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UNVEILING THE PATENT LANDSCAPE OF BIOLOGIC DRUGS

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ABSTRACT—It is undeniable that the escalating price of biopharmaceuticals is a critical issue, as high prices limit patients' access to life-saving medications and strain our healthcare system. Biologics, or large-molecule drugs, which are revolutionizing modern healthcare, are significantly contributing to the escalating cost of prescription drugs. While biologic drugs represent only 2% of all U.S. prescriptions, they comprise close to 50% of net drug spending.

Policymakers have proposed a series of interventions to decrease drug prices that target the patent practices of pharmaceutical firms. Yet due to differences in law, we have a robust source of patenting information for small-molecule drugs and a woefully incomplete source of patenting information for biologics. As a result, policymakers are attempting to solve a problem without understanding the patenting landscape of biologics, which comprises the most expensive segment of the prescription drug market.

To fill this gap, we build the first comprehensive patent database associated with all 515 Food and Drug Administration approved biologics, which comprises over 11,500 patents. We then utilize our novel database to examine the controversial patenting practices of pharmaceutical firms. We find that both patent thicketing—building a dense web of patents for each drug—and patent evergreening—extending the exclusivity period of a drug by obtaining more patents—are significantly more prevalent with biologics than small-molecule drugs. We also find that patents are more effective at delaying biosimilar entry in the biologic market than generics in the small-molecule market. Finally, we utilize our novel database to evaluate various policy proposals aimed at decreasing patent thickets and provide much needed empirical evidence at how many biological patents these proposals would affect.

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INTRODUCTION

Michelle Dehetre, a mother of five, passed out at the wheel while driving her son home.[1] She was taken to the emergency room as her blood sugar dropped too low.[2] This is not unusual for Michelle, as she cannot pay for her diabetes medication. Even with insurance, the medication costs nearly $300 a month.[3]

Pamela Holt has an incurable but treatable blood cancer.[4] The drug that will keep her cancer in remission costs over $12,000 a year with insurance.[5] Pamela cannot afford this amount.[6]

Donnette Smith was born with a heart defect.[7] After Donnette's third heart surgery, she was told to reduce her cholesterol level dramatically.[8] Donnette's cardiologist believed a new drug could help but Donette's insurance did not cover the drug.[9] Without insurance, the drug costs $14,000 a year, an amount that is prohibitively expensive for Donnette.[10]

These stories are not uncommon. Last year, approximately 21% of Americans did not fill at least one prescription due to financial considerations.[11] Eight out of ten Americans describe prescription drug prices as "unreasonable."[12] Voters from both parties report that the "rising price of prescription drugs was an important factor" in their voting decisions

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[1] *The Complex Web of Prescription Drug Prices, Part I: Patients Struggling with Rising Costs: Hearing Before the S. Special Committee on Aging*, 116th Cong. (2019) (statement of Michelle Dehetre), https://www.aging.senate.gov/imo/media/doc/SCA_Dehetre_3_6_19.pdf, [https://perma.cc/H67T-FZJ9].

[2] *Id.*

[3] *Id.*

[4] *The Complex Web of Prescription Drug Prices, Part I: Patients Struggling with Rising Costs: Hearing Before the S. Special Committee on Aging*, 116th Cong. (2019) (statement of Pamela Holt), https://www.aging.senate.gov/imo/media/doc/SCA_Holt_3_6_19.pdf, [https://perma.cc/NJ7N-PQQ7].

[5] *Id.*

[6] *Id.*

[7] *The Complex Web of Prescription Drug Prices, Part I: Patients Struggling with Rising Costs: Hearing Before the S. Special Committee on Aging*, 116th Cong. (2019) (statement of Donnette Smith), https://www.aging.senate.gov/imo/media/doc/SCA_Smith_3_6_19.pdf, [https://perma.cc/RA35-B46F].

[8] *Id.*

[9] *Id.*

[10] *Id.*

[11] Alex Montero, Grace Sparks, Ashley Kirzinger, Isabelle Valdes & Liz Hamel, *KFF Health Tracking Poll July 2023: The Public's Views Of New Prescription Weight Loss Drugs And Prescription Drug Costs*, KFF (Aug. 4, 2023), https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-july-2023-the-publics-views-of-new-prescription-weight-loss-drugs-and-prescription-drug-costs/, [https://perma.cc/TDV3-WMS4].

[12] Ashley Kirzinger, Lunna Lopes, Bryan Wu & Mollyann Brodie, *KFF Health Tracking Poll – February 2019: Prescription Drugs*, KFF (Mar. 1, 2019), https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-february-2019-prescription-drugs, [https://perma.cc/WMV8-R7Z3].

in the 2020 election.[13] The annual cost of prescription drugs in the United States exceeds half a trillion dollars and accounts for nearly 17% of the nation's personal health care bill.[14] Prescription drugs are among the fastest-growing segments of health care spending.[15]

Given these facts, it is undeniable that the escalating cost of biopharmaceuticals is a critical issue.[16] High prescription drug prices are now a dominant policy concern on Capitol Hill. Congress has held a half-dozen hearings and introduced a number of bills to address prescription drug prices.[17] Many of these bills have targeted the patenting practices of firms that manufacture large-molecule drugs, which are also known as biologics.[18]

Biologics have complex molecular structures and are derived from living organisms.[19] The mRNA vaccines for COVID-19 are biologic drugs, as is Humira, a leading treatment for rheumatoid arthritis.[20] While biologics hold enormous potential to treat an array of diseases, they represent only a small share of all prescription drugs. The vast majority of drugs are so-called small-molecule drugs, which have simple molecular structures that can be chemically synthesized in a laboratory.[21] Examples of small-molecule drugs include Prozac, Prilosec, and aspirin.

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[13] Coal. Against Pat. Abuse & Morning Consult, *Reforming the Patent System* 1 (Nov. 2020), https://www.capanow.org/wp-content/uploads/2020/11/CAPA_Memo_MC.pdf [https://perma.cc/NB4Y-KNEH].

[14] MAKING MEDICINES AFFORDABLE: A NATIONAL IMPERATIVE xiv (Norman R. Augustine, Guru Madhavan & Sharyl J. Nass eds., Nat'l Acads. Press 2018), https://nap.nationalacademies.org/read/24946/chapter/1 [https://perma.cc/L8KM-5E8V].

[15] *See id.* at 12.

[16] *Id.* at 1 ("[T]he cost of biopharmaceuticals [is] a serious national concern with broad political implications").

[17] *See, e.g.*, Emily Kopp, *Echoes of Big Tobacco Fight in Big Pharma Hearings*, ROLL CALL (Apr. 25, 2019), https://rollcall.com/2019/04/25/echoes-of-big-tobacco-fight-in-big-pharma-hearings/ [https://perma.cc/34L2-MLGR] (reporting "the House and Senate have held a half dozen [Committee hearings on drug prices] this year"); KEVIN J. HICKEY, ERIN H. WARD & WEN W. SHEN, DRUG PRICING AND INTELLECTUAL PROPERTY LAW: A LEGAL OVERVIEW FOR THE 116TH CONGRESS 35–51 (Cong. Rsch. Serv. ed., 5th ed. 2019), https://www.congress.gov/crs-product/R45666?q=%7B%22search%22%3A%22r45666%22%7D&s=2&r=6 [https://perma.cc/SDS3-U9LM] (providing a general overview of selected bills).

[18] Hickey, Ward & Shen, *supra* note [*17], at 35–51.

[19] *Id.* at 21.

[20] *See* U.S. Food & Drug Admin., *Coronavirus (COVID-19) | CBER-Regulated Biologics*, FDA, https://www.fda.gov/vaccines-blood-biologics/industry-biologics/coronavirus-covid-19-cber-regulated-biologics? [https://perma.cc/Q3ER-7RUJ] (last visited Oct. 16, 2025) (explaining that biologics include "prophylactic and therapeutic vaccines," such as those developed to prevent COVID-19); Abbvie, HUMIRA, https://www.humira.com/ [https://perma.cc/4RVG-YXT2].

[21] Helen Wang, *Small vs Big: Understanding the Differences between Small Molecule Drugs and Biologic Drugs*, IMMpress Magazine (Aug. 19, 2019), https://www.immpressmagazine.com/small-vs-big-understanding-the-differences-between-small-molecule-drugs-and-biologic-drugs/ [https://perma.cc/3TRM-UTC4].

Although biologics comprise a small proportion of prescriptions, they have an outsized effect on drug expenditures. That is, while biologic drugs represent only 2% of all U.S. prescriptions, they comprise nearly 50% of net drug spending.[22] Fortunately, biosimilars, the generic form of biologic drugs, can reduce drug prices.[23] When a biosimilar enters the market, biologic prices decrease, sometimes dramatically.[24] Yet to date, very few biosimilars have entered the U.S. market.

Although several factors contribute to the high cost of biologic drugs and to the delayed entry of biosimilars, one likely culprit is the patenting practices of firms that manufacture biologics. Two patenting practices are especially controversial, both of which stem from the fact that drug manufacturers obtain a series of patents on a Food and Drug Administration (FDA) approved drug, rather than a single patent. The first practice is pejoratively referred to as "evergreening," whereby a pharmaceutical firm seeks additional patents years after filing the primary patent—i.e., the patent on the molecule that forms the basis of the drug product.[25] Given that patent terms run twenty years from filing, these later-filed patents expire later and thereby extend the exclusivity period of the relevant drug.[26] The second controversial patenting strategy is known as patent "thicketing."[27] Firms obtain numerous patents associated with a drug product to form a patent thicket surrounding each drug.[28] The primary goal of patent thickets is not necessarily to extend the exclusivity period of a drug, but rather to build a

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[22] *Biosimilars Can Significantly Reduce Employer Pharmacy Costs. Are You Missing Out?*, KAISER PERMANENTE, (Oct. 24, 2023), https://business.kaiserpermanente.org/california/healthy-employees/pharmacy/biosimilar-reduce-costs [https://perma.cc/G6UU-KJHB?type=image] (noting that biologics comprise 47% of prescription drug spending); *c.f.* Andrew W. Mulcahy, Jakub P. Hlavka & Spencer R. Case, *Biosimilar Cost Savings in the United States: Initial Experience and Future Potential*, 7 RAND HEALTH Q. 4 (2018), https://pmc.ncbi.nlm.nih.gov/articles/PMC6075809/ [https://perma.cc/88TS-M752] ("While only 1–2 percent of the U.S. population is treated with a specialty drug each year . . . biologics alone accounted for 38 percent of U.S. prescription drug spending in 2015."); *c.f.* Scott Gottlieb, Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilars Action Plan (July 18, 2018) https://wayback.archive-it.org/7993/20201227173138/https://www.fda.gov/news-events/press-announcements/remarks-fda-commissioner-scott-gottlieb-md-prepared-delivery-brookings-institution-release-fdas [https://perma.cc/RB9D-C7RG] ("While less than 2 percent of Americans use biologics, they represent 40% of total spending on prescription drugs").

[23] KAISER PERMANENTE, *supra* note [*22].

[24] *Id.*

[25] *See infra* notes [*86–88] and accompanying text.

[26] 35 U.S.C. § 154 (2015).

[27] See *infra* notes [*89–90] and accompanying text.

[28] *Id.*

dense web of patents for each drug to ensure that at least some patents survive legal challenges against the patent portfolio.[29]

If biologic firms obtain a thicket of patents, then a biosimilar company that successfully challenges one or even several patents associated with an approved biologic does not necessarily enter the market. Instead, the biosimilar company may simply face more patent roadblocks. How many patents are associated with the average biologic drug, and how successful are these patents at keeping biosimilars at bay? We just don't know the answers to these questions.

Much of what we know about the drug-patent landscape is based on research of small-molecule drugs. U.S. law has mandated since 1984 that brand-name manufacturers of small-molecule drugs disclose to the FDA patents that would be infringed if generics were to launch before the expiration of the relevant drugs' patents.[30] The FDA publicly disseminates the resulting patent lists in something known as the Orange Book,[31] which scholars have exploited to study the patent practices of firms that manufacture small-molecules.[32]

In contrast, we know virtually nothing about the patenting landscape associated with large-molecule drugs or biologics. The law that governs transparency of patent rights works quite differently in the context of biologics than small-molecule drugs.[33] It was not until 2020 that Congress initiated a process by which the FDA would publish the patent lists associated with biologics in something known as the Purple Book, a biologics counterpart to the Orange Book.[34] However, the information to be disclosed under this 2020 Act is initiated by an essentially voluntary process. Moreover, the disclosure requirements do not cover all patents that can be

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[29] *Id.*

[30] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, §101, 98 Stat. 1585, 1585–92 (1984).

[31] U.S. Food and Drug Admin., *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations,* FDA, https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book [https://perma.cc/AFD7-LSLX].

[32] *See, e.g.*, C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents*, 8 J. EMPIRICAL L. STUD. 613, 619–20 (2011) (using the Orange Book patent data "[t]o assess changes in brand-name patenting and generic challenges over time"); C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327, 329 (2012) (using the Orange Book patent data to study trends in generic patent challenges).

[33] *See infra* Part III.C.

[34] Biological Product Patent Transparency Act ("BPPT"), Pub. L. No. 116–260 (H.R. 133, 116th Congress), Div. BB, Section 325. The core language of the BPPT was originally introduced to the House in March 2019 as the "Purple Book Continuity Act" (H.R. 1520, 116th Congress), before it was placed in the year-end omnibus bill.

potentially infringed by competitors.[35] Our analysis demonstrates that the Purple Book identifies *less than* 4% of the relevant patents associated with approved biologics.

The result is that scholars lack a patent reference to study the most expensive segment of the pharmaceutical industry—biologics. This gap in the patent landscape of biologics is significant for a host of reasons. Perhaps most saliently, policymakers and commentators have suggested a plethora of proposals to decrease prescription drug prices from restricting the number of patents a pharmaceutical company may obtain,[36] to limiting the number of patents a biologics company may assert during patent litigation, [37] to increasing the resources to the U.S. Patent & Trademark Office (USPTO) to make better patentability determinations.[38] Knowing which solution is best can only occur after a proper diagnosis of the problem. With no robust empirical evidence on the patent landscape of biologics, policymakers are throwing darts in the dark.

To fill this gap, we built the first comprehensive patent database associated with all 515 FDA-approved biologics, which are comprised of over 11,500 patents. Despite the long-felt need for such a database, no one had taken up the task. This is partly due to the time-consuming nature of building such a database and the need for both scientific and legal expertise. We obtained a grant from the National Institute of Health to help build this database.[39] With this funding we hired a full-time post-doctoral student, who under our supervision, worked for two years on the most significant step in building this database: conducting structured searches of patent texts utilizing Orbit Intelligence patent analytic and search software.

This Article provides the first large-scale overview of the patent landscape associated with all 515 FDA approved biologics. We find that both patent thicketing and patent evergreening are significantly more prevalent with biologics than small-molecule drugs.[40] We also examine the extent to

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[35] *See infra* Part III.C.

[36] Robin Feldman, *'One-and-Done' for New Drugs Could Cut Patent Thickets and Boost Generic Competition*, STAT NEWS (Feb. 11, 2019), https://www.statnews.com/2019/02/11/drug-patent-protection-one-done/ [https://perma.cc/4BP2-GEUH].

[37] *See infra* Part VII.

[38] Michael D. Frakes & Melissa F. Wasserman, *Investing in Ex Ante Regulation: Evidence from Pharmaceutical Patent Examination*, 15 AM. ECON. J.: ECON. POL'Y 151 (2023); Michael D. Frakes & Melissa F. Wasserman, *Irrational Ignorance at the Patent Office*, 72 VAND. L. REV. 975 (2019); Michael D. Frakes & Melissa F. Wasserman, *Is the Time Allocated to Review Patent Applications Inducing Examiners to Grant Invalid Patents? Evidence from Microlevel Application Data*, 99 REV. ECON. & STAT. 550 (2017).

[39] *Impacts of Enhanced Drug Examination,* National Institute of Health, National Institute on Aging, R01, 1R01AG076586-01A1*,* 2023-2027 ($1,266,480) [https://perma.cc/6H5J-9M74].

[40] *See infra* Part V.

which these patents successfully delay biosimilar entry. We find the effective patent length of biologics that do not face biosimilar competition to be close to 19 years, which is also longer than the effective patent length of small-molecule drugs.[41] Finally, we conclude by utilizing our novel patent biologics database to evaluate various policy proposals that aim to increase biosimilar competition by targeting patent thicketing. In doing so, we provide policymakers with much needed empirical evidence on how many biologic patents these various proposals would affect.

This Article proceeds in five parts. Part I describes small-molecule drugs and the promise of large-molecule, or biologics drugs. It also documents the skyrocketing costs of prescription drugs. Part II introduces the controversial patent practices of pharmaceutical companies, while Part III explains how U.S. law mandates the disclosure of patents associated with FDA approved small-molecule drugs but not for biologics, creating a gap in knowledge on the patent landscape of large-molecule drugs. Part IV outlines the building of the biologics patents database. We present our findings on patent evergreening and patent thicketing in Part V. Part VI examines how effective patents are at keeping biosimilars off the market. Finally, Part VII utilizes our novel patent database to evaluate the effectiveness of several bills to diminish patent thicketing.

I. BACKGROUND

This Part begins by explaining the differences between small-molecule and large-molecule or biologics drugs. It then turns to documenting the rising prescription drug prices and the extent to which biologics contribute to our current level of drug expenditures.

A. Small-Molecule Drugs and the Promise of Biologics

Historically, scientists have developed prescription drugs by chemically processing small molecules in a laboratory.[42] These drugs have simple structures, so once the chemical structure of the drug is known, a firm can typically reverse-engineer a process by which the compound can be created.[43] Examples of small-molecule drugs include penicillin, Lipitor,

[41] *See infra* Part VI.

[42] Kaiser Permanente Inst. for Health Policy, *Drug Policy 101: Breaking Down Different Types of Drug Products* (Oct. 2019) 1, https://www.kpihp.org/wp-content/uploads/2019/10/drug_Policy_101_breaking_down_drug_products_v6_FINAL.pdf [https://perma.cc/462R-24G2].

[43] *Id.*

Lyrica, and aspirin. Today, 90% of all medicines approved in the United States are small-molecule drugs.[44]

Starting in the 1970s, scientists began to develop more complex drugs, known as biologics.[45] Biological products are a class of drugs derived from living organisms or their components and are characterized by their large, complex molecular structures, often consisting of proteins, antibodies, or cell-based therapies.[46] Many commentators believe that biologics are the future of medicine, as biologics more easily target specific parts of the body, increasing their efficacy and decreasing their side effects in comparison to small-molecule drugs.[47] Biologic drugs are best known for treating certain types of cancer and autoimmune diseases, but they hold enormous potential for preventing and treating a wide range of diseases and health conditions.[48] The mRNA vaccines available for COVID-19 are biologic drugs, as is Humira, the blockbuster drug that is used to treat rheumatoid arthritis.[49]

Although biologics are revolutionizing healthcare, they are more expensive to develop and manufacture than small-molecule drugs.[50] Because the ingredients of a biologic come from a living organism, scientists must reproduce, grow, copy, extract, and purify the biologic in a laboratory to create the final product, all of which add to their cost of production.[51] Although biologic drugs are thought to be particularly time-intensive to develop—hence contributing to their greater expense to develop than small

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[44] Wang, *supra* note [*21].

[45] KRISTINA M.L. ACRI, NÉE LYBECKER, BIOLOGICS AND BIOSIMILARS: A PRIMER, FRASER INST., 6 (2020), https://www.fraserinstitute.org/sites/default/files/biologics-and-biosimilars-a-primer.pdf. [https://perma.cc/L4XZ-CJEQ].

[46] Favour Danladi Makurvet, *Biologics vs. Small Molecules: Drug Costs and Patient Access*, 9 MED. DRUG DISCOVERY 1,1 (2021).

[47] *Id.* at 2. Allucent, Points to Consider in Drug Development of Biologics and Small Molecules, available at https://www.allucent.com/resources/blog/points-consider-drug-development-biologics-and-small-molecules?utm_source=chatgpt.com.

[48] Giovanni Adami, *Balancing Benefits and Risks in the Era of Biologics*, 11 THERAPEUTIC ADVANCES IN MUSCULOSKELETAL DISEASE 1, 1 (2019).

[49] Abbvie, *supra* note [*20].

[50] Makurvet, *supra* note [*46], at 1.

[51] This also means that batches of biologics are not identical. Paul J. Declerck, *Biologicals and Biosimilars: A Review of the Science and Its Implications*, 1 GENERICS AND BIOSIMILARS INITIATIVE JOURNAL 13, 13 (2012). This adds complexities and costs because manufacturers must ensure that each batch acts in the same way and has a predictable effect on all people who take the medication. Makurvet, *supra* note [*46], at 1.

molecules[52]—several recent studies have cast doubt on this contention.[53] Regardless, it is undeniable that biologics are more complex and difficult to manufacture than small molecules, which in part drives their higher development costs. Policymakers do not agree on exactly how much more costly it is to develop and manufacture a new biologic drug than a small-molecule drug, with estimates ranging from approximately 25% more to more than twice as much.[54]

B. High Prices of Biologic Drugs

Annual spending on prescription medications in the United States exceeds half a trillion dollars, representing approximately 17 percent of total personal health-care expenditures.."[55] Prescription drugs are among the fastest-growing segments of healthcare spending[56] and biologics are playing an increasingly important role in these expenditure levels. During the past decade, expenditures on biologics in the United States increased from $100 billion to $260 billion, representing a 160% increase.[57] On average, biologics cost $45 per day or $16,425 per year compared with $2 per day or $730 per year for traditional, small-molecule drugs.[58] Moreover, the most expensive

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[52] Reed F. Beall, Thomas J. Hwang & Aaron S. Kesselheim, *Pre-market Development Times for Biologic Versus Small-Molecule Drugs,* 37 NATURE BIOTECH. 708, 708–709 (2019) ("The lengthy development process attributed to biologic drugs was cited by legislators when the US Congress passed the Biologics Price Competition and Innovation (BPCIA) in 2009, which granted new biologics 12 years of guaranteed exclusivity," instead of 5 years which is granted to new chemical entities—i.e., small molecule drugs.).

[53] *Id.* at 708 (finding that "[m]edian total pre-market development times were not different between biologic and small-molecule drugs"); Olivier J. Wouters, Matthew Vogel, William B. Feldman, Reed F. Beall, Aaron S. Kesselheim & S. Sean Tu, *Differential Legal Protections for Biologics vs Small-Molecule Drugs in the US*, 332 JAMA 2101, 2103 (2024) (same).

[54] There is a range of estimates for the increased costs of developing a biologic versus a small-molecule drug. *See, e.g.*, Joel Lexchin, *Affordable Biologics for All*, JAMA NETWORK OPEN (Apr. 27, 2020) https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2764808 [https://perma.cc/LKE7-ATCR] (reporting the development costs for a biologic is $391 million versus $309 million for a small-molecule drug); Wouters, *supra* note [*53], at 2101 (estimating the develop costs for a biologic is $3.0 billion versus $2.1 billion for a small-molecule drug); *Biologics vs Small Molecules: A New Era in Drug Development*, SYNER-G BIOPHARMA GROUP, (Jan. 21, 2025), https://synergbiopharma.com/biologics-vs-small-molecules/ [https://perma.cc/BSW9-9584] (reporting that development costs for a biologic averages $2–4 billion versus averages of $1–2 billion for a small molecule drug).

[55] NATIONAL IMPERATIVE, *supra* note [*14], at xiv.

[56] *Id.* at 12.

[57] Charlie Katebi, *Federal Barriers Make Biologic Drugs Unaffordable*, AM. FIRST POL'Y INST. (Jan. 9, 2024), https://www.americafirstpolicy.com/issues/executive-summary-federal-barriers-make-biologic-drugs-unaffordable [https://perma.cc/FKA8-9U9W].

[58] Robert J. Shapiro, Karan Singh & Megha Mukin, *The Potential American Market for Generic Biological Treatments and the Associated Cost Savings* 4 (Feb. 2008), https://www.sonecon.com/docs/studies/0208_GenericBiologicsStudy.pdf [https://perma.cc/7K53-FNXA].

biologics can exceed $500,000 per year.[59] Although biologics comprise less than 2% of prescriptions they constitute close to 50% of prescription drug expenses.[60]

Given these price tags, it is not surprising that some people struggle to afford their prescription drugs or go without treatment. A recent National Health Interview Survey found that approximately 60% of adults took at least one prescription drug at some point in the past 12 months, and that 8.2% of adults reported not taking medications as prescribed due to cost.[61] That is 9.2 million adults—basically the population of New Jersey.[62]

Biosimilars, which are highly similar copies of the original biologic drug, offer the potential to bring down prescription drug prices. The Biologics Price and Innovation Act of 2009 (BPCIA) created an abbreviated pathway for the approval of biosimilars.[63] The goal of this abbreviated pathway is to demonstrate biosimilarity between the proposed biosimilar and its reference product—that is, to show that the biosimilar has no clinically meaningful difference from the existing FDA-approved biologic.[64]

Manufacturers of biosimilars do not have to independently establish the safety and efficacy of the biosimilar but can instead, to different extents, rely

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[59] 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 Ruling Do Not Solve Fundamental Barriers to Competition*, 78 DRUGS 1777, 1777 (2018).

[60] KAISER PERMANENTE, *supra* note [*22] (noting that biologics comprise 46% of prescription drug spending); Andrew W. Mulcahy, Jakub P. Hlavka & Spencer R. Case, *Biosimilar Cost Savings in the United States*, RAND HEALTH Q. (Mar. 2018), https://pmc.ncbi.nlm.nih.gov/articles/PMC6075809/ [https://perma.cc/SXB4-PMMP] (finding that biologics is "one of the main drivers of spending growth" despite the fact that only 1–2% of the population is treated with one each year); Scott Gottlieb, Comm'r, Food & Drug Admin., Remarks at the Brookings Institution: Cultivating a Vibrant U.S. Market for Biosimilars (July 18, 2018), (transcript available at https://www.brookings.edu/wp-content/uploads/2018/07/es_20180718_biosimilars_transcript.pdf) [https://perma.cc/7BTT-ZNEZ] (noting that "[w]hile less than 2 percent of Americans use biologics, they represent 40 percent of total spending on prescription drugs.").

[61] Laryssa Mykyta & Robin A. Cohen, *Characteristics of Adults Aged 18-64 Who Did Not Take Medication as Prescribed to Reduce Costs: United States, 2021*, NAT'L CTR. HEALTH STAT. DATA BRIEF NO. 470 (June 2023), https://www.cdc.gov/nchs/products/databriefs/db470.htm? [https://perma.cc/Y6BS-UDCG].

[62] *New Jersey,* U.S. CENSUS BUREAU, https://data.census.gov/profile/New_Jersey?g=040XX00US34 [https://perma.cc/NX2L-Z5B4] (last visited Sept. 29, 2025).

[63] The BPCIA was enacted as part of the Patient Protection and Affordable Care Act. *See* Biologics Price Competition Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001–7002, 124 Stat. 119, 804–21 (2010) (adding § 351(k)(7) to the Public Health Service Act, ch. 373, 58 Stat. 682 (1944)).

[64] 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." *See* Biologics Price Competition Innovation Act § 7002(b)(3) (codified at 42 U.S.C. § 262(i)(2)).

upon the clinical trials of the biologic.[65] As a result, original biologic manufacturers spend on average over a billion dollars on the approval process, while biosimilar manufacturers spend on average $100–200 million.[66] The first biosimilar was approved by the FDA in 2015 and since then the FDA has approved 73 biosimilars associated with 21 unique biologic drugs.[67] The lower development costs of biosimilars are reflected in their prices, which can be anywhere from 10% to 50% less than the brand biologic price at the time of the biosimilar's launch.[68] The price savings associated with biosimilars increase with each additional biosimilar entry.[69] It is estimated that biosimilars have saved over 23 billion dollars, and the savings in 2022 are estimated to be 9.4 billion dollars alone.[70] Moreover, since 2018, biosimilar savings have grown by approximately $2 billion each year.[71] The savings associated with biosimilars accrue broadly across the health care system: patients benefit through lower out-of-pocket costs and improved access, insurers and pharmacy benefit managers capture reduced reimbursement obligations, and public programs such as Medicare and Medicaid realize substantial budgetary relief. Employers that provide health coverage also save through lower drug spending, which can moderate premium growth.[72]

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[65] *Id. at* § 7002(a)(2).

[66] PFIZER, INC., PATIENTS AT OUR CENTER PFIZER 2018 ANNUAL REVIEW 17 (2018), https://www.pfizer.com/sites/default/files/investors/financial_reports/annual_reports/2018/assets/pdf/pfizer-2018- annual-review.pdf [https://perma.cc/NT7Y-NCKA]; *see also* Erwin A. Blackstone & Joseph P.Fuhr, Jr., *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS: BUS. 469, 471–73 (2013).

[67] *Biosimilar Product Information*, U.S. FOOD & DRUG ADMIN. (last visited Oct. 2, 2025), https://www.fda.gov/drugs/biosimilars/biosimilar-product-information [https://perma.cc/XDG5-6YEW].

[68] ASSOCIATION FOR ACCESSIBLE MEDICINES, THE U.S. GENERIC & BIOSIMILAR MEDICINES SAVINGS REPORT 8–9 (2023), https://accessiblemeds.org/sites/default/files/2023-09/AAM-2023-Generic-Biosimilar-Medicines-Savings-Report-web.pdf [https://perma.cc/NPV6-ANSC]; *see also* Richard G. Frank, Mahnum Shahzad, Aaron S. Kesselheim, & William Feldman, *Biosimilar Competition: Early Learning*, 31 HEALTH ECONOMICS 647, 653 (2022).

[69] Frank, Shahzad, Kesselheim & Feldman, *supra* note [*68] at 653.

[70] ASSOCIATION FOR ACCESSIBLE MEDICINES, *supra* note [*68], at 7, 9.

[71] *Id.* at 27.

[72] *See* Giuliana Grossi, *Prescription Costs and Inflation Drive 2025 Health Insurance Premium Hikes*, AJMC (Aug. 14, 2024) https://www.ajmc.com/view/prescription-costs-and-inflation-drive-2025-health-insurance-premium-hikes [https://perma.cc/8U4E-R4WG] ("Prescription drug spending is outpacing general medical spending, adding upward pressure on health insurance premiums.").

II. ROLE OF PATENTS IN PHARMACEUTICAL INNOVATION: A DRIVER OF INNOVATION OR A TOOL FOR ABUSE?

While a number of factors contribute to the high cost of biologics,[73] patents are thought to play an important role in the level of biologic spending.[74] The purpose of the patent system is to encourage socially valuable investments in research and development that firms would not otherwise make due to the profit-eroding effects of competition.[75] Given the market realities of the pharmaceutical industry—that is, biologic firms must invest close to a billion dollars in clinical trials on their drug before they can be sold to the public, while biosimilar rivals are exempted from those requirements and can enter the market at lower cost—it is easy to see the import of patents to pharmaceutical innovation.[76] Patents enable firms to recoup their research and development expenses of developing a drug by giving firms a twenty-year exclusive right to make, use, and sell their drug, thereby protecting them from the effects of biosimilar competition.[77] After

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[73] Aaron S. Kesselheim, Jerry Avorn & Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 860–62 (2016) (discussing sources of high drug prices in the United States).

[74] *See, e.g.*, *id.* at 861 ("The most important factor that allows manufacturers to set high drug prices for brand-name drugs is market exclusivity. . . ."); I-MAK, OVERPATENTED, OVERPRICED: HOW EXCESSIVE PHARMACEUTICAL PATENTING IS EXTENDING MONOPOLIES AND DRIVING UP DRUG PRICES 11 (2018), https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf [https://perma.cc/KBT2-QDLW] (finding that twelve best selling drugs are associated with hundreds of patent applications which extend their monopolies far beyond twenty years).

[75] WILLIAM D. NORDHAUS, INVENTION, GROWTH, AND WELFARE: A THEORETICAL TREATMENT OF TECHNOLOGICAL CHANGE 76 (1969); Ian Ayres & Gideon Parchomovsky, *Tradable Patent Rights*, 60 STAN. L. REV. 863, 867 (2007); Keith Leffler and Christofer Leffler, *Efficiency Trade-offs in Patent Litigation Settlements: Analysis Gone Astray?*, 39 U.S.F. L. REV. 33, 33 (2004).

[76] For a concise summary of this evidence, *see* F.M. Scherer, *The Political Economy of Patent Policy Reform in the United States*, 7 J. Telecom & High Tech. L. 167, 173–75 (2009). *See also* Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT'L J. TECH. MGMT. 98, 109–17 (2000); Henry G. Grabowski & Margaret Kyle, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, 28 MANAGERIAL & DECISION ECON. 491, 492 (2007). *See also* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1676–77 (2003) (using pharmaceutical development as an example of where the patent system is essential for promoting innovation).

[77] *See* WILLIAM M. LANDES & RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 299–300 (2003); FTC v. Actavis, Inc., 570 U.S. 136, 147 (2013) ("[Patent rights] may permit the patent owner to charge a higher-than-competitive price for the patented product."). The patentability standards reflect a balance between encouraging innovation and avoiding drains on consumer welfare. *See id* at 161. In order for an invention to be patent eligible it must be both new and represent a nontrivial advancement over current scientific understanding. 35 U.S.C. §§ 102–103. If an invention was obvious to the person of ordinary skill in the art or was already in the public domain, the invention would have likely arisen without the patent incentive. In contrast, an invention that represents a significant advancement in the art may not have arisen but for the patent inducement. Michael Abramowicz & John F. Duffy, *The Inducement Standard of Patentability*, 120 YALE L.J. 1590, 1594

the twenty-year patent term expires, biosimilars can enter the market, which drives down drug prices and increases access to life-saving pharmaceuticals.

There is, however, growing concern that the patent system is not working properly.[78] More specifically, pharmaceutical companies may be utilizing—or in more pejorative terms, "gaming"—the patent system to strengthen their monopoly positions to an extent beyond what is necessary to incentivize innovation in the first place. That is, while some of the patents associated with a given drug may characterize patents in their intended form—i.e., are pursued to justify cost recovery for developing a novel innovation—others may be pursued to generate profits beyond that point and to further delay biosimilar competition. Providing the opportunity for patenting activities of both varieties is the fact that pharmaceutical companies do not simply obtain a single patent on a drug product but instead obtain a series of patents on different aspects of a drug.[79]

The first patents associated with a drug are typically filed early in the research phase and often protect a potential active ingredient that forms the basis of the new drug.[80] Patents on the active ingredient of a drug product are referred to as primary patents and are typically the strongest means of protecting a newly invented drug.[81] Later in the drug discovery process, pharmaceutical companies often file patents on peripheral features of the

(2011). For the patent system to function as intended it is also important that the Patent Office not allow too many invalid patents. An invalid patent—i.e. a patent that represents only a trivial advancement over the public domain—would impose the costs of patents on society without providing any innovative benefit.

[78] *See, e.g.*, Maya M. Durvasula & Lisa Larrimore Ouellette, *Beyond the Pharmaceutical Patent Arms Race*, 43 YALE J. REG. (forthcoming 2026) (arguing that it is infeasible to fix the patent system to optimize pharmaceutical innovation and that we should promote pharmaceutical innovation through data exclusivities).

[79] C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327 (2012) ("[O]bservers have identified the increasing acquisition of additional patents by brand-name drug makers . . . in order to delay generic competition.").

[80] Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 539 (2009) ("Pharmaceutical patents are typically filed when drugs are in early preclinical research. . . ."); Harold C. Wegner & Stephen B. Maebius, *The Global Biotech Patent Application*, *in* BIOTECHNOLOGY LAW: BIOTECHNOLOGY PATENTS & BUSINESS STRATEGIES IN THE NEW MILLENNIUM 87, 129–30 (2001); Tahir Amin & Aaron S. Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study of How Patents on Two HIV Drugs Could be Extended for Decades*, 31 HEALTH AFFAIRS 2286, 2286 (2012).

[81] *See* Roin, *supra* note [*80], at 548–49 n.243. Anyone who makes, uses, or sells a product in which the molecule is present infringes the primary patent. 35 U.S.C. § 271 (2018). Although patent law prohibits the patenting of products of nature, many biologics are modifications of products that exist and nature and hence a primary patent may be obtained. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 576 (2013) (holding that isolated, naturally occurring DNA sequences are not patent eligible due to the products of nature exemption from patentable subject matter).

drug.[82] These patents are referred to as secondary patents and offer narrower protection than primary patents.

One such example of a secondary patent is a formulation patent, which typically claims the combination of an active drug ingredient with various inactive ingredients that allow for the delivery of the active ingredient.[83] Some formulations relate to the mode of the administration, such as injections, which are administered by a needle that releases the biologic under the skin, or infusions, in which a needle is used to deliver the drug directly into the vein.[84] Because injections can often be painful, innovations in this area could include new formulations that reduce swelling and irritation at the injection site. Another example of a secondary patent is a method-of-use patent.[85] A method-of-use patent claims a method of using the drug for medical treatment, such as a method for treating cancer by administering an effective amount of biologic A.[86] Yet another example of a secondary patent is a method-of-manufacturing patent, which protects a new way of making the drug.

Taking advantage of this expansive scope of pharmaceutical patent types, pharmaceutical firms have been alleged to engage in at least two controversial patenting practices.[87] The first is critically referred to as "evergreening" and involves a pharmaceutical company seeking to extend its monopoly period by obtaining secondary patents associated with an approved drug product or a slightly modified drug product.[88] In general, patents expire twenty years from filing.[89] Because secondary patents are mostly filed after the active ingredient patent, they expire later and extend the exclusivity period of the drug.[90] As a result, a drug may have a monopoly

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[82] Amin & Kesselheim, *supra* note [*80], at 2286.

[83] JOHN R. THOMAS & CHRISTOPHER HOLMAN, THOMAS AND HOLMAN ON PHARMACEUTICAL PATENT LAW CH. 2, § III.B (2024) (ebook).

[84] *Id.* In contrast to small molecules whose mode of administration is typically oral—i.e., tablet, biologics are normally administered by injection or infusion. Natasa Skalko-Basnet, *Biologics: The Role of Delivery Systems in Improved Therapy*, 8 BIOLOGICS 107, 108 (2014).

[85] THOMAS, *supra* note [83], at ch. 2, § III.I.

[86] *Id.* at ch. 2, § III.J.

[87] *See, e.g.*, Kesselheim, Avorn & Sarpatwari, *supra* note [*73], at 861 ("The most important factor that allows manufacturers to set high drug prices for brand-name drugs is market exclusivity. . . ."); *I-MAK*, OVERPATENTED, OVERPRICED: HOW EXCESSIVE PHARMACEUTICAL PATENTING IS EXTENDING MONOPOLIES AND DRIVING UP DRUG PRICES (2018) (finding that twelve best selling drugs are associated with hundreds of patent applications which extend their monopolies far beyond twenty years).

[88] Aaron S. Kesselheim & Jerry Avron, *Biomedical Patents and the Public's Health: Is There a Role for Eminent Domain*?, 295 J. AM. MEDICAL ASS'N 434, 435 (2006).

[89] 35 U.S.C. § 154(a)(2) (2018).

[90] Brand name pharmaceutical companies cannot indefinitely file and obtain secondary patents for a drug. The greater the length of time between the filing of active ingredient patent and the secondary

period far beyond the twenty-year term associated with the initial patent. Pharmaceutical companies may utilize this extended monopoly to keep biosimilars off the market.

The second controversial patenting strategy is referred to as "patent thickets."[91] Patent thickets refer to pharmaceutical companies obtaining numerous, often overlapping patent rights on a drug.[92] The primary goal of patent thickets is not necessarily to extend the exclusivity period of a drug but instead to protect the drug with a dense web of patents, making it almost impossible for a biosimilar firm to challenge these patents and gain FDA approval before they all expire.[93] Thus, patent thickets work to discourage competitors from entering the market or to make it too costly and risky to do so.

The debates surrounding both patent strategies coalesce around the legitimacy of secondary patents. The normative desirability of secondary pharmaceutical patents has become such an important issue that secondary patents have been the subject of multiple reports by the National Academies and the Federal Trade Commission[94] as well as the target of Congressional reforms that seek to stem the rising costs of prescription medications.[95] As discussed above, some biologics patents may constitute novel innovations and thus result in legitimate extensions of the monopoly term, whereas others may impose artificial barriers that improperly delay biosimilar competition. Commentators are divided over whether the bulk of secondary patents fall on one of these sides or the other. That is, critics of secondary patents argue that such patents are of questionable legal validity, offering only trivial

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patent, the harder it becomes for the pharmaceutical company to obtain the secondary patent. The rules of patentability require that patents be issued only to inventions that are new and represent more than a non-trivial advancement over the current understanding in the field. However, what counts as prior art—the knowledge of the art such as scientific publications—for a patent includes information known before its filing date. As a result, the world of prior art grows for later filed secondary patents, decreasing the likelihood they will meet the patentability standards and be issued by the USPTO.

[91] Michael A. Carrier and Sean S. Tu, *Why Pharmaceutical Patent Thickets are Unique*, 32 TX. INT'L PROP. L.J. 79, 81–83 (2024).

[92] *Id.* at 81.

[93] *Id.* at 101.

[94] MAKING MEDICINES AFFORDABLE, *supra* note [*14], at xxi–xxiv; *see also* FED. TRADE COM., REPORT ON STANDALONE SECTION 5 TO ADDRESS HIGH PHARMACEUTICAL DRUG AND BIOLOGIC PRICES 1 (2019) (highlighting the FTC's broader interest in addressing anticompetitive practices in the pharmaceutical industry); Luke M. Olson & Brett W. Wendling, *The Effect of Generic Drug Competition on Generic Drug Prices During the Hatch-Waxman 180-Day Exclusivity Period* 1 (Bureau of Econ. Fed. Trade Comm'n, Working Paper No. 317, Apr. 2013) (demonstrating the FTC's empirical research into pharmaceutical competition and market dynamics).

[95] TERM Act of 2019, H.R. 3199; REMEDY Act, S. 1209/H.R. 3812; Second Look at Drugs Patents Act of 2019, S. 1617; Affordable Prescriptions for Patients Act of 2019, S. 1416; Orange Book Transparency Act of 2019, H.R. 1529; Biologic Patent Transparency Act, S. 659; Preserve Access to Affordable Generics and Biosimilars Act, S. 1096/H.R. 2374.

modifications over the active ingredient patent, and in many cases should not have been allowed to be issued by the USPTO in the first place.[96] More provocatively, another set of critics argue all secondary patents are illegitimate.[97] These critics contend that the patentability standards are set too low and that each drug product should only be associated with one patent.[98] Accordingly, both sets of critics contend that secondary patents unfairly delay biosimilar entry in the marketplace, keeping drug prices arbitrarily high.[99] Defenders contend that there is nothing inherently dubious about secondary patents, which are subject to the same requirements for patentability as any other patent.[100] Moreover, defenders argue that secondary patents stem from continuous research and development and offer important clinical and therapeutic benefits over the patent on the active ingredient.[101]

III. THE TRANSPARENCY OF PATENTS ASSOCIATED WITH SMALL- AND LARGE-MOLECULE DRUGS

The full extent to which firms engage in these strategic patent practices and their effects on blocking competitors' entry, however, remains unclear.

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[96] Julian W. Marrs, *Forever Green? An Examination of Pharmaceutical Patent Extensions*, 18 OR. REV. INT'L L. 81, 83-89 (2016); Aaron S. Kesselheim, *Think Globally, Prescribe Locally: How Rational Pharmaceutical Policy in the U.S. Can Improve Global Access to Essential Medicines*, 34 AM. J.L. & MED. 125, 136 (2008) ("Loose interpretation of patent laws has permitted patent evergreening, where overly broad or otherwise inappropriate patents have been granted on peripheral aspects of pharmaceutical products . . ."); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 354 (2007) (noting that although "innovating firms have succeeded in getting [secondary] patents issued by the PTO . . . [t]he industry's track record in actually winning these infringement claims . . . has been considerably worse"); Hemphill & Sampat, *supra* note [*79], at 328–29.

[97] Feldman, *supra* note [*36].

[98] *Id.*

[99] *Id.*

[100] *See, e.g. GSK Public Policy Positions: Evergreening*, GLAXOSMITHKLINE (January 2014), at 1, https://us.gsk.com/media/v0hpvdgu/evergreening-policy.pdf [https://perma.cc/GH6R-HLVM] ("Patents for improvements to existing products, in the field of pharmaceutical and other technologies, are only available if they meet the requirements of patentability (i.e., that they are new, useful and involve an inventive step) as assessed by trained patent examiners."); Christopher M. Holman, Timo Minssen & Eric M. Solovy, *Patentability Standards for Follow-On Pharmaceutical Innovation*, 37 BIOTECH. L. REPORT 131, 132 (2018); Christopher M. Holman, *In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination*, 50 IND. L. REV. 759, 761 (2017) (critiquing UN guidelines advising patent offices to apply heightened patentability requirements to secondary pharmaceutical patent applications); Christopher M. Holman, *Congress Should Decline Ill-Advised Legislative Proposals Aimed at Evergreening of Pharmaceutical Patent Protection*, 51 U. PAC. L. REV. 493, 496 (2020) (arguing that legislative proposals addressing evergreening should focus on misuse of patents, rather than secondary patents).

[101] *See* GLAXOSMITHKLINE, *supra* note [*100], at 3; Holman, *Patentability Standards*, *supra* note [*100], at 135; Holman, *In Defense of Secondary Pharmaceutical Standards, supra* note [*100], at 782.

As this part illustrates, while U.S. law mandates the disclosure of patents associated with FDA-approved small-molecule drugs, it does not do so for biologics. As a result, much of what we know about the drug-patent landscape is based on research of small-molecule drugs. We know virtually nothing about the patenting landscape of large-molecule drugs, even though these drugs increasingly make up an increasing portion of U.S. prescription drug spending. This Part begins by explaining how the law encourages transparency of patent rights associated with small-molecule drugs and does not with respect to biologics. This Part also summarizes what we know about the small-molecule patent landscape for both patent thicketing and patent evergreening.

A. Transparency of Patents Associated with Small-Molecules Drugs

The Hatch-Waxman Act, which governs competition between small-molecule brands and generic pharmaceutical companies, establishes a high degree of transparency of patent rights as part of the small-molecule approval process.[102] When a brand-name pharmaceutical company submits a new drug application for a small-molecule drug, it is required to provide the FDA with a list of patents that would be infringed if a generic is launched before the expiration of those patents.[103] The FDA is required to keep a public record of the patent rights associated with approved small-molecule drugs.[104] The FDA publishes this record of patent rights in a publication that is commonly known as the Orange Book.[105]

The Hatch-Waxman Act also created an abbreviated pathway for generics. Generics do not have to replicate the clinical trials of brand-name small-molecule drugs but can rely on the safety and efficacy data presented by the brand-name company and simply demonstrate that their product is bioequivalent to the small-molecule drug.[106] When a generic manufacturer submits an Abbreviated New Drug Application (ANDA), it must engage in

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[102] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1585–92 (1984). The statute's goal is two-fold: to incentivize drug innovation through the protection of patent rights of brand-name drug manufacturers while facilitating earlier generic entry to ensure the access of these medicines at reasonable prices. H.R. REP. NO. 98-857(1), at 14–15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647–48.

[103] 21 C.F.R. § 314.53(b) (2021). If the brand name pharmaceutical company obtains additional patents after this initial disclosure, then the company must inform the FDA of these new patents within thirty days of issuance. 21 U.S.C. § 355(c)(2) (2018); 21 C.F.R. § 314.53(c)(ii)(T)(4)(d).

[104] 21 U.S.C. § 355(j)(7)(A)(iii).

[105] OFFICE OF GENERIC DRUGS, FDA, ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book [https://perma.cc/3RJZ-TYW3].

[106] 21 U.S.C. § 355(j)(2)(A)(iv).

a specialized certification process for each Orange Book-listed patent for the drug product in question if they want to enter the market.[107] Orange Book-listed patents affect when the FDA can approve a generic. Depending upon the generic's choice of certification, the FDA can either approve the generic after the Orange Book-listed patents expire or after a thirty-month stay during which the generic and brand engage in specialized patent dispute procedures, which often result in litigation.[108]

Given the important role that Orange Book-listed patents play in the approval of generics, clarification was needed regarding which type of patents could be listed in the Orange Book. The FDA promulgated regulations that require brand-name pharmaceuticals to list patents that claim the active ingredients, drugs products, or methods-of-use that would be infringed if a generic is launched in the Orange Book.[109] Congress codified FDA regulations of Orange Book-listed patents in 2020 with the passage of the Orange Book Transparency Act.[110]

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[107] 21 U.S.C. § 355(j)(2)(A)(vii)(I)–(IV). In particular, the generic applicant must provide one of four certifications under the following paragraphs: (I) there is no patent information listed; (II) the patent has expired; (III) the date the patent will expire; or (IV) the patent is invalid and/or not infringed by the generic applicant. *Id.* There is a narrow exception to this certification process. With respect to patents that claim a method of using a drug, the generic applicant may file a "section viii" statement when seeking approval only for a use that is not claimed in the listed patent. 21 U.S.C § 355(j)(2)(A)(viii). Paragraph (I) and (II) certifications do not affect FDA's ability to approve the generic drug. 21 U.S.C. § 355(j)(5)(B)(i).

[108] 21 U.S.C. § 355(j)(5)(B)(i)–(iii). If the generic applicant makes a Paragraph (III) certification, however, FDA may not approve the generic version of the drug until the patent at issue has expired. 21 U.S.C. § 355(j)(5)(B)(ii). A Paragraph (IV) certification triggers the Hatch-Waxman's specialized patent dispute procedures, which often results in litigation. Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S, 566 U.S. 399, 407 (2012). The generic applicant must give notice of its intent to market the drug and the Paragraph (IV) certification to the patentee and brand-name manufacturer. 21 U.S.C. § 355(j)(2)(B)(i)–(iv). The patent holder then has forty-five days to sue the generic applicant. 21 U.S.C. § 355(j)(5)(B)(iii) . If the brand-name manufacturer sues, the FDA cannot approve the generic for up to thirty months while the parties litigate the patent dispute—even if the patent listed in the Orange Book is likely invalid. 21 U.S.C. § 355(j)(5)(B)(iii). Finally, as an incentive for a generic to enter the market, Hatch-Waxman also provides 180 days of marketing exclusivity to the first generic to make a Paragraph (IV) certification. 21 U.S.C. § 355(j)(5)(B)(iv)(I).

[109] 21 C.F.R. § 314.53(b).

[110] Orange Book Transparency Act, Pub. L. No. 116-290, 134 Stat. 4889, 4889–93 (2021).

However, the FDA has taken the position that it plays only a "ministerial role" in listing patents in the Orange Book. Rebecca S. Eisenberg & Daniel A. Crane, *Patent Punting: How FDA and Antitrust Courts Undermine the Hatch-Waxman Act to Avoid Dealing with Patents*, 21 MICH. TELECOMM. & TECH. L. REV. 197, 200 (2015). That is, the FDA generally defers to judgement of pharmaceutical firm that a patent meets the listing requirements rather than conducting its own independent analysis. *Id.* This void in administrative oversight has enabled brand name pharmaceutical companies to list patents in the Orange Book that do not claim an approved method of use, the active ingredient or drug product. *Id.* at 218–19. The only way for a generic manufacturer to remove an improperly listed patent from the Orange Book is to go to court, which delays generic entry and reduces patient access to more affordable

It is undeniable the Orange Book has resulted in a rich database of patents associated with small-molecule drugs. As discussed in the next section, researchers have extensively relied upon Orange Book-listed patents to study the patenting practices of small-molecule drug manufacturers.

B. Patenting Landscape of Small-Molecule Drugs

Much of what we know about the patenting behavior of brand-name pharmaceutical companies with respect to small-molecule drugs stems from the patent data in the Orange Book.[111] This subpart provides a sample of studies that used Orange Book patent data to examine both patent thicketing and evergreening. This subpart is not meant to be an exhaustive survey of studies examining the patenting behavior of small-molecule firms, but instead to provide an illustrative sample of such studies.

There is some evidence of both patent thicketing and patent evergreening in the small-molecule drug market. Several studies have examined the number and type of patents listed in the Orange Book for small-molecule drugs.[112] For example, there are, on average, about three to four patents listed for each drug product registered in the Orange Book.[113]

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prescription drugs. FED. TRADE COMM'N, FEDERAL TRADE COMMISSION STATEMENT CONCERNING BRAND DRUG MANUFACTURERS' IMPROPER LISTING OF PATENTS IN THE ORANGE BOOK, 4, https://www.ftc.gov/system/files/ftc_gov/pdf/p239900orangebookpolicystatement092023.pdf [https://perma.cc/7Z6K-WFAX]. Concerns over the improper listing of patents in the Orange Book spurred the Federal Trade Commission (FTC) to issue a policy statement in September 2023 announcing an evaluation of whether improper Orange Book listing "may constitute an unfair method of competition in violation of Section 5 of the FTC Act." *Id.* at 3. A few months later, the FTC sent letters to pharmaceutical manufacturers identifying more than 100 patents the agency believed were improperly listed in the Orange Book. Fed. Trade Comm'n, *FTC Challenges More Than 100 Patents as Improperly Listed in the FDA's Orange Book*, (Nov. 7, 2023), https://www.ftc.gov/news-events/news/press-releases/2023/11/ftc-challenges-more-100-patents-improperly-listed-fdas-orange-book [https://perma.cc/JFJ7-7WYV].

[111] Heidi Williams digitized the Orange Book patent and exclusivity data and published the database on the NBER website. Maya Durvasula, C. Scott Hemphill, Lisa Larrimore Ouellette, Bhaven N. Sampat & Heidi L, Williams, *The NBER Orange Book Dataset: A User's Guide* 3–5(Nat'l Bureau of Econ. Rsch., Working Paper No. 30628, 2023).

[112] *See, e.g.*, Amy Kapczynski, Chan Park, and Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PLOS ONE 1 (2012) (examining 1,304 patents listed in the Orange Book for the 528 new molecular entities approved by the FDA between 1988 and 2005); Lisa Larrimore Ouellette, Note, *How Many Patents Does It Take to Make a Drug? Follow-on Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299 (2010) (examining patents listed in the Orange Book for the 938 new drug applications approved by the FDA from 1988 to 2005); Robin Feldman, *May Your Drug Price Be Evergreen,* 5 J.L. & BIOSCIENCES 590 (2018) (examining patents listed in the Orange Book for all 3,372 new drug applications between 2005 and 2015).

[113] Hemphill & Sampat, *supra* note [*32], at 619–20. *See* Ouellette, *supra* note [*112], at 314 (finding, on average, 2.97 patents listed per drug product listed in the Orange Book); *see also infra* note 182 and accompanying text (we find that on average 3.8 patents listed per drug listed in the Orange Book).

Scott Hemphill and Bhaven Sampat have found that the number of patents listed for a drug has been increasing over time.[114] Moreover, several studies have demonstrated that there is substantial heterogeneity in the number of patents listed per drug and that a small-molecule drug is more likely to have a secondary patent listed than an active ingredient patent.[115]

Other studies have examined whether secondary patents are of lower quality and hence less likely to be valid than primary patents, a concern that critics of secondary patents have expressed.[116] Scott Hemphill and Bhaven Sampat utilized court outcomes as a validity marker for pharmaceutical patents. Hemphill and Sampat found that secondary patents which are litigated to finality are far more likely to be invalidated than primary patents.[117] Michael Frakes and Melissa Wasserman utilized another marker of validity by focusing on U.S.-issued patents whose underlying innovations were also the subject of patent applications at the European Patent Office (EPO), a patent office with substantially similar patentability standards to that of the U.S.[118] Frakes and Wasserman use the allowance outcome at the EPO as a benchmark to assess the allowance outcome at the USPTO.[119] In doing so, Frakes and Wasserman likewise find evidence that active ingredient patents are of stronger validity than secondary patents, although their findings also suggest that much of secondary patenting activity reflects meaningful underlying innovation.[120] These studies show that secondary patents are, on average, lower quality than primary patents, suggesting that at least some secondary patent activity may unnecessarily delay generic entry.

Taken together, these results suggest that to the extent patent thickets are a problem in the small-molecule market, they may be more localized to the most profitable drugs and not widespread within the small-molecule drug market. Because each small-molecule drug has, on average, less than 4 patents listed in the Orange Book, a generic pharmaceutical company should be able to litigate and invalidate these patents if they are of low quality and

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[114] Hemphill & Sampat, *supra* note [*113], at 619–20.

[115] Kapczynski, Park & Sampat, *supra* note [*112]; Ouellette, *supra* note [*112], at 314.

[116] *See* Carrier & Tu, *supra* note [*91], at 110.

[117] C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life in Pharmaceuticals*, 31 J. HEALTH ECON. 327, 328 (2012) ("Later issued, later expiring patents tend to be weaker, in the sense that a court is less likely to conclude that they are valid and infringed by a competing generic product.").

[118] Michael D. Frakes & Melissa F. Wasserman, *Investing in Ex Ante Regulation: Evidence from Pharmaceutical Patent Examination*, 15 AM. ECONOMIC J.: ECONOMIC POL'Y 151, 158–59 (2023).

[119] *Id.* at 159.

[120] *Id.*

hence enter the market.[121] Nevertheless, it is important to keep in mind that even a small delay in generic entry may result in substantial welfare loss to the public, as brand-name drugs are typically priced substantially higher than generic drugs.

What evidence do we see for patent evergreening? On average, a secondary patent adds six to seven years of patent life to an approved drug.[122] There is also evidence that pharmaceutical companies obtain more secondary patents for more profitable drugs.[123] These results suggest that firms routinely obtain secondary patents and utilize secondary patents to extend their monopoly period of the drug. Still, other studies have examined the effective market life of pharmaceutical drugs—that is, the exclusivity period a brand-name drug enjoys before it faces generic competition.[124] These studies help probe how effective secondary patents have been over time at elongating the exclusivity period of drugs. Hemphill and Sampat find that while the number of patents per drug product is increasing, so too are litigation challenges to secondary patents.[125] Challenges to secondary patents are more common for higher-sales drugs and focus on later-filed and lower quality patents.[126] Importantly, these studies find that the effective market life—the time period that a small-molecule drug does not face generic competition—is stable across drug sales categories and has hardly changed over the previous decade.[127] As a result, they conclude that secondary patent

[121] Other studies have examined whether secondary patents are of lower quality and hence less likely to be valid than primary patents, a concern that critics of secondary patents have expressed. Scott Hemphill and Bhaven Sampat utilized court outcomes as a validity marker for pharmaceutical patents. Hemphill and Sampat find that secondary patents that are litigated to finality are far more likely to be invalidated than primary patents that are litigated to finality. Hemphill & Sampat, *supra* note [*117], at 328 ("Later issued, later expiring patents tend to be weaker, in the sense that a court is less likely to conclude that they are valid and infringed by a competing generic product."). Michael Frakes and Melissa Wasserman utilized another marker of validity by focusing on U.S-issued patents whose underlying innovations were also the subject of patent applications at the European Patent Office (EPO), a Patent Office with essentially similar patentability standards to that of the U.S. Frakes & Wasserman, *supra* note [*118]. Frakes and Wasserman use the allowance outcome at the EPO as a benchmark to assess what the allowance outcome at the USPTO. In other words, Frakes and Wasserman treat a U.S. issued Orange Book patent as valid if its "twin" application is allowed at the EPO. Doing so Frakes and Wasserman likewise find evidence that active ingredient patents are of stronger validity than secondary patents, although their findings also suggest that much of secondary patenting activity reflects meaningful underlying innovation. *Id.* These studies suggest that secondary patents are on average, lower quality than primary patents, suggesting that at least some secondary patent activity may be unnecessarily delaying generic and biosimilar entry.

[122] Kapczynski, Park & Sampat, *supra* note [*112], at 7 tbl. 3.

[123] *Id.* at 5.

[124] Hemphill & Sampat, *supra* note [*117], at 327.

[125] *Id.* at 327–31.

[126] *Id.* at 327–30.

[127] *Id.* at 336.

"challenges serve to maintain, not reduce, the historical baseline of effective market life, thereby limiting the effectiveness of 'evergreening' by branded firms,"[128] though not without the substantial expense of litigating and invalidating patents.

C. Transparency of Patents Associated with Biologics

Congress chose to take a different approach to the transparency of patent rights associated with biologics. While an abbreviated pathway for generics of small molecules has been in effect since 1984, it was not until 2010, with the passage of the Biologics Price Competition and Innovation Act (BPCIA), that the FDA was empowered to develop an abbreviated pathway to approve biosimilars.[129] In contrast to the Hatch-Waxman Act, the BPCIA neither links FDA approval of biosimilars to the patent rights associated with biologics nor does it require biologic companies to provide patent information to the FDA upon the filing of a license application.[130] Instead, patent rights are disclosed as part of a complicated sequence of negotiations between the biologic companies and the biosimilar companies known as "the patent dance" and only if the biosimilar agrees to participate in this exchange of patent rights.[131]

If the biosimilar sponsor wants to obtain patent information from the biologic manufacturer, then after filing its application with the FDA, the biosimilar applicant transmits a copy of the application and other

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[128] *Id.* at 327. There are also a handful of studies that have utilized sophisticated empirical methodologies that enable causal inferences to be drawn from observational data. One such example is the work of Frakes and Wasserman, who explore whether increasing the resources to the Patent Office would result in the Agency issuing fewer invalid secondary pharmaceutical patents. *See* Frakes & Wasserman, *supra note* [*118], at 151. Because patent applications are presumed valid when filed, a patent examiner who does not have enough time to find and articulate a basis to reject the application, may be forced to allow legally invalid patent. *Id.* at 152. Invalid pharmaceutical patents may illegitimately delay generic entry and limit the public access to lower cost drugs. Frakes and Wasserman found that a fifty percent increase in the time given a patent examiners to review patent applications would result in a 12.8 percentage point decrease in the number of invalid secondary pharmaceutical patents being issued. *Id.* at 174. They also estimated this would lead to a whopping seventeen years of earlier generic entry across the small-molecule marketplace which would be result in consumer savings of between $2.53 billion and $5.28 billion per year from lower prices and increased access to drugs. *Id*. at 174–76.

[129] Biologics Price Competition and Innovation Act, Pub. L. No. 111-148, § 7001, 124 Stat. 119, 804 (2010). There are two paths to negotiate this early litigation subset. First, the parties can reach an agreement within 15 days of exchanging legal positions on which patents should be litigated, the resulting list of patents is called the "4A" list. 42 U.S.C. § 262 (l)(4)(A)–(B) (2010). Second, the parties may unilaterally declare lists of patents to be litigated, based on a procedure specified in the law. This resulting list of patents is called the "5B" list. 42 U.S.C. § 262(l)(5)(B).

[130] *See* Eva A. Temkin, Vanessa Y, Yen, Evan D. Diamond & Christina M. Markus, "*Purple Book" Patent Listing Under Biological Product Patent Transparency Act: What is Required, and What to Expect?*, 33 IP & TECH. L.J. 1, 1 (2021).

[131] *Id.* at 1–2. *See also* Sandoz Inc. v. Amgen Inc., 582 U.S. 1, 14–15 (2017).

manufacturing data to the biologic manufacturer.[132] The biologic manufacturer in turn provides a list of patents known as the "3A" list,[133] which identifies the specific patents that the biologic firm believes may be infringed by the biosimilar if approved and marketed.[134] But it was not until the passage of the Biological Product Patent Transparency Act (BPPT) in 2020 that these patent lists were required to be submitted to the FDA.[135] And it was not until June 25, 2021, that the FDA was required to make these patent lists public.[136] The FDA now publishes the patent rights associated with a biologic in a publication that is commonly known as the Purple Book—an analog to the Orange Book.

The BPPT and BPCIA arguably fall short on several important dimensions regarding the transparency of patent rights associated with biologics. First is the elective nature of the patent exchange process. While the Hatch-Waxman Act mandates the disclosure of patent rights at the time of a new drug application,[137] in the biologic arena patent rights are only disclosed if the biosimilar rights holder agrees to participate in the patent dance.[138] However, a biosimilar company may opt out of the patent dance for a host of reasons, including if they feel confident that the company can successfully navigate relevant patents without disclosing key manufacturing details to the biologic firm—a requirement of the patent dance.[139] Second is the timing of the patent disclosure. The Hatch-Waxman Act requires brand name drugs to disclose their patent rights at the time of filing a new drug

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[132] 42 U.S.C. § 262(l)(2)(A).

[133] 42 U.S.C. § § 262(l)(3)(A). The sponsor must update this list if new patents issue thereafter. 42 U.S.C. § 262(l)(7).

[134] Based on the production of the 3A list, the biosimilar applicant and the reference product sponsor exchange their legal analyses of the patents identified and negotiate a subset of the 3A list for early litigation. 42 U.S.C. § 262(l)(4)(A)–(B).

[135] Biological Product Patent Transparency Act, Pub. L. No. 116-260, div. BB, § 325, 134 Stat. 2936–37 (2020). The core language of the BPPT was originally introduced to the House in March 2019 as the "Purple Book Continuity Act" (H.R. 1520, 116th Congress), before it was placed in the year-end omnibus bill.

[136] BPPT took effect on this date..

[137] 21 U.S.C. § 355(b) (2018).

[138] Yun Dong, *Keep on Dancing: The Success and Failures of Patent Dance as Shown by BPCIA Litigation Cases Filed after* Sandox v. Amgen, 83 U. PITT. L. REV. ONLINE 1, 11–12 (2022) (examining 19 patent infringement lawsuits and finding that 3 biosimilar applicants opted out of the patent dance completely, 4 biosimilar applicants terminated the patent dance after the first stage, and that the rest largely failed to comply with all the procedures provided by the BPCIA).

[139] Stuart Watt, Emily Johnson & Raymond Doss, *Response to 'The Puzzle Of Biologics Manufacturing Platforms Patents,'* 43 NATURE BIOTECHNOLOGY 1227, 1228 (2025) (noting that "many biosimilar manufacturers choose not to participate in the 'patent dance'"); Dong, *supra* note [*138], at 13 (finding disputes over the exchange of the biosimilar's manufacturing processing information during the patent dance).

application.[140] As a result, generic manufacturers know the landscape of relevant patents before deciding to invest in their own version of the drug. In contrast, the biologic firm must only provide patent information to the FDA for listing in the Purple Book after it engages in the patent dance with a biosimilar.[141] Thus, the manufacturer of a biosimilar has to make decisions as to whether to invest in developing its own version of the drug without fully understanding the patent landscape associated with the biologic. Third is the scope of disclosure. The biologic firm does not need to disclose all the patents that cover its product, as is required in the small-molecule regime, but only those that it believes will be infringed by the *specific* biosimilar. A biologic manufacturer might assert a different set of patents against another follow-on biosimilar. Ropka and Mathias found that a survey of previous BPCIA litigation shows that biologic manufacturers can and do assert different patents against different follow-on biosimilars.[142]

Given these realities, it is not surprising that there is a growing understanding that the Purple Book largely fails to provide meaningful information about the patent rights of biologics.[143] We find that the Purple Book contains less than 425 patents, which is less than 4% of all patents associated with FDA approved biologics.[144]

D. Empirical Studies on the Biologics Patent Landscape

In contrast to the small-molecule drugs, we know very little about the patent landscape associated with biologics. As previewed above and as demonstrated by the empirical analysis in Part IV, the Purple Book contains only a tiny fraction of the relevant patents associated with large-molecule drugs. Moreover, there is reason to suspect that biologics may be associated with greater evergreening and thicketing practices given that the complexity

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[140] 21 U.S.C. § 355(b).

[141] 42 U.S. Code § 262(k)(9)(iii) (2018).

[142] Stacie Ropka & Ted Mathias, *Opinion: Purple Book Patent Listings Are Only a First Step*, THE CENTER FOR BIOSIMILARS (May 8, 2021), https://www.centerforbiosimilars.com/view/opinion-purple-book-patent-listings-are-only-a-first-step [https://perma.cc/ZP89-57V9].

[143] Robin Feldman & Gideon Schor, *Purple is the New Orange: A Comparison of Competitive Information (?) in Generic and Biologics*, 2024 U. ILL. L. REV. 1075, 1113 (2024) (noting that "the Purple Book fails to provide more than a minimal amount of information on the patents and exclusivities held in relation to biologic medicines"); Sean Tu, Aaron Kesselheim, & Bernard Chao, *Extent of Drug Patents with Terminal Disclaimers and Obviousness-Type Double Patenting Rejections*, 332 JAMA 837, 837 (2024) ("Limitations include that for biologics, this study examined only patents listed in the Purple Book, which does not include most currently marketed biologic drugs.").

[144] *Purple Book Database of Licensed Biological Products*, U.S. FOOD & DRUG ADMIN., https://purplebooksearch.fda.gov/patent-list (last updated June 11, 2025). [https://perma.cc/E9GW-9N25]. *See* infra Part V.

associated with manufacturing and delivering biologics brings with it the greater potential for secondary patenting.

Mapping the patent rights associated with large-molecule drugs is complex and both resource and time-intensive. Identifying the patent rights associated with FDA-approved biologics requires a team with a specific and unique skill set that is rarely available to create a non-proprietary database.[145] Identifying all the patents on a specific drug requires access to costly subscription patent databases and individuals skilled in patent informatics and patent searching. Highly skilled scientists and patent attorneys must analyze each of the hundreds to thousands of patents identified for possible relevancy.

As a result, only a handful of studies have examined the patenting behavior of the manufacturers of large molecule drugs. None of these studies have examined a substantial portion of approved biologics but have instead focused on a very small number of large-molecule drugs. Perhaps the most high-profile public database of patents associated with biologics is maintained by the Initiative for Medicines, Access & Knowledge (I-MAK).[146] I-MAK has disclosed patent information for the top-ten selling drugs, of which 6 are biologics.[147] Horrow and coauthors provide the most in-depth analysis of I-MAK's database on the top 6 selling large-molecule drugs, which include Humira, Keytruda, Stelara, Eylea, Trulicity, and Enbrel.[148] Horrow and coauthors find that 463 patents are associated with these 6 biologics and they report evidence of extensive patent thickets.[149] While the top 6 selling biologics were associated with a median of 8 patents when initially approved by the FDA, the number of patents associated with these blockbuster large-molecule drugs peaked at 41 approximately 13 years after FDA approval.[150] Moreover, Horrow and coauthors find that approximately a quarter of the patents are active-ingredient patents and the

[145] We spoke with several individuals while building our biologics patent database who were working on aspects of an biologics patents database but for commercial purposes only—there was no intention to make the database publicly available.

[146] *The Drug Patent Book*, I-MAK, https://drugpatentbook.i-mak.org/ (last visited Sept. 28, 2025). [https://perma.cc/RJ93-PWM2]

[147] *Overpatented, Overpriced: Curbing Patent Abuse: Tackling the Root of the Drug Pricing Crisis*, I-MAK 2 (Sept. 2022), https://www.i-mak.org/wp-content/uploads/2022/09/Overpatented-Overpriced-2022-FINAL.pdf. [https://perma.cc/S4NU-H8RR]

[148] Caroline Horrow, Sarah M. E. Gabriele, S. Sean Tu, Ameet Sarpatwari & Aaron S. Kesselheim, *Patent Portfolios Protecting 10 Top-Selling Prescription Drugs*, 184 JAMA INTERNAL MED. 810, 812 (2024).

[149] *Id.* at 814.

[150] *Id.*

remaining three-quarters are secondary patents.[151] They conclude that there are substantial patent thickets with these top-selling drugs.[152]

While this study is illuminating, Horrow and coauthors acknowledge that their results are likely not generalizable to all large-molecule drugs.[153] That is, the patenting profiles of top-selling drugs likely differ from that of the average drug.[154] Moreover, we found that the I-MAK database of patents includes a number of patents that would not necessarily be infringed by the launch of a biosimilar, such as method-of-use patents of non-approved indications, which suggests the database is overinclusive to study the effects of biosimilar entry.[155]

Alternatively, scholars have utilized patent data disclosed in the Purple Book or focused solely on patents that have been litigated in the biologics space to begin to understand the patenting behavior of biologics firms.[156] Again, these studies provide insight into patenting practices of biologics, but they include at most a few hundred patents. The dearth of patent data included in the Purple Book and the fact that litigated patents differ from

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[151] *See id.* at 811.

[152] *Id.* at 816.

[153] *Id.* at 815–16.

[154] There is evidence that firms obtain more patents for more profitable small molecule drugs. Kapczynski, Park & Sampat, *supra* note [*112], at 5.

[155] Given the saliency of drug prices, it is not too surprising that I-MAK's patent database has been scrutinized. Most prominently, Adam Mosoff has critiqued I-MAK's patent database on reliability and accuracy grounds. *See* ADAM MOSSOFF, HUDSON INST., UNRELIABLE DATA HAVE INFECTED THE POLICY DEBATES OVER DRUG PATENTS 2–3 (2022), https://s3.amazonaws.com/media.hudson.org/Mossoff_Unreliable%20Data%20Have%20Infected%20the%20Policy%20Debates%20Over%20Drug%20Patents.pdf. [https://perma.cc/SH57-8KY4]. Adam Mossoff's critique spurred Senator Thom Tillis (R-NC) to write to I-MAK requesting more information about its data and methodology. Letter from Thom Tillis, Ranking Member, U.S. Senate, to Tahir Amin, Co-Founder and Co-Exec. Dir., I-MAK (Jan. 31, 2022), https://ipwatchdog.com/wp-content/uploads/2022/02/1.31.2022-LTR-from-Senator-Tillis-to-IMAK-re-Patent-Data-Sources.pdf. [https://perma.cc/42YY-NQJZ]. I-MAK responded that its methodology was "clearly explained in the Methodology section" of its report and that it "stands by its findings." Letter from Tahir Amin, Co-Founder and Co-Exec. Dir., I-MAK, to Thom Tillis, Ranking Member, U.S. Senate (Mar. 9, 2022), https://www.i-mak.org/wp-content/uploads/2022/03/Letter-to-Senator-Tillis-re-I-MAK-Patent-Data-9-March-2022-1.pdf. [https://perma.cc/YAS8-MREN]

[156] *See, e.g.*, Tu, Kesselheim & Chao, *supra* note [*143], at 837 (analyzing the 240 patents listed in the Purple Book to calculate the percentage of biologics patents associated with a terminal disclaimer); S. Sean Tu, Rachel Goode & William B. Feldman, *Biologic Patent Thickets and Terminal Disclaimers*, 331 JAMA 355, 355 (2023) (analyzing the 271 patents they identified in biologics litigation to calculate the percentage of biologic patents associated with a terminal disclaimer). *See also* Rachel Goode & Bernard Chao, *Biological Patent Thickets and Delayed Access to Biosimilars, an American Problem*, 9 J. L. & BIOSCIENCES 1, 4 (2022) (studying litigated patents associated with Humira in United States, Canada, and United Kingdom, and finding that later market entry in the United States correlates with the larger number of patents and a larger number of non-patently distinct patents linked together by terminal disclaimers).

patents more generally substantially limit the generalizability of their findings.[157]

Given these shortcomings, developing a robust database of patents associated with the majority of large-molecule drugs is of critical import. There is growing concern associated with the rising prices of prescription drugs, which is increasingly being driven by biologics. Patents are thought to play a key role in explaining this level of spending, offering firms the potential to exclude competitors from the market. Policymakers have set forth a number of policy proposals that aim at increasing biosimilar competition by targeting patent thickets.[158] However, policymakers cannot make informed decisions about improving the prescription drug market and possibly lowering prescription drug prices without first understanding the patenting practices of manufacturers of biologics and how effective patents are at keeping biosimilars off the market.[159]

IV. BIOLOGICS PATENT DATABASE

This section outlines the methods utilized to build the first comprehensive patent database associated with FDA-approved biologics. We obtained funding to build the database and conduct research on the patenting practices of biologic firms from the National Institutes of Health.[160] Our database of patent rights associated with biologics will be publicly available and housed by the National Bureau of Economic Research.

A. Methods

Comprehensive patent landscaping was conducted between November 2023 and January 2025 to identify granted patents (currently active and expired) and patent applications (currently pending and abandoned) associated with all 515 FDA biologics licensed and approved by the FDA as of January 2025. Given that innovation incentives and markets differ

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[157] *See* John R. Allison, Mark A. Lemley, Kimberly A. Moore & R. Derek Trunkey, *Valuable Patents*, 92 GEO. L. J. 435, 437–38 (2004) (finding that litigated patents differ from non-litigated patents on a number dimensions, including litigated patents tend to be owned by domestic rather than foreign companies, litigated patents tend to be issued to individuals or small companies, not to large companies; litigated patents cite more prior art than non-litigated patents, etc.).

[158] *See infra* Part VII.

[159] Transparency of patent rights associated with biologics may also encourage more biosimilar entry. If biosimilar manufacturers know what patents are associated with a biologic ahead of time, they can make better informed decisions about biosimilar launch, which could spur more biosimilars entering the market.

[160] *Impacts of Enhanced Drug Examination,* Nat'l Inst. of Health, Nat'l Inst. on Aging, (Jan. 23, 2025), https://reporter.nih.gov/search/_kRJaWHJ0EyPaZxPIq5Kow/project-details/11019760 [https://perma.cc/62WG-KVVP] .

considerably between preventives and treatments,[161] we focus our analysis on therapeutic biological drugs and exclude vaccines from the study. Before discussing the search steps that we took to construct the biologics patent database, we first address the theoretical foundations underlying its scope.

1. Inclusion Criteria

To select the patents to include in our biologics patent database, we utilize the following criterion: we include patents and patent applications that would likely be infringed if a biosimilar were launched (assuming the patent application matriculated into an issued patent) to compete with the focal drug product. With this framing of the database, we characterize biologics patent portfolios in a manner reflective of their competitive blocking potential. We wish to avoid taking a broader framing of the inclusion criterion as doing so might overstate the degree of market interference actually threatened by biologics patent portfolios.

Consider the following examples to help flesh out our inclusion criteria. A biologic, Drug Alpha, is FDA approved to treat breast cancer and is marketed by Firm Omega. Moreover, consider a U.S. Patent '100, which is assigned to Firm Omega and which claims a method of treating breast cancer by administering an effective amount of Drug Alpha. The claims of a patent define the scope of the invention and hence define what the patent does and does not cover. Assume Firm Gamma seeks approval of a Biosimilar of Drug Alpha to treat breast cancer. The FDA may grant Firm Gamma the approval to enter the market with its Biosimilar of Drug Alpha and compete against Firm Omega's Drug Alpha; however, Firm Omega may attempt to block this entry by asserting its U.S. Patent '100 against Firm Gamma. This patent will be included in our sample as it may meaningfully block biosimilar entry.

In contrast, now assume Firm Omega receives U.S. Patent '200 which claims a method of treating Alzheimer's disease by administering an effective amount of Drug Alpha. The FDA has only approved Drug Alpha to treat breast cancer and has not approved Drug Alpha to treat Alzheimer's disease. The approval and entry of Biosimilar of Drug Alpha to treat breast cancer will not be blocked in any way by this new patent. The FDA will also not approve Biosimilars of Drug Alpha to treat any other indications until Drug Alpha itself has been approved for such other indications. Because of this, there is no possible biosimilar that has relevance to Patent '200. Accordingly, the inclusion criterion fails, and this patent would not be included in our database.

[161] Michael Kremer & Christopher M. Snyder, *Preventives Versus Treatments*, 130 Q. J. ECON. 1167, 1168 (2015).

Because our inclusion criterion was designed to include those biologics patents that may meaningfully forestall competition, we include only patents that are specifically relevant to biosimilar infringement. If the FDA had only approved the biologic drug alone, we did not include combination patents that claimed an FDA-approved biologic and another chemical compound, as this patent would not be infringed by the launch of a biosimilar. As the above examples illustrate, method-of-treatment patents for the biologic were only included if the claimed treatment was for an FDA approved indication. Likewise, if a biologic was only approved with a certain route of delivery (i.e. topical, intravenously, etc.) then patents were omitted if they claimed an FDA-approved biologic to a non-FDA approved route of delivery.[162] We emphasize that our decisions here track those taken by Congress in calling for the construction of the Orange Book in the small-molecule context, of course substituting "[generic] patents . . .[for] which . . . a claim of . . . infringement could reasonably be asserted" with "patents likely to be infringed by biosimilar entry."[163]

2. Search Process

The methodology and resources used to build the patent landscape for each drug included the following steps: (1) identifying patents listed in the Purple Book; (2) where applicable and publicly available, identifying patents asserted in litigation in the United States in relation to the biologic; (3) where applicable and publicly available, identifying patents asserted in Patent Trial and Appeal Board (PTAB) proceedings relating to the biologic; (4) identifying patents that received a patent term extension under 35 U.S.C. § 156, which is designed to restore the portion of a patent term lost during the FDA's review process; and (5) conducting patent searches utilizing Orbit Intelligence patent analytic and search software.[164] Any patent that was listed in the Purple Book, or asserted in federal litigation or in a PTAB proceeding, was automatically included in the patent database. However, we took a different approach with the patent searches.

By far the most time-intensive step associated with building the biologics patent database was the last: conducting the patent searches. The

[162] More details regarding our search procedure and patents that were included in the database can be found in Online Appendix.

[163] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1585–92 (1984).

[164] One benefit of Orbit Intelligence software is that it allows for the easy grouping of assignees of patents based on the responsible corporate entity—i.e., the entity that filed the biologic's license application, including all subsidiaries that may have a different name. For example, searches for biologics owned by Johnson & Johnson would include results for Janssen Pharmaceuticals, Centocor, and Actelion among others. Including all corporate entities with direct ties to the responsible marketing party gives the highest likelihood of finding relevant publications.

patent searches led to the identification of over 99% of the patents included in our patent database for FDA-approved biologics. Indeed, a key challenge in implementing the patent searches is that patent documents do not contain text fields that directly bear on our inclusion criterion. For instance, assume that we search over Stelara's chemical name ustekinumab and identify a patent with ustekinumab in its claims text. However, further assume that the claim language of the patent speaks to treating indications with ustekinumab that have not been approved by the FDA. Per the above discussion, it would be inaccurate to include that patent as a Stelara patent in our database. Similarly, assume that a careful read of the patent text suggests that the claims speak to treating an FDA approved indication of ustekinumab but only in combination with a second drug that has not been approved by the FDA. For the reasons indicated above, this would further render the patent ineligible for inclusion in our database.

Lacking immediate text-based means of applying our inclusion criterion—e.g., by simply pulling all patents with the word ustekinumab in its claim—it became necessary to take a deeper dive into each candidate patent to assess the application of the inclusion criterion and to screen out failures of this nature. To avoid the risk of inaccurate assessments, we elected not to take an algorithmic, machine-based approach. Rather, we chose to read and hand-code all patents that were identified utilizing our search methodology before including them in our database. Further, given the complexity of patent documents and the time involved with each assessment, it became necessary to design a search protocol to ensure the feasibility of this validation exercise. In short, we aimed to cast a net that is wide enough to capture all likely patents, but not so wide as to render the validation process unmanageable. To balance these goals, we implemented our search protocol in different stages, where we traded off on the scope of different search parameters across the stages.

Our initial search of all patent types focused on identifying relevant patents owned by the corporate entity that filed the license for the biologic and any additional corporate entity where there was significant evidence of involvement in the development, marketing, ownership, or licensing history of the biologic.[165] This initial search included keywords related to the biologic, including the Trade name (e.g., Humira), the chemical name (e.g., adalimumab), the internal identification code of the biologic (e.g., D2E7), and the drug class of the biologic (e.g., Tumor Necrosis Factor). These keywords were cross referenced using Orbit Intelligence with the title,

[165] Additional parties are sometimes involved in the development, marketing, or ownership of a biologic that are not the reference product sponsor. These additional entities were identified by either a general internet search, the use of AdisInsight database by Springer, or the use of LexisNexis database.

abstract, and claims of the patent documents. If no results were returned within the corporate tree, then the search was expanded to also include matches within the full text of the patent document. In some cases, the text of a document made clear that it read on a particular biologic, but the claims only referenced to "drug" or some other general term. We only included a patent if the claims indicated the biologic in question was the subject of the claim.

An additional initial search was conducted for patents related to delivery of biologic drugs through approved delivery methods (e.g., infusion, injection, etc.)—i.e., device patents—only. This additional search focused on the same corporate entities and the same keywords as the initial search. However, this additional search for device patents was broader in one aspect and narrower in another aspect than the initial search. It was narrower in that it required the word "device" or other delivery methods related to the biologic (e.g., inhaler, etc.) to be in the claims of the patent document. The additional search of device patents was broader than the initial search in that the keywords (i.e., the Trade name, the chemical name, the internal identification code of the biologic, and the drug class of the biologic) were not limited to matches within the title, abstract, and claims of the patent documents but instead within the full text of the patent document.

The second patent search of all patent types was also broader in one aspect and narrower in another aspect than the initial search. The second patent search across all patent types did not restrict the patent search to be within the corporate entities that either filed the license, were involved in the development, marketing, or ownership of the biologic, or both. However, the second search was narrower in that it did not include keywords related to the drug class of the biologic (e.g., Tumor Necrosis Factor), as doing so returned far too many non-relevant results. That is, the keywords in our second search included those related to the Trade name (e.g., Humira), the chemical name (e.g., adalimumab), and internal identification code of the biologic (e.g., D2E7), which were cross-referenced using Orbit Intelligence with the title, abstract, and claims of the patent documents. Importantly, for this second stage, we searched patents assigned to any assignee, not just those that are part of the corporate entity that filed the biologic license.

Finally, we conducted a third search of all patent types using biosequences (nucleotides or amino acids) for the FDA-approved biologic to find any results where the biologic was only referred to in the claims of the patent as a numbered sequence rather than by its chemical name, trade name, or internal identifier. Sequences were obtained from DrugBank Online or Kegg Drug in most instances. If sequences could not be found in those two sources, then previously found publications were searched for reported

sequences that were designated as matching that of the biologic by name. Patent documents were searched for inclusion of the matching sequence within the claims section of the document. A matching sequence was determined to be either a full sequence match to the reported sequence or one that comprised part of the sequence. Some genetic mutations were included if there was enough other evidence to indicate that the mutant in question was indeed a variant of the indicated biologic and the mutant had a greater than 95% match with the reported sequence of the biologic.

Although the methodology utilized to build our patent biologics database is comprehensive, we acknowledge that it will not find every relevant patent that could possibly be asserted in biologics patent litigation. Perhaps most saliently, our methodology will not identify biologic-agnostic manufacturing patents unless these patents were either asserted in federal patent litigation, asserted before the PTAB, subject to a patent term extension under 35 U.S.C. § 156, or listed in the Purple Book.[166]

B. Patent Types

Every patent or patent application included in our database was categorized into one of six different patent types. When determining the type of patent or patent application, we evaluated the main claim as reported by Orbit Intelligence and, if no main claim was reported, we evaluated the first independent claim.[167] Every patent or patent application was assigned to only one type. Those types are defined as follows:

(1) *Main Compound*: A patent that claims a biological compound, including a specific amino acid sequence,[168] a specific conjugate,[169] or a specific post-translational modification to a protein or antibody.

(2) *Method of Treatment*: A patent that claims the use of a biologic to treat an indication or group of indications.[170] Method of treatment patents were included

[166] By biologic-agnostic manufacturing patents we mean manufacturing patents whose claims, abstract, or title do not include the chemical name, trade names, internal identification code, or drug class of a biologic. *See* Osmat Azzam Jefferson, W. Nicholson Price II, S. Sean Tu, Saurabh Vishnubhakat & Arti K. Rai, *The Puzzle of Biologics Manufacturing Platform Patents*, 43 NATURE BIOTECHNOLOGY 295, 296 (2025) (noting that platform patents covering multiple biologics cannot be found through searches for a given biologic).

[167] Orbit Software states the main claim is determined by the USPTO and they are unaware of the criteria utilized to identify the main claim. Our review of the main claims of patents suggests they are in fact the first independent claim of the patent.

[168] *See, e.g.*, U.S. Patent No. 2017/0349665 (filed June 16, 2017) (claiming specific anti-human-CD52 antibody comprising amino acid sequence).

[169] *See, e.g.*, U.S. Patent Application No. 14/721,761 (filed May 26, 2015) (claiming a conjugate between a water-soluble polymer and peptide).

[170] *See, e.g.*, U.S. Patent No. 11,116,808 (issued Sept. 14, 2021) (claiming use of *Candida albicans* for treatment of warts).

in our database only if the biologic was FDA-approved for the claimed indication.

(3) *Method of Manufacturing*: A patent that claims a process utilized to manufacture a biologic,[171] including methods to chromatographically separate the biologic, methods to culture the biologic, or other methods involved in the biological manufacture process.[172]

(4) *Formulation*: A patent that claims the way a biologic is formulated, administered, or both, including routes of administration, dosages, and formulations including non-active additives,[173] non-conjugated drug carriers, extended release, etc.

(5) *Device*: A patent that claims a specific device used in the administration or preparation of a biologic, including kits, injection devices,[174] or other such objects.

1. Characteristics of Patents

We used U.S. patent numbers and U.S. patent application numbers to merge our dataset with numerous public sources, such as the Patent Examination Research Dataset (PatEx), to collect various patent characteristics for each patent in our biologics database.[175] In the Online Appendix, we briefly describe the various patent characteristics collected from numerous public sources for each patent in our biologics database. Beyond the patent-type flags just discussed, such information includes identifying patent information, claims characteristics (including claims text and linguistic summary statistics), identities of the patentee(s) and assignee(s), patent citation statistics, and terminal disclaimer filings, among other things. Some of these forty-plus variables are relevant for the investigation into the patent thicketing and evergreening practices of biologics manufacturers that will follow in this Article and, importantly, for the analysis of various policies proposed by Congress and the Patent Office to curb these practices. Other variables are likely to be relevant for future applications of this novel database.

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[171] *See, e.g.*, U.S. Patent Application No. 16/840,293 (filed Apr. 3, 2020) (claiming manufacture of a drug product with parameters on the glycoprotein composition).

[172] *See, e.g.*, U.S. Patent No. 6,281,336 (issued Aug. 28, 2001) (claiming process for purifying immunoglobulin from crude mixture).

[173] *See, e.g.*, U.S. Patent No. 9,241,897 (issued Jan. 26, 2016) (claiming preparation of an immunoglobin with an added concentration of proline to adjust the viscosity of preparation).

[174] *See, e.g.*, U.S. Patent No. 11,806,507 (issued Nov. 7, 2023) (claiming an infusion device for administration of biologic).

[175] *Patent Examination Research Dataset (PatEx)*, U.S. PAT. OFF. (Apr. 14, 2025, 2:32 PM), https://www.uspto.gov/ip-policy/economic-research/research-datasets/patent-examination-research-dataset-public-pair [https://perma.cc/J56Z-BXES] (showing that PatEx is published by the U.S. Patent and Trademark Office).

V. ANALYSIS OF PATENT THICKETING AND PATENT EVERGREENING

This Part begins by providing an overview of our patent database and then turns to providing some preliminary background on the patent application process that helps to illuminate how certain patents are more likely to contribute to patent evergreening while others are more likely to contribute to patent thicketing. Finally, this section concludes by providing empirical evidence suggestive of both patent thicketing and patent evergreening associated with FDA-approved biologics.[176]

Our dataset consists of 11,595 drug/patent pairs across the 515 therapeutic biologics approved by the FDA to date. Six of these biologics do not have any patents (issued or pending) in their portfolios. Roughly 73% of biologics patents are unique to a single drug product, whereas 27% of biologics patents are associated with more than one drug—e.g., the same patented manufacturing process is associated with more than one approved biologic.[177]

Table 1 breaks down the drug/patent pairs into patent type. Main compound patents account for 13% of the sample. The remainder are accounted for by the various types of secondary drug patents, including device patents (16%), manufacturing or process patents (25%), formulation patents (19%), and method of treatment patents (27%). The most common type of patent is method of treatment patents followed by method of manufacturing or process patents. The least common type of patent is main compound or primary patent.

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[176] Our primary results will include pending patent applications in the associated patent portfolios. We do so given that biologic patenting activity has particularly accelerated in recent years, and the vast majority (over 75%) of these applications will ultimately issue. Thus, their inclusion is consistent with our goals of depicting the degree to which biologics patenting activity may forestall competitors moving forward. Moreover, we note that our goal is not necessarily to provide a snapshot of biologics patent portfolios at the present but rather to provide a sense of the blocking effects of portfolios when they were active. As such, we include patents that have expired to provide a sense of the portfolios associated with older biological drugs. Nonetheless, we exclude applications that have been formally abandoned with the Patent Office, as they will ostensibly never issue nor have a blocking effect.

[177] *See, e.g.*, U.S. Patent No. 12,031,151 (issued July 9, 2024) (showing this patent as relevant for multiple biologics, including Evkeeza, Eylea, Inmazeb, Dupixent, and Kevzara).

TABLE 1: NUMBER OF PATENTS BY PATENT TYPE, ACROSS SAMPLE OF DRUG/PATIENT PAIRS

Patent Type	Number of Patent/Drug Pairs	Percentage of Sample
Main Compound	1,478	12.8%
Device	1,826	15.8%
Formulation/Drug Delivery	2,193	18.9%
Method of Manufacture/Process	2,926	25.3%
Method of Treatment	3,158	27.3%

Note. Data are from 11,595 patent/drug pairs associated with 515 biologics approved by the FDA. Patent type was not detectable for 14 of these patent/drug pairs.

Table 2 provides the mean number of patents by patent type as well as the percentage of biologics with at least one patent of the indicated type. A biologic, on average, has 2.9 primary patents or patents on the compound that forms the basis of the biologic drug. It might strike the reader as strange that this number exceeds one, but our definition of compound patents includes patents that claim a biological compound, a specific conjugate, or a specific posttranslational modification to a protein or antibody, which is a modification that occurs after the protein or antibody has been synthesized.[178] A posttranslational modification is essentially a way to fine-tune a protein's activity after the protein has been made, and such patents are common for biologics.[179]

The remainder represent different types of secondary patents. On average, a biologic has 6.2 method of treatment patents, 5.7 manufacturing patents, 4.3 formulation patents, and 3.6 device patents. These results suggest that many biologics are approved for more than one indication, as the only method of treatment claims included in our database are ones for FDA-approved indications. Also notable is that, on average, a biologic is associated with approximately 6 manufacturing patents, reflecting the import of innovation activity associated with the complex manufacturing process of biologics.

[178] Qian Zhong, Xina Xiao, Yijie Qiu, Zhiqiang Xu, Chunyu Chen, Baochen Chong, Xinjun Zhao, Shan Hai, Shuangqing Li, Zhenmei An, & Lunzhi Dai, *Protein Posttranslational Modifications in Health and Diseases: Functions, Regulatory Mechanisms, and Therapeutic Implications*, 4 MEDCOMM 1, 4 (2020) (explaining how posttranslational modifications can alter the protein's function, localization, or stability by adding or removing chemical groups like phosphate, sugar, or methyl groups to specific amino acids on the protein chain. Common posttