoleculewatch.com/bpcia-patent-litigations [https://perma.cc/P8LU-JBJ4] (last visited Apr. 15, 2021) [hereinafter *BPCIA Litigations*]. Big Molecule Watch, a blog by the law firm Goodwin, collects and publishes up-to-date information on biosimilars, including litigation. *Big Molecule Watch*, GOODWIN, https://www.bigmoleculewatch.com [https://perma.cc/BX73-SK8C].

94. BLOOMBERG L., https://www.bloomberglaw.com [https://perma.cc/48ZY-LAF4]. The number of patents in dispute varied widely from litigation to litigation and ranged from 1 to 84, with a median of 5.5. *See supra* note 90.

95. In patent jargon, the priority date is the date the patent was effectively filed. *See* 35 U.S.C. § 100(i)(1) ("'[E]ffective filing date' . . . means . . . the actual filing date of the patent or the application for the patent containing a claim to the invention; or . . . the filing date of the earliest application for which the patent or application is entitled . . . .").

96. GOOGLE PATENTS, https://patents.google.com [https://perma.cc/7W92-8VDA].

97. *Drugs@FDA: FDA-Approved Drugs*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/daf/ [https://perma.cc/Y6QJ-T4CS].

I first examined patents' titles, abstracts, and claims and classified them as active pharmaceutical ingredient ("API"),[98] formulation,[99] method of use,[100] manufacturing process, or administration device patents. Where patents listed several claims with multiple potential classifications, the classification came from the first claim, because the first claims tend to have the broadest scope and "represent what the inventor sees as the most important" claim.[101]

By comparing patents' priority and FDA approval dates, I identified the patents that were filed more than one year after the FDA approval of original biologics. Of the 511 patents asserted during BPCIA litigations to date, 262 patents, or 52 percent, covered manufacturing processes, and 311 patents, or 61 percent, were filed more than one year after FDA approval. Of the 262 manufacturing patents, about 186 patents, or 71 percent, were filed more than one year after FDA approval.[102] To put it differently, 71 percent of manufacturing patents could not have been used to make products at launch, yet were asserted to block biosimilar competition.

98. The API refers to "[a]ny substance . . . intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body." CTR. FOR DRUG EVALUATION & RSCH. & CTR. FOR BIOLOGICS EVALUATION & RSCH., U.S. FOOD & DRUG ADMIN., Q7 GOOD MANUFACTURING PRACTICE GUIDANCE FOR ACTIVE PHARMACEUTICAL INGREDIENTS: GUIDANCE FOR INDUSTRY 48 (2016).

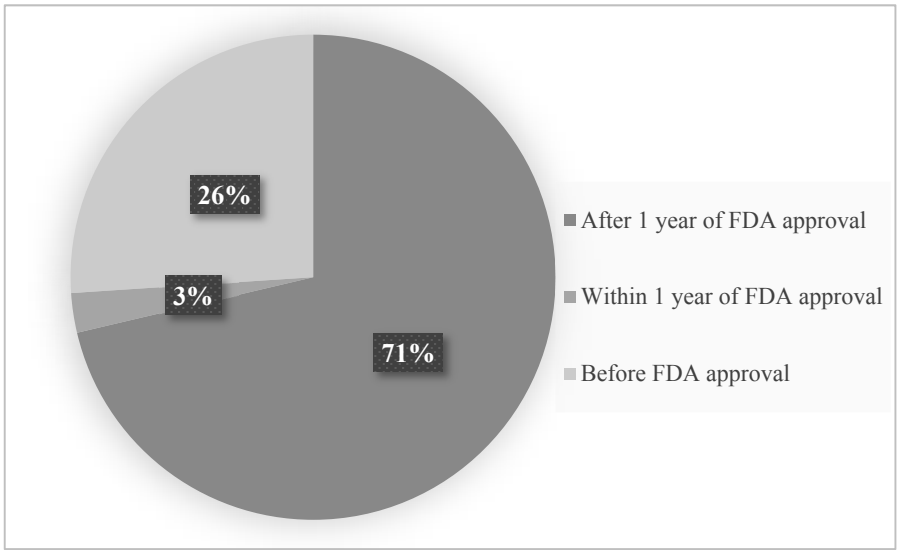
99. Formulation is "the composition[] of the final product," which usually contains the API and inactive ingredients, which perform different functions such as improving stability or adjusting the pH. Heled, *Patents vs. Statutory Exclusivities*, *supra* note 39, at 445 n.114.

100. "[M]ethod-of-use patent[s are] issued when an inventor . . . discover[s] . . . a 'novel, useful, and non-obvious' way" to use a patent. Roger D. Blair & Anita N. Walsh, *Method-of-Use Patents, Appropriability, and Antitrust Policy*, 56 REV. INDUS. ORG. 651, 651 (2020). For example, Rogaine was originally patented as a treatment of high blood pressure, but the inventor later obtained a method-of-use patent in stimulating hair growth. *Id.* at 651–52.

101. Arti K. Rai & W. Nicholson Price II, *An Administrative Fix for Manufacturing Process Patent Thickets*, 39 NATURE BIOTECHNOLOGY 20, 21 (2021).

102. For a list of the patents, see *infra* Appendix B. Similar findings were reported in literature. Price & Rai, *An Administrative Fix for Manufacturing Process Patent Thickets*, *supra* note 101, at 21 (reporting that out of 552 patents asserted in 34 BPCIA litigations, 192 were "manufacturing process patents filed over [one] year after [the] FDA approval" date).

Figure 1: Classification by Patents' Filing Dates (Manufacturing Process Patents)



Lastly, I examined the titles, abstracts, backgrounds, summaries of the invention, and claims, and then conducted key word searches using product names and known molecule names of the patents filed more than one year after FDA approval.[103] If there was any reference to the product, I classified it as a "product-specific" patent, because the inventor at least considered practicing the invention for that product. The list is likely overinclusive because I was conservative in using the "non-product-specific" classification. Some patents listed more than several dozen molecules without any information specific to an individual molecule, but I still classified them as a product-specific patent.

About 100 manufacturing patents, or 43 percent, were non-product-specific.[104] The percentage of non-product-specific patents would have been even higher if Humira patents were excluded because all patents asserted during Humira litigations contained product references. Most of these patents were manufacturing patents that

103. Molecule names were pulled from the Drugs@FDA database. *See supra* note 97.

104. For a list of the patents and their classifications, see *infra* Appendix B.

lacked references to not just the product in the scope of litigation, but also any product-identifying information.[105]

Given stringent post-approval regulatory requirements, original biologics' manufacturing processes likely do not use all of these patents. The FDA requires extensive studies to prove that the changes do not impact drugs' efficacy or safety and an approval before implementing any major manufacturing changes.[106] For example, Genentech, a brand-name manufacturer, asserted a 8,771,988 patent (or "'988 patent") which disclosed "a method for the recombinant production of a secreted heterologous immunoglobulin in a CHO cell."[107] The adoption of this invention requires a new master cell line,[108] which is rarely, if ever, done.[109] For these types of changes, the FDA requires extensive validation studies and potentially new clinical trials, because any genetic manipulation of the master cell line creates a high risk of affecting the product's "identity, strength, quality, purity, or potency."[110] In three separate litigations, Genentech asserted an 8,633,302 patent (or "'302 patent") describing "a method for concentrating an immunoglobulin solution by tangential flow

105. *Id.*

106. 21 C.F.R. §§ 314.70(g), 601.12 (2021). *See generally* CTR. FOR BIOLOGICS EVALUATION & RSCH. & CTR. FOR DRUG EVALUATION & RSCH., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED APPLICATION FOR SPECIFIED BIOTECHNOLOGY AND SPECIFIED SYNTHETIC BIOTECHNOLOGY PRODUCTS 3–4 (1997) [hereinafter FDA, GUIDANCE FOR INDUSTRY] (listing examples of changes that require FDA approval prior to distribution).

107. Protein Expression from Multiple Nucleic Acids, U.S. Patent No. 8,771,988 col. 12 l. 1–3 (filed Oct. 9, 2008) [hereinafter '988 Patent]. Redacted Complaint at 10, 18, Genentech v. Amgen, No. 18-924 (D. Del. July 2, 2018).

108. The Master Cell Bank refers to a selected clone of genetically modified cells that actively produce active pharmaceutical ingredients. John Conner, Don Wuchterl, Maria Lopez, Bill Minshall, Rabi Prusti, Dave Boclair, Jay Peterson & Chris Allen, *Chapter 26: The Biomanufacturing of Biotechnology Products*, *in* BIOTECHNOLOGY ENTREPRENEURSHIP: STARTING, MANAGING, AND LEADING BIOTECH COMPANIES 366–67 (Craig Shimasaki ed., 1st ed. 2014).

109. Changes to the Master Cell Bank are not described in the FDA's guidance document listing classifications of common manufacturing changes. *See generally* FDA, GUIDANCE FOR INDUSTRY, *supra* note 106 (listing FDA classifications of common manufacturing changes).

110. 21 C.F.R. § 601.12(a)(2) (2021); *see* Hugo Hamel & Hye-Na Kang, *Quality Changes to Approved Biotherapeutic Product: Simulated Case Studies on Reporting Categories & Supporting Data Requirements*, 62 BIOLOGICALS 1, 5 (2019) (classifying a generation of a new Master Cell Bank "from the same expression construct with same or closely related cell line" as a major change).

filtration."[111] Practicing this patent likely means adding a new or significantly modifying the tangential flow filtration step. In either case, the FDA requires expensive and lengthy validation studies and its approval prior to implementation.[112]

The manufacturers are highly resistant even to moderate or minor changes because the costs associated with regulatory filings often outweigh the benefits derived from these improvements.[113] Even moderate changes tend to introduce uncertainty[114] that arises from expensive and lengthy validation studies and regulatory filings.[115] In addition, manufacturers have to seek approvals from over one hundred countries, because most biologics are marketed globally.[116] Some countries spend over twenty-four months reviewing a proposed change, and rolling submissions can easily turn into a multiyear endeavor.[117] During this time, manufacturers must maintain both pre-

111. Variable Tangential Flow Filtration, U.S. Patent No. 8,633,302 col. 2 l. 1–3 (filed July 15, 2008). Redacted Complaint at 46–47, Genentech, Inc. v. Amgen Inc., No. 17-1471 (D. Del. Oct. 26, 2017); Complaint at 8, Genentech, Inc. v. Pfizer Inc., No. 17-1672 (D. Del. Nov. 17, 2017); Complaint at 14, Genentech, Inc. v. Celltrion, Inc., No. 18-1025 (D. Del. July 11, 2018).

112. *See* Ivan Soto, *Validation Cost Reduction*, IVT NETWORK (Aug. 29, 2014, 10:00 AM), https://www.ivtnetwork.com/article/validation-cost-reduction [https://perma.cc/D348-XZBC] ("Traditional validation processes are not efficient and cost effective. These deficiencies are caused by excessive document reviews and approvals, duplicate roles and responsibilities, inconsistent practices, institutional silos, and other problems. These negatively impact project timelines, increase costs, and cause non-value-added work.").

113. *See* Price & Rai, *Manufacturing Barriers*, *supra* note 16, at 1061 ("Firms reinforce this regulatory resistance [to postapproval changes] by tending to view the manufacturing process to be largely set at the time of approval.").

114. *See* INT'L CONF. ON HARMONISATION OF TECH. REQUIREMENTS FOR REGISTRATION OF PHARMS. FOR HUM. USE, FINAL CONCEPT PAPER: Q12: TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT 1 (2014) [hereinafter ICH, FINAL CONCEPT PAPER], https://database.ich.org/sites/default/files/Q12%20Concept%20Paper.pdf [https://perma.cc/DL68-H2C2] ("[L]ack of alignment has led to confusion on the necessary information and level of detail in the dossier and its impact on change management and regulatory reporting.").

115. Soto, *supra* note 112.

116. *See* ICH, FINAL CONCEPT PAPER, *supra* note 114, at 2 (stressing the need for harmonization of post-approval change requirements across health authorities around the world); *see also* Julia Radzihovsky, Claus-Dieter Schiller, Ralf Gleixner & Barbara Jentges, *Post-Approval Change Management on a Global Scale: An Inconvenient Complexity for Pharma?*, SCRIP (Nov. 19, 2015), https://scrip.pharmaintelligence.informa.com/PS118451/Post-Approval-Change-Management-On-A-Global-Scale-An-Inconvenient-Complexity-For-Pharma [https://perma.cc/RN8N-5NXK] ("Managing the post-approval regulatory change process for pharmaceuticals at the global level is complex, unpredictable and time consuming because of regional differences and frequent changes in procedures, requirements and timelines.").

117. Radzihovsky et al., *supra* note 116.

and post-change manufacturing processes, as different versions of products are supplied to different countries depending on their approval status.

The empirical analysis revealed that a majority of patents asserted during BPCIA litigations could not have been used to make products at launch.[118] Moreover, examining post-approval manufacturing patents showed that these patents were not only unnecessary to make a biosimilar, but also unlikely to be practiced when making the original biologic.[119] The following Section shows why such a setup contradicts the intents behind the BPCIA and the U.S. patent system.

B. Problematic Assertions of Manufacturing Patents

Assertion of these manufacturing patents is problematic on several levels. First, these patents are written broadly such that other biosimilar manufacturers cannot practice these patents solely based on their descriptions. Second, through the patent dance, brand-name manufacturers can detect instances of infringements that would not have been otherwise detected. Moreover, even though these technologies play a limited role in producing biosimilars, brand-name manufacturers assert these patents to block the entry of biosimilars altogether. Third, because of their non-product-specific nature, biosimilar manufacturers cannot proactively seek invalidation of these patents at the PTO. As a result, biosimilar manufacturers face the unenviable task of mimicking the brand-name manufacturer's process as closely as possible to ensure safety and efficacy while, at the same time, avoiding all patented processes and technologies.

This Note does not dispute that manufacturing innovations are critical in cutting manufacturing costs and improving drug quality. Indeed, patents are crucial incentives to innovate and disclose inventions in exchange for an exclusive right to practice that innovation.[120] Such disclosure fosters growth of the industry as a whole by ensuring that up-to-date technical information becomes publicly accessible.[121] However, at least in the field of biologics, these

118. *See supra* note 90.

119. *Id.*

120. *See supra* notes 47–49 and accompanying text.

121. Heled, *Patents vs. Statutory Exclusivities*, *supra* note 39, at 426 ("An underlying premise of this theory is that the required disclosure of the invention by the inventor, once made, will enable the public to build upon the disclosed technology to further innovation.").

manufacturing patents are not fulfilling their teaching role.[122] The patents lack sufficient detail and context for biosimilar manufacturers to learn how the technology ties into the rest of the manufacturing processes.[123] For example, the earlier example of the '302 patent teaches the use of tangential flow filtration for immunoglobulin concentration.[124] The claims list multiple ranges of protein concentration and transmembrane pressures, but lack target ranges for specific molecules and descriptions of other important variables.[125] Deviations at this step—even if small—can cause proteins to sustain too much shear stress and form clumps.[126] A long line of court precedents forced inventors to choose between obtaining a time-limited, but exclusive, patent right, or maintaining trade secrecy.[127] However, these patents' broad descriptions essentially allow manufacturers to enjoy both patent protections and trade secrecy at a product level.

As part of the BPCIA's patent dance, the original biologic manufacturer gains access to the biosimilar application submitted to the FDA and engages in a thorough review to detect any potential infringements of its patents.[128] Without the patent dance provisions, brand-name manufacturers would not have detected these instances of infringement, especially since biosimilar manufacturing processes are

122. *Id.* ("[M]any patents withhold vital information necessary for utilizing the inventions without additional, sometimes substantial, research and development ('R&D').").

123. *See* Price & Rai, *Manufacturing Barriers*, *supra* note 16, at 1050 (showing that despite the patent statute's explicit "disclosure" requirement, the disclosure is likely ineffective for biologics patent applications).

124. *See supra* notes 111–12. Examples of missing or insufficiently discussed variables are filter pore size, flow rate, volume, target protein size, aggregation rate, and temperature.

125. *See* Variable Tangential Flow Filtration, U.S. Patent No. 8,633,302 col. 12 l. 36–62 (filed July 15, 2008) (providing an example of the transmembrane pressure only when the target concentration was set at 90 mg/ml). The '302 patent is far from the worst example. The principal patent for Enbrel "describes expressing the protein in . . . at least eight bacterial strains, yeast, and at least ten different cell culture types from multicellular organisms including hamsters, monkeys, and humans." Price & Rai, *Manufacturing Barriers*, *supra* note 16, at 1050. The patent for yeast alone describes "at least 20 different [ways of] expressing the [desired] protein." *Id.*

126. Jessica J. Hung, Ameya U. Borwankar, Barton J. Dear, Thomas M. Truskett & Keith P. Johnston, *High Concentration Tangential Flow Ultrafiltration of Stable Monoclonal Antibody Solutions with Low Viscosities*, 508 J. MEMBRANE SCI. 113, 113 (2016) ("If the shear stress is too large, it may cause protein denaturation and aggregation . . . .").

127. *See supra* note 92 and accompanying text.

128. *See supra* notes 61–63 and accompanying text.

also shrouded in trade secrecy.[129] Even if the original biologic manufacturers had been aware, the cost and length of patent infringement suits would have deterred them from asserting their patents. [130] Costs of bringing patent infringement suits range from $700,000 to $4 million or more,[131] and infringement suits last "about two and a half years, with post-trial activities often delaying the final decision for months."[132]

Despite the costs and uncertainties associated with these litigations, the brand-name manufacturers litigate these patents in district courts, not because of the inherent worth of these manufacturing patents, but because they can extend monopoly rights of original biologics. In general, method claims are disfavored and deemed less valuable than product claims because detecting infringement of method claims is difficult, and infringers can easily design around method claims.[133] But in the BPCIA context, even a patent of marginal improvement can foreclose biosimilar access entirely and allow the brand-name manufacturer to reap rewards from the biologic itself, not from the patents' inherent societal value.[134] To illustrate the scale of these litigations, a blockbuster biologic, Humira, generated over $20 billion in revenue in 2020 alone.[135] The actual worth of these manufacturing patents does not matter. As long as these

129. *See* David W. Plant, *The Impact of Biotechnology on Patent Law*, 5 TECH. SOC'Y 95, 101 (1983) ("Detecting and proving infringement of process claims is frequently difficult in any field.").

130. *See supra* notes 84–87and accompanying text.

131. Russ Krajec, *Current Patent Litigation Costs Are Between $2.3 to $4M - from the BlueIron Blog*, ASSOCIATED PRESS (July 10, 2020), https://apnews.com/press-release/news-direct-corporation/a5dd5a7d415e7bae6878c87656e90112 [https://perma.cc/KJ5V-QKP7] (reporting survey results from the American Intellectual Property Lawyer's Association showing that the low-stakes patent lawsuits (where less than $1 million was at risk) cost $700,000, and the high-stake lawsuits (where more than $25 million was at risk) cost $4 million or more).

132. Jason E. Stach & Jeffrey A. Freeman, *District Court or the PTO: Choosing Where To Litigate Patent Invalidity*, FINNEGAN (Mar./Apr. 2014), https://www.finnegan.com/en/insights/articles/district-court-or-the-pto-choosing-where-to-litigate-patent.html [https://perma.cc/B942-DX4F].

133. *Part 6: Protect Your Method with Method Claims*, CHILDS L. (Apr. 7, 2020), https://childspatentlaw.com/part-6-protect-your-method-with-method-claims [https://perma.cc/Y9RG-NXK3].

134. *See* Price & Rai, *How Logically Impossible Patents Block Biosimilars*, *supra* note 40, at 863 (noting that drug patents do not "match the social benefit of the innovation to the reward to the innovator" and that "even a marginal patent on a small innovation can entirely forestall biosimilar . . . access").

135. Kevin Dunleavy, *1. Humira*, FIERCE PHARMA (May 3, 2021, 3:00 AM), https://www.fiercepharma.com/special-report/top-20-drugs-by-2020-sales-humira [https://perma.cc/T3M7-TD4V].

patents can delay the launch of biosimilars and allow original biologics to generate billions of dollars in revenue, the patents will be litigated in every possible way, even if the possibility of injunctions is remote or nonexistent.[136]

At least some of these patents may indeed be "bad patents."[137] In the United States, patent examiners spend shockingly little time evaluating individual patents: approximately eighteen hours over three years.[138] The intensive examination of patents occurs post-issuance and often in federal district courts.[139] However, this delay tactic and reliance on district court litigation led to issuing too many bad patents.[140] In 2011, Congress introduced an inter partes review to serve as a cheaper and faster substitute to district court litigation.[141] Once a third party files a petition for inter partes review, the PTO can reexamine the patentability and invalidate doubtful patents.[142]

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136. *See* Price & Rai, *How Logically Impossible Patents Block Biosimilars*, *supra* note 40, at 863 ("Patents, by providing the exclusive right to practice that innovation, should create incentives for drugmakers to innovate in exactly that way. However, the size of the reward fails to match the size of the innovation.").

137. Mark Lemley, Doug Lichtman & Bhaven Sampat, *What To Do About Bad Patents?*, REGULATION, Winter 2005–2006, at 10. Professor Mark Lemley and coauthors coined "bad patents" to describe patents with obvious and impossible concepts:

> Bad patents are everywhere: covering obvious inventions like the crustless peanut butter and jelly sandwich, ridiculous ideas like a method of exercising a cat with a laser pointer, and impossible concepts like traveling faster than the speed of light. More troubling, countless patents that seem reasonable to a lay audience overreach in technical fields as blatantly as that peanut butter sandwich overreaches in a familiar one.

Id.

138. *Id.*

139. *Id.* at 10–12 (explaining that since most patents are not asserted, postponing an intensive determination to the post-issuance stage saves the PTO's resources that would otherwise have been spent on reviewing nonasserted patents); *see also* Heled, *Patents vs. Statutory Exclusivities*, *supra* note 39, at 465 ("[I]t is not uncommon that inventions that lack any value to society are granted patents just because they happen to 'satisfy' the requirements of patent law.").

140. Lemley et al., *supra* note 137, at 12; *see also Patent Quality Improvement: Post-Grant Opposition*: *Hearing Before the Subcomm. on Courts, the Internet, and Intellectual Prop. of the H. Comm. on the Judiciary,* 108th Cong. 29 (2004) (statement of Michael K. Kirk, Executive Director, Am. Intell. Prop. L. Ass'n) (stating that the exorbitant litigations costs and delays prevent inventors from challenging the validity of bad patents).

141. Leahy–Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 299–305 (2011); MERGES & DUFFY, *supra* note 49, at 18; Stach & Freeman, *supra* note 132.

142. 35 U.S.C. § 311; *see id.* §§ 311–319 (describing the inter partes review process); *Inter Partes Review*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/patents/ptab/trials/inter-partes-review [https://perma.cc/Q44G-B7HF] (last updated Sept. 4, 2020) ("Inter partes review is a trial proceeding conducted at the Board to review the patentability of one or more claims in a patent only on a ground that could be raised under §§ 102 or 103 . . . .").

However, since most patents are non-product-specific, biosimilar applicants cannot anticipate which patents will be asserted against them and cannot proactively seek invalidation under inter partes review. For Herceptin, for example, a total of forty-six unique patents were asserted during BPCIA litigations, but only eleven patents were challenged through inter partes review proceedings.[143] Eight out of eleven patents were Herceptin-specific patents that biosimilar manufacturers could easily predict being challenged in BPCIA litigations.[144] In short, a lack of product-identifying information hinders biosimilar applicants' ability to invalidate "bad patents" proactively.

The nature of biologics dictates that "the [manufacturing] process . . . is the product," and biosimilar manufacturers have to mimic the brand-name manufacturer's process as closely as possible to ensure the biosimilar's efficacy and safety.[145] Yet, biosimilar manufacturers are not only systematically kept in the dark under pervasive trade secrecy, but they also have to avoid using brand-name manufacturers' patented processes under the threat of BPCIA litigation. In the next Section, the Note proposes several solutions to this dilemma.

III. LEGISLATIVE SOLUTIONS

This Note proposes legislative solutions to increase transparency before and during the patent dance and the elimination of an injunctive remedy for secondary disputes. First, the disclosure of associated patents at the time of FDA approval and the two-way exchange of FDA license information between brand-name and biosimilar manufacturers would ensure that non-product-specific patents are not asserted during BPCIA litigations. Second, the elimination of an injunctive remedy would encourage biosimilar manufacturers to launch their products despite the pending litigation and would pressure parties to negotiate a fair price that matches the actual value of the patented technology.

143. The list of inter partes proceedings was pulled from the Big Molecule Watch Website. *See Big Molecule Watch: PTAB Tracker*, GOODWIN, https://www.bigmoleculewatch.com/iprs [https://perma.cc/VR3W-CUT7] (listing inter partes proceedings associated with Herceptin).

144. *See id.* (listing eight inter partes proceedings associated with Herceptin).

145. *See supra* notes 37–38 and accompanying text.

A. Increased Transparency Before and During the Patent Dance

In December 2020, Congress passed the Biological Product Patent Transparency Act ("BPPT"), which requires the FDA to publish the list of exchanged patents between the brand-name and biosimilar manufacturers.[146] During the patent dance, the parties exchange the "list of patents for which the [brand-name manufacturer] believes a claim of patent infringement could reasonably be asserted" against the biosimilar applicant.[147] Under the BPPT, the FDA will receive this list of patents and publish it in the Purple Book, which is "a searchable, online database that contains information about biological products, including biosimilar[s]."[148] By mandating public disclosure, the BPPT will enable subsequent biosimilars to "design around" certain manufacturing patents or seek invalidation through inter partes review.[149]

Nevertheless, the BPPT reflects a compromise and does not tackle all issues arising from a lack of transparency. On the small molecule side, the applicants must submit patent information with their drug application[150] within thirty days of either the FDA's approval[151] or the issuance of new patents.[152] Adopting a similar approach would address major shortcomings of the current BPCIA framework. The early publication would allow biosimilars either to challenge the patents proactively or design around them early in the drug development process, avoiding unnecessary changes once at a commercial scale.

146. Consolidated Appropriations Act, 2021, Pub. L. No. 116-260, § 325, 134 Stat. 1182, 2936–38 (2020) (codified at 42 U.S.C. § 262(k)(9)).

147. 42 U.S.C. § 262(*l*)(3)(A).

148. *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or [https://perma.cc/JLQ2-JTKC] (last updated Aug. 3, 2020); 42 U.S.C. § 262(k)(9)(iii); Christopher E. Loh, *New Legislation Requires Certain Patent Information To Be Published in FDA Purple Book for Biological Products*, VENABLE (June 15, 2021), https://www.venable.com/insights/publications/2021/06/new-legislation-requires-certain-patent-info [https://perma.cc/NR3H-77N3].

149. The earlier analysis of Herceptin inter partes review proceedings suggests that the mandated disclosure in the Purple Book will likely lead to a higher number of inter partes review challenges. *See supra* notes 143–44 and accompanying text.

150. 21 U.S.C. § 355(b)(1)(A)(viii); 21 C.F.R. § 314.53(a) (2021).

151. 21 U.S.C. § 355(c)(2); 21 C.F.R. § 314.53(c)(2)(ii) (2021).

152. 21 U.S.C. § 355(c)(2); 21 C.F.R. § 314.53(d)(3) (2021).

Brand-name manufacturers will also be limited in their ability to assert post-approval patents.

Increased communication and exchange between the PTO and FDA could act as an additional check against patent thickets.[153] In *Belcher Pharmaceuticals, LLC v. Hospira, Inc.*,[154] the evidence at trial showed that the manufacturer presented conflicting information to the FDA and PTO. The manufacturer presented a journal article to the FDA to prove that racemization of the drug—a consideration in formulation—was "a well-known process,"[155] but withheld that same article from the PTO.[156] The article shows that the drug formulation was not a new innovation and would have blocked the issuance of a patent.[157] The suit prompted Senators Patrick Leahy and Thom Tillis, the Chair and Ranking Member of the Senate Judiciary Subcommittee on Intellectual Property, to send a letter to the PTO to "take steps to reduce patent applicants' making inappropriate conflicting statements in submissions to the PTO and other federal agencies."[158] The very next day, the FDA also sent a letter to the PTO inviting a dialogue and joint collaboration to curb possible misuses of the patent system such as patent thickets.[159] Had the FDA not only published, but also actively monitored validity and relevancy of patents jointly with the PTO, the PTO would not have granted the patent to the manufacturer in *Belcher*, thus negating the need for a follow-on patent litigation.[160]

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153. *See* Price & Rai, *How Logically Impossible Patents Block Biosimilars*, *supra* note 40, at 863 ("Better coordination between FDA and the USPTO would also help limit the problematic disconnect between these two sources of expertise . . . .").

154. Belcher Pharms., LLC v. Hospira, Inc., 11 F.4th 1345 (Fed. Cir. 2021).

155. *Id.* at 1347–48, 1348 n.3.

156. *Id.* at 1351–52.

157. *Id.* at 1352–53.

158. *See* Letter from Senator Patrick Leahy & Senator Thom Tillis, United States Senate, to Andrew Hirshfeld, Acting Dir. of the U.S. Pat. & Trademark Off. 1–2 (Sept. 9, 2021), https://www.leahy.senate.gov/imo/media/doc/20210909%20Letter%20to%20PTO%20on%20FDA%20submissions.pdf [https://perma.cc/YT8V-5956] (raising concerns about contradictory statements being provided in applications to the FDA and PTO).

159. Letter from Janet Woodcock, Acting Comm'r of the U.S. Food & Drug Admin., to Andrew Hirschfeld, Acting Under Sec'y of Com. for Intell. Prop. & Acting Dir. of the U.S. Pat. & Trademark Off. 1–2, 4–5 (Sept. 10, 2021), https://www.fda.gov/media/152086/download [https://perma.cc/M8YP-DBAV].

160. The earlier versions of the BPPT would have required the disclosure of patents within thirty days of drug approval and would have penalized untimely disclosure of patents by strictly limiting enforcement. *E.g.*, Biologic Patent Transparency Act, S. 659, 116th Cong. § 2(a), (c) (2019).

In addition, the two-way exchange of the FDA licensing information during the patent dance will allow biosimilar applicants to identify any non-product-specific patents. Although a biosimilar applicant submits its FDA application to the brand-name manufacturer, the brand-name manufacturer does not share its license with biosimilar applicants.[161] If this exchange went both ways, a biosimilar applicant could evaluate the relevancy of asserted patents to the original biologic. In the earlier example, Genentech asserted a '988 patent which disclosed "a method for the recombinant production of a secreted heterologous immunoglobulin in a CHO cell."[162] With Genentech's FDA license in hand, the biosimilar applicant can determine whether the '988 patent was practiced in creating the master cell line. Lack of any relationship to the original product will present a powerful argument against an injunctive remedy and an argument for resolution outside of BPCIA litigation.

The BPCIA's duty of confidentiality can be extended to all parties engaged in the patent dance to preserve trade secrets. The BPCIA statutorily imposes a strict duty of confidentiality for the materials exchanged during the patent dance.[163] Only designated counsel can view the biosimilar application to determine the possibility of patent infringement, and counsel cannot share its contents with any other persons, including employees of brand-name manufacturers.[164] Imposing the duty of confidentiality on both parties can prevent potential disclosure of trade secrets.

161. *See supra* note 63 and accompanying text.

162. *See* '988 Patent, *supra* note 107, at [57]; *see also supra* notes 107–09 and accompanying text.

163. 42 U.S.C. § 262(*l*)(1)(B).

164. *Id.* § 262(*l*)(1)(B)(ii), (C).

B. Eliminating Injunctive Remedy for Secondary Patents

Further, Congress could ban an injunctive remedy for secondary patents.[165] Under this proposal, courts can only grant monetary relief,[166] and brand-name manufacturers can no longer seek the nuclear option of blocking the entry of biosimilars. The review of all twenty-nine BPCIA complaints revealed that the brand-name manufacturer sought the injunctive remedy in all BPCIA cases. Removing the injunction as an option will give more bargaining power to biosimilar manufacturers and encourage launches of biosimilars at risk, despite pending litigation.

Patent rights "have the attributes of personal property"[167] and include "the right to exclude others from making, using, offering for sale, or selling the invention."[168] Hence, courts can grant injunctive relief, but only if "in accordance with the principles of equity."[169] Courts apply a four-factor test: injunctive remedy is warranted when the plaintiff

> has suffered an irreparable injury; . . . remedies available at law, such as monetary damages, are inadequate to compensate for that injury; . . . considering the balance of hardships between the plaintiff

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165. Banning injunctive remedies altogether would also mean that courts are prohibited from issuing preliminary injunctions. Although the constitutionality of legislative limitation of the injunctive power exceeds the scope of this Note, Congress has repeatedly exercised its power to limit the use of the injunction in federal courts. *See generally Congressional Limitation of the Injunctive Power*, JUSTICIA, https://law.justia.com/constitution/us/article-3/14-congressional-limitation-of-the-injunctive-power.html#fn-311 [https://perma.cc/K4JU-AGDG] (providing historical examples of Congress limiting courts' injunctive power).

166. The patent holders can receive "reasonable royalt[ies]." 35 U.S.C. § 284 ("Upon finding for the claimant the court shall award the claimant damages adequate to compensate for the infringement, but in no event less than a *reasonable royalty* for the use made of the invention by the infringer, together with interest and costs as fixed by the court." (emphasis added)). For calculation of the reasonable royalties, courts use *Georgia-Pacific Corp. v. United States Plywood Corp.*, 318 F. Supp. 1116 (S.D.N.Y. 1970), factors, which include "[t]he rates paid by the licensee for the use of other patents comparable to the patent in suit," and "[t]he portion of the realizable profit that should be credited to the invention as distinguished from non-patented elements, the manufacturing process, business risks, or significant features or improvements added by the infringer." *Id.* at 1120; *see also* Lucent Techs., Inc. v. Gateway, Inc., 580 F.3d 1301, 1324–35 (Fed. Cir. 2009) (applying the *Georgia-Pacific Corp.* factors to determine damages).

167. *See* 35 U.S.C. § 261 ("[P]atents shall have the attributes of personal property.").

168. *Id.* § 154(a)(1).

169. *See id.* § 283 ("The several courts having jurisdiction of cases under this title may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable.").

> and defendant, a remedy in equity is warranted; and . . . the public interest would not be disserved by a permanent injunction.[170]

Secondary patents are unlikely to survive the courts' four-factor injunction test. Brand-name manufacturers do not suffer an irreparable harm that cannot be sufficiently compensated by monetary damages. If an injunction is granted, defendants are likely unable to recover the hundreds of millions of dollars they had already invested in developing a biosimilar. Lastly, the injunctive remedy will harm the public as patients and payers continue to lack cheaper alternatives. While courts have not granted an injunctive remedy in BPCIA cases to date, fifteen out of twenty-eight cases have settled.[171] The cases with looming threats of injunction likely settled prior to reaching a final judgment.

Courts are unlikely to adopt this approach because courts grant an injunction in accordance with "traditional principles of equity," and the calculus for injunctive remedy is, by design, a fact-intensive inquiry specific to each case.[172] In *eBay v. MercExchange, L.L.C.*,[173] the Supreme Court adopted a new test for determining whether an injunction should be granted in a patent infringement case.[174] The Federal Circuit had a "general rule that courts will issue permanent injunctions against patent infringement absent exceptional

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170. eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388, 391 (2006). The "public interest" prong defines public health broadly and considers many levels of "public interests at stake: broad public policy concerns, such as health; disruption to consumers of enjoined products; the impact on the infringer's employees and community; and the public interest in spurring innovation by granting inventors, for limited times, exclusive rights to their inventions." MERGES & DUFFY, *supra* note 49, at 801. The patentee could also attain a preliminary injunction to block the launch of a biosimilar during the trial. The patentee must demonstrate the likelihood of success on the merits; the likelihood of irreparable harm if an injunction is not granted; that the balance of hardships tips in its favor; and an injunction's favorable impact on the public interest. Winter v. Nat. Res. Def. Council, Inc., 555 U.S. 7, 20 (2008).

171. *BPCIA Litigations*, *supra* note 93. While this Note was in late editing stage, the Court granted an injunction against a biosimilar defendant, Samsung Bioepsis. Final Judgment at 1, Amgen v. Samsung Bioepsis, No. 1:19-cv-11755-CCC-LDW (D.N.J. Nov. 3, 2021). The two patents in dispute, 8,063,182 and 8,163,522, are not secondary patents, but protect APIs.

172. *eBay Inc.*, 547 U.S. at 394; *see* 35 U.S.C. § 283 ("The several courts having jurisdiction of cases under this title may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable.").

173. eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388 (2006).

174. *Id.* at 390.

circumstances."[175] Numerous amici briefs emphasized the possibility of a patent holdup, where a minor, yet essential patent to a successful product can be used to extort disproportionate and excessive royalties under the threat of an injunction.[176] The Supreme Court empowered district courts to deny injunctions by rejecting the Federal Circuit's general rule and emphasized the principles of equity such as "the balance of hardships between the plaintiff and defendant" and the "public interest" in deciding injunctive remedies.[177]

The possibility of patent holdup arises in enforcement of secondary patents.[178] The infringer, a biosimilar applicant, has already invested hundreds of millions of dollars in developing a biosimilar without knowledge of infringed patents.[179] The biosimilar company's investments, not the merits of the patented technology, give enormous leverage to the brand-name manufacturers. In many cases, designing around patented technology is an extremely difficult task. For manufacturing process changes, manufacturers may need to modify equipment, execute time-consuming and expensive validation studies, update all associated documents, retrain employees, and seek approval from the FDA.[180]

The pharmaceutical industry filed a brief in support of MercExchange that essentially argued in favor of injunction protections and in defense of "patent trolls."[181] Legal scholars

175. *Id.* at 391 (quoting MercExchange, L.L.C. v. eBay, Inc., 401 F.3d 1323, 1339 (Fed. Cir. 2005)).

176. *See, e.g.*, Brief *Amici Curiae* of 52 Intellectual Property Professors in Support of Petitioners at 5–8, eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388 (2006) (No. 05-130) (raising the concern "that patent owners . . . use the threat of an injunction against a complex product based on one infringing piece to hold up the defendant and extract a greater share of the value of that product than their patent warrants"); Brief *Amici Curiae* of Yahoo! Inc. in Support of Petitioners at 2, eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388 (2006) (No. 05-130) ("Issuing trolls automatic injunctions upon a finding of infringement allows them to extort settlements that vastly exceed the true economic value of their patents and imposes enormous social costs . . . .").

177. *eBay Inc.*, 547 U.S. at 391.

178. While outside the scope of this Note, a similar argument could apply to small molecule patents as well.

179. *See supra* note 78 and accompanying text.

180. *See, e.g.*, *supra* notes 112–17 and accompanying text (describing patents regarding manufacturing process innovations and their associated requirements).

181. *See* Brief of Amicus Curiae Pharmaceutical Research and Manufacturers of America in Support of Respondent at 5–8, eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388 (2006) (No. 05-130) (arguing that injunctions are essential to patent holders in the pharmaceutical industry). "The term 'patent troll[s]' . . . [is used] to describe 'companies "that try to make a lot of money off a patent that they are not practicing and have no intention of practicing and in most cases

explained that pharmaceutical companies favor injunctive remedies because "the billion-dollar molecules" are protected by a single or handful of patents.[182] However, the analysis from this Note shows that brand-name manufacturers are more likely to act as patent trolls against biosimilars, because the BPCIA gives them a unique position to detect any minor infringements and provides a mechanism to assert patents in a streamlined manner.[183] By the time statutory exclusivity periods end, most primary patents would have expired or are about to expire shortly.[184]

Patents "provid[e an] exclusive right to practice" as an incentive for drug manufacturers to continuously innovate.[185] Weakening protections for secondary patents could hamper innovations by discouraging knowledge sharing of new innovations.[186] However, despite robust patent protections available today, the know-how of biologics manufacturing is concentrated in just a handful of companies. Just eight companies own all biosimilars approved to date, and four

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never practiced."'" Jeremiah S. Helm, Comment, *Why Pharmaceutical Firms Support Patent Trolls: The Disparate Impact of* eBay v. MercExchange *on Innovation*, 13 MICH. TELECOMM. & TECH. L. REV. 331, 331 n.1 (2006) (quoting Alan Murray, *War on 'Patent Trolls' May Be Wrong Battle*, WALL ST. J. (Mar. 22, 2006, 12:01 AM), https://www.wsj.com/articles/SB114298577458004598 [https://perma.cc/L8E7-QBTC]).

182. *See* Helm, *supra* note 181, at 339 ("Whereas a firm like eBay utilizes a number of different patents in its product, [allowing] a troll to extract more than the actual value of a patent, a pharmaceutical firm can ensure market exclusivity for a drug with a single patent on the active molecule.").

183. *See supra* notes 60–63 and accompanying text.

184. *See supra* note 82 and accompanying text. The recent ruling from the Federal Circuit in *Amgen Inc. v. Sanofi* likely means most primary antibody patents are invalid for failing to meet the enablement requirement. Amgen Inc. v. Sanofi, 987 F.3d 1080, 1088 (Fed. Cir. 2021).

185. Price & Rai, *How Logically Impossible Patents Block Biosimilars*, *supra* note 40, at 863.

186. *See* KEVIN T. RICHARDS, KEVIN J. HICKEY & ERIN H. WARD, CONG. RSCH. SERV., R46221, DRUG PRICING AND PHARMACEUTICAL PATENTING PRACTICES 17–18 (2020) ("If the brand could not patent the new use . . . , one commentator has argued that insufficient incentives would have existed to make the investment in R&D necessary to bring the drug to market."); *cf., e.g.*, Kevin Madigan, *An Ever-Weakening Patent System Is Threatening the Future of American Innovation*, ANTONIN SCALIA L. SCH. (Apr. 28, 2017), https://cpip.gmu.edu/2017/04/28/an-ever-weakening-patent-system-is-threatening-the-future-of-american-innovation [https://perma.cc/DXQ8-RJ7V] (describing how "changes to the US patent system are driving . . . research and [investment] outside [of the U.S.]"); Eileen McDermott, *Patent Masters' Warning: U.S. Patents Are Weak, Innovation Is Going Overseas*, IPWATCHDOG (Mar. 27, 2019), https://www.ipwatchdog.com/2019/03/27/patent-masters-warning-u-s-patents-weak-innovation-going-overseas/id=107758 [https://perma.cc/C2WH-U8K2] (explaining how developments in patent law over the last twenty years are driving innovation overseas).

companies own all nine original biologics.[187] Thus, in total, the "competition . . . occur[s] between 11 pharmaceutical companies," with one company manufacturing both brand-name biologics and biosimilars.[188] Patent protections failed to spur new innovations outside of this handful of companies. Most of the key technologies remain shrouded in trade secrecy,[189] and patents do not contain sufficient description to become a source of technical information.[190] Moreover, there are less costly methods of overcoming barriers in biologics manufacturing such as public investment in manufacturing technology and specialized training programs.[191]

The injunctive remedy of blocking biosimilars does not match the size of incremental innovation captured in secondary patents.[192] Developing a biosimilar costs somewhere between $100 and $250 million.[193] Yet, my empirical analysis showed that most secondary patents covered incremental improvements to the original molecule, and a majority of these patents could not have been used to make products at launch.[194] Eliminating injunctive remedies for secondary patents will lower litigation costs and pressure parties to negotiate a fair price that matches the actual value of the patented technology.

CONCLUSION

Biologics mark a new frontier in medicine and promise new cures and treatments. But their promises are meaningless if their price tags remain out of reach for most Americans. Patent thickets are the main tools used by brand-name manufacturers to block the entry of biosimilars as affordable alternatives. This Note analyzed all patents disputed in BPCIA litigations and revealed that a significant number

187. Heled, *The Biologics Price Competition and Innovation Act*, *supra* note 20, at 85.

188. *Id.*

189. *See supra* notes 72 and accompanying text.

190. *See supra* notes 121–25 and accompanying text.

191. A public initiative such as the National Institute of Standards and Technology ("NIST") could be a meaningful first step in generating fundamental knowledge and sharing it in the public domain. *See generally* Price & Rai, *Manufacturing Barriers*, *supra* note 16, at 1031, 1057 (describing potentials of the NIST program in fostering innovation in the biotechnology sector). For more information about the NIST program, see *Biomanufacturing Initiative*, NAT'L INST. OF STANDARDS & TECH., https://www.nist.gov/programs-projects/biomanufacturing-initiative [https://perma.cc/EF65-MQ6M] (last updated May 4, 2021).

192. *See supra* notes 134–36 and accompanying text.

193. Heled, *The Case for Disclosure*, *supra* note 36, at 57.

194. *See supra* note 90; app B.

of these patents do not contain any references to original biologics and are unlikely to be practiced in manufacturing original biologics.

Unless Congress fixes the abusive patent assertions highlighted in this Note, the older biologics will have perpetually high prices. Employers, taxpayers, and patients will continue to shoulder billions in excess drug costs. The early disclosure of applicable patents, the two-way exchange of the FDA license information, and the elimination of injunctive remedies for secondary patents offer starting points in ensuring that drug prices fall when they should.

Appendix A: List of BPCIA Litigations

Case	Docket Number	Complaint Filing Date	Number of Patents Asserted
Amgen v. Sandoz	14-cv-004741	Oct. 24, 2014	0
Janssen v. Celltrion	15-cv-10698	Mar. 6, 2015	6
Amgen v. Apotex	15-cv-61631	Aug. 6, 2015	2
Amgen v. Hospira	15-cv-00839	Sept. 18, 2015	2
Amgen v. Apotex	15-cv-62081	Oct. 2, 2015	2
Immunex v. Sandoz	16-cv-01118	Feb. 26, 2016	5
Amgen v. Sandoz	16-cv-02581	Mar. 4, 2016	2
Abbvie v. Amgen	16-cv-00666	Aug. 4, 2016	61
Amgen v. Coherus	17-cv-00546	May 10, 2017	1
Janssen v. Samsung Bioepis	17-cv-03524	May 17, 2017	3
Abbvie v. BI	17-cv-01065	Aug. 2, 2017	74
Amgen v. Mylan	17-cv-01235	Sept. 22, 2017	2
Genentech v. Amgen	17-cv-01471	Oct. 6, 2017	25
Genentech v. Pfizer	17-cv-01672	Nov. 17, 2017	40

Genentech v. Sandoz	17-cv-13507	Dec. 21, 2017	24
Genentech v. Celltrion	18-cv-01025	July 11, 2018	40
Genentech v. Celltrion	18-cv-00574	July 5, 2018	18
Amgen v. Kashiv	18-cv-03347	Mar. 8, 2018	17
Genentech v. Amgen	18-cv-00924	June 21, 2018	37
Amgen v. Apotex	18-cv-61828	Aug. 7, 2018	1
Abbvie v. Sandoz	18-cv-12668	Aug. 10, 2018	84
Genentech v. Samsung Bioepis	18-cv-01363	Sept. 4, 2018	21
Genentech v. Pfizer	19-cv-00638	Apr. 5, 2019	22
Immunex v. Samsung Bioepsis	19-cv-11755	Apr. 29, 2019	5
Amgen v. Tanvex	19-cv-01374	July 23, 2019	1
Amgen v. Hospira	18-cv-01064	July 18, 2018	1
Amgen v. Hospira	20-cv-00201	Feb. 11, 2020	1
Genentech v. Samsung Bioepis	20-cv-00859	June 28, 2020	14

Appendix B: List of Manufacturing Process Patents Filed One Year After FDA Approval and Their Classifications

Patent Number	**Title**	**Classification**
Janssen v. Celltrion		
7,598,083	Chemically Defined Media Compositions	Non-Product Specific
6,900,056	Chemically Defined Medium for Cultured Mammalian Cells	Non-Product Specific
6,773,600	Use of Clathrate Modifier, to Promote Passage of Proteins During Nanofiltration	Non-Product Specific
Amgen v. Apotex (15-cv-61631)		
8,952,138	Refolding Proteins Using a Chemically Controlled Redox State	Non-Product Specific
5,824,784	N-Terminally Chemically Modified Protein Compositions and Methods	Non-Product Specific
Amgen v. Apotex (15-cv-62081)		
8,952,138	Refolding Proteins Using a Chemically Controlled Redox State	Non-Product Specific
Amgen v. Sandoz		
8,940,878	Capture Purification Processes for Proteins Expressed in a Non-Mammalian System	Non-Product Specific
Abbvie v. Amgen		
8,663,945	Methods of Producing Anti-TNF-Alpha Antibodies in Mammalian Cell Culture	Product-Specific

8,906,646	Fed-Batch Method of Making Human Anti-TNF-Alpha Antibody	Product-Specific
8,911,964	Fed-Batch Method of Making Human Anti-TNF-Alpha Antibody	Product-Specific
9,073,988	Fed Batch Method of Making Anti-TNF-Alpha Antibodies	Product-Specific
9,090,867	Fed-Batch Method of Making Anti-TNF-Alpha Antibody	Product-Specific
9,234,032	Fed-Batch Methods for Producing Adalimumab	Product-Specific
9,284,371	Methods of Producing Adalimumab	Product-Specific
9,206,390	Methods to Control Protein Heterogeneity	Product-Specific
9,290,568	Methods to Control Protein Heterogeneity	Product-Specific
9,234,033	Methods to Control Protein Heterogeneity	Product-Specific
9,346,879	Protein Purification Methods to Reduce Acidic Species	Product-Specific
9,150,645	Cell Culture Methods to Reduce Acidic Species	Product-Specific
9,359,434	Cell Culture Methods to Reduce Acidic Species	Product-Specific
Amgen v. Coherus		
8,273,707	Process for Purifying Proteins	Non-Product-Specific
Janssen v. Samsung Bioepis		
7,598,083	Chemically Defined Media Compositions	Non-Product-Specific
6,900,056	Chemically Defined Medium for Cultured Mammalian Cells	Non-Product-Specific

6,773,600	Use of Clathrate Modifier, to Promote Passage of Proteins During Nanofiltration	Non-Product-Specific
Abbvie v. BI		
8,663,945	Methods of Producing Anti-TNF-Alpha Antibodies in Mammalian Cell Culture	Product-Specific
8,895,009	Purified Antibody Composition	Product-Specific
8,906,372	Purified Antibody Composition	Product-Specific
8,906,646	Fed-Batch Method of Making Human Anti-TNF-Alpha Antibody	Product-Specific
8,911,964	Fed-Batch Method of Making Human Anti-TNF-Alpha Antibody	Product-Specific
8,916,153	Purified Antibody Composition	Product-Specific
8,946,395	Purification of Proteins Using Hydrophobic Interaction Chromatography	Product-Specific
9,018,361	Isolation and Purification of Antibodies Using Protein A Affinity Chromatography	Product-Specific
9,062,106	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific
9,073,988	Fed Batch Method of Making Anti-TNF-Alpha Antibodies	Product-Specific
9,090,688	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific
9,090,867	Fed-Batch Method of Making Anti-TNF-Alpha Antibody	Product-Specific
9,150,645	Cell Culture Methods to Reduce Acidic Species	Product-Specific

9,193,787	Human Antibodies that Bind Human TNF-Alpha and Methods of Preparing the Same	Product-Specific
9,206,390	Methods to Control Protein Heterogeneity	Product-Specific
9,234,032	Fed-Batch Methods for Producing Adalimumab	Product-Specific
9,234,033	Methods to Control Protein Heterogeneity	Product-Specific
9,249,182	Purification of Antibodies Using Hydrophobic Interaction Chromatography	Product-Specific
9,255,143	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific
9,284,371	Methods of Producing Adalimumab	Product-Specific
9,290,568	Methods to Control Protein Heterogeneity	Product-Specific
9,346,879	Protein Purification Methods to Reduce Acidic Species	Product-Specific
9,359,434	Cell Culture Methods to Reduce Acidic Species	Product-Specific
9,365,645	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific
9,499,614	Methods for Modulating Protein Glycosylation Profiles of Recombinant Protein Therapeutics Using Monosaccharides and Oligosaccharides	Product-Specific
9,505,834	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific

9,512,214	Methods to Control Protein Heterogeneity	Product-Specific
9,683,033	Cell Culture Methods to Reduce Acidic Species	Product-Specific
Amgen v. Mylan		
8,273,707	Process for Purifying Proteins	Non-Product-Specific
9,643,997	Capture Purification Processes for Proteins Expressed an A Non-Mammalian System	Non-Product-Specific
Genentech v. Amgen		
8,460,895	Method for Producing Recombinant Proteins With A Constant Content of pCO2 in the Medium	Non-Product-Specific
8,512,983	Production of Proteins in Glutamine-free Cell Culture Media	Non-Product-Specific
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
8,633,302	Variable Tangential Flow Filtration	Non-Product-Specific
9,441,035	Cell Culture Media and Methods of Antibody Production	Product-Specific
9,487,809	Decreasing Lactate Level and Increasing Polypeptide Production by Downregulating the Expression of Lactate Dehydrogenase and Pyruvate Dehydrogenase Kinase	Product-Specific
Amgen v. Kashiv		
7,083,948	Polypeptide Purification Reagents and Methods for Their Ise	Non-Product-Specific

7,118,884	Method for Controlling Metallophosphate Precipitation in High Cell Density Fermentations	Non-Product-Specific
7,384,765	Cell Culture Performance with Betaine	Non-Product-Specific
7,427,659	Process for Purifying Proteins in a Hydrophobic Interaction Chromatography Flow-through Fraction	Non-Product-Specific
7,662,930	Polishing Steps Used in Multi-step Protein Purification Processes	Non-Product-Specific
7,735,525	Thermally Insulated Apparatus for Liquid Chromatographic Analysis	Non-Product-Specific
7,781,395	Process for Purifying Proteins	Non-Product-Specific
8,191,566	Valve for Controlling the Flow of Steam and Other Fluids	Non-Product-Specific
8,273,707	Process for Purifying Proteins	Non-Product-Specific
8,940,878	Capture Purification Processes for Proteins xpressed in a Non-Mammalian System	Non-Product-Specific
8,952,138	Refolding Proteins Using a Chemically Controlled Redox State	Non-Product-Specific
9,418,416	Methods and Apparati for Nondestructive Detection of Undissolved Particles in a Fluid	Non-Product-Specific
9,632,095	Device and Method for Determining Reaction Kinetics	Non-Product-Specific
9,643,997	Capture Purification Processes for Proteins Expressed in a Non-Mammalian System	Non-Product-Specific

9,704,239	Video Trigger Synchronization for Improved Particle Detection in a Vessel	Non-Product-Specific
9,856,287	Refolding Proteins Using a Chemically Controlled Redox State	Non-Product-Specific
Genentech v. Pfizer (17-cv-01672)		
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
7,485,704	Reducing Protein A Leaching During protein A Affinity Chromatography	Product-Specific
7,807,799	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific
6,586,206	Methods for Making Recombinant Proteins Using Apoptosis Inhibitors	Non-Product-Specific
6,716,602	Metabolic Rate Shifts in Fermentations Expressing Recombinant Proteins	Non-Product-Specific
7,390,660	Methods for Growing Mammalian Cells In Vitro	Non-Product-Specific
8,357,301	Chromatography Equipment Characterization	Non-Product-Specific
8,460,895	Method for Producing Recombinant Proteins With a Constant Content of pCO2 In the Medium	Non-Product-Specific
8,512,983	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
8,633,302	Variable Tangential Flow Filtration	Non-Product-Specific
8,771,988	Protein Expression From Multiple Nucleic Acids	Non-Product-Specific

8,822,655	Pre-Filtration Adjustment of Buffer Solutes	Non-Product-Specific
9,047,438	Chromatography Equipment Characterization	Non-Product-Specific
9,080,183	Promoter	Non-Product-Specific
9,428,548	Enhanced Protein Purification Through a Modified Protein A Elution	Product-Specific
9,428,766	Protein Expression From Multiple Nucleic Acids	Non-Product-Specific
9,487,809	Decreasing Lactate Level and Increasing Polypeptide Production by Downregulating the Expression of Lactate Dehydrogenase and Pyruvate Dehydrogenase Kinase	Product-Specific
9,714,293	Production of Proteins in Glutamine-Free Cell Culture Media	Product-Specific
Genentech v. Sandoz		
6,610,516	Cell Culture Process	Non-Product-Specific
6,870,034	Protein Purification	Product-Specific
7,485,704	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific
7,807,799	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific
8,314,225	Heavy Chain Mutant Leading to Improved Immunoglobulin Production	Non-Product-Specific
8,512,983	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific

8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
8,710,196	Protein Purification	Non-Product-Specific
9,714,293	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
Genentech v. Amgen		
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
8,771,988	Protein Expression From Multiple Nucleic Acids	Non-Product-Specific
9,428,766	Protein Expression From Multiple Nucleic Acids	Non-Product-Specific
9,487,809	Decreasing Lactate Level and Increasing Polypeptide Production by Downregulating the Expression of Lactate Dehydrogenase and Pyruvate Dehydrogenase Kinase	Product-Specific
8,710,196	Protein Purification	Non-Product-Specific
8,357,301	Chromatography Equipment Characterization	Non-Product-Specific
8,512,983	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
8,460,895	Method for Producing Recombinant Proteins With a Constant Content Of pCO2 in the Medium	Non-Product-Specific
6,586,206	Methods for Making Recombinant Proteins Using Apoptosis Inhibitors	Non-Product-Specific

8,044,017	Protein Purification	Non-Product-Specific
9,493,744	Methods for Viral Inactivation and Other Adventitious Agents	Non-Product-Specific
6,870,034	Protein Purification	Product-Specific
9,047,438	Chromatography Equipment Characterization	Non-Product-Specific
9,080,183	Promoter	Non-Product-Specific
8,314,225	Heavy Chain Mutant Leading to Improved Immunoglobulin Production	Non-Product-Specific
9,714,293	Production of Proteins in Glutamine-Free Cell Culture Media	Product-Specific
9,868,760	Protein Purification	Non-Product-Specific
Genentech v. Celltrion (18-cv-01025)		
6,610,516	Cell Culture Process	Non-Product-Specific
7,485,704	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific
7,807,799	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
Genentech v. Celltrion (18-cv-00574)		
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
7,485,704	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific

7,807,799	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific
6,586,206	Methods for Making Recombinant Proteins Using Apoptosis Inhibitors	Non-Product-Specific
6,716,602	Metabolic Rate Shifts in Fermentations Expressing Recombinant Proteins	Non-Product-Specific
7,390,660	Methods for Growing Mammalian Cells In Vitro	Non-Product-Specific
8,357,301	Chromatography Equipment Characterization	Non-Product-Specific
8,460,895	Method for Producing Recombinant Proteins With a Constant Content of pCO2 in the Medium	Non-Product-Specific
8,512,983	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
8,633,302	Variable Tangential Flow Filtration	Non-Product-Specific
8,771,988	Protein Expression From Multiple Nucleic Acids	Non-Product-Specific
8,822,655	Pre-Filtration Adjustment of Buffer Solutes	Non-Product-Specific
9,047,438	Chromatography Equipment Characterization	Non-Product-Specific
9,080,183	Promoter	Non-Product-Specific
9,428,548	Enhanced Protein Purification Through a Modified Protein A Elution	Product-Specific
9,428,766	Protein Expression From Multiple Nucleic Acids	Non-Product-Specific

9,487,809	Decreasing Lactate Level and Increasing Polypeptide Production by Downregulating the Expression of Lactate Dehydrogenase and Pyruvate Dehydrogenase Kinase	Product-Specific
9,714,293	Production of Proteins in Glutamine-Free Cell Culture Media	Product-Specific
Amgen v. Apotex		
9,856,287	Refolding Proteins Using a Chemically Controlled Redox State	Non-Product-Specific
Abbvie v. Sandoz		
8,663,945	Methods of Producing Anti-TNF-Alpha Antibodies in Mammalian Cell Culture	Product-Specific
8,906,646	Fed-Batch Method of Making Human Anti-TNF-Alpha Antibody	Product-Specific
8,911,964	Fed-Batch Method of Making Human Anti-TNF-Alpha Antibody	Product-Specific
9,018,361	Isolation and Purification of Antibodies Using Protein A Affinity Chromatography	Product-Specific
9,073,988	Fed Batch Method of Making Anti-TNF-Alpha Antibodies	Product-Specific
9,085,618	Low Acidic Species Compositions and Methods for Producing and Using the Same	Product-Specific
9,090,867	Fed-Batch Method of Making Anti-TNF-Alpha Antibody	Product-Specific
9,150,645	Cell Culture Methods to Reduce Acidic Species	Product-Specific
9,234,032	Fed-Batch Methods for Producing Adalimumab	Product-Specific

9,255,143	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific
9,290,568	Methods to Control Protein Heterogeneity	Product-Specific
9,346,879	Protein Purification Methods to Reduce Acidic Species	Product-Specific
9,359,434	Cell Culture Methods to Reduce Acidic Species	Product-Specific
9,365,645	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific
9,505,834	Methods for Controlling the Galactosylation Profile of Recombinantly-Expressed Proteins	Product-Specific
9,683,033	Cell Culture Methods to Reduce Acidic Species	Product-Specific
9,957,318	Protein Purification Methods to Reduce Acidic Species	Product-Specific
Genentech v. Samsung Bioepsis (18-cv-01363)		
6,407,213	Method for Making Humanized Antibodies	Product-Specific
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
7,390,660	Methods for Growing Mammalian Cells In Vitro	Non-Product-Specific
7,485,704	Reducing Protein a Leaching During Protein A Affinity Chromatography	Product-Specific
7,807,799	Reducing Protein A Leaching During Protein A Affinity Chromatography	Product-Specific

8,512,983	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
9,714,293	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
Genentech v. Pfizer (19-cv-00638)		
7,846,336	Chromatographic Methods	Non-Product-Specific
8,314,225	Heavy Chain Mutant Leading to Improved Immunoglobulin Production	Non-Product-Specific
8,512,983	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
9,441,035	Cell Culture Media and Methods of Antibody Production	Product-Specific
9,714,293	Production of Proteins in Glutamine-Free Cell Culture Media	Product-Specific
9,884,904	Methods for Purifying Polypeptide Solutions	Non-Product-Specific
Amgen v. Tanvex		
9,856,287	Refolding Proteins Using a Chemically Controlled Redox State	Non-Product-Specific
Genentech v. Samsung Bioepis (20-cv-00859)		
8,460,895	Method for Producing Recombinant Proteins with a Constant Content of pCO2 in the Medium	Non-Product-Specific

8,512,983	Production of Proteins in Glutamine-Free Cell Culture Media	Non-Product-Specific
8,574,869	Prevention of Disulfide Bond Reduction During Recombinant Production of Polypeptides	Non-Product-Specific
9,441,035	Cell Culture Media and Methods of Antibody Production	Product-Specific
9,487,809	Decreasing Lactate Level and Increasing Polypeptide Production by Downregulating the Expression of Lactate Dehydrogenase and Pyruvate Dehydrogenase Kinase	Product-Specific
9,714,293	Production of Proteins in Glutamine-Free Cell Culture Media	Product-specific
10,513,697	CO2 Profile Cultivation	Non-Product-Specific
10,662,237	Method to Improve Virus Filtration Capacity	Non-Product-Specific
10,676,710	Cell Culture Compositions	Non-Product-Specific
Amgen v. Hospira (18-cv-01064)		
9,643,997	Capture Purification Processes for Proteins Expressed in a Non-Mammalian System	Non-Product-Specific
Amgen v. Hospira (20-cv-00201)		
8,273,707	Process for Purifying Proteins	Non-Product-Specific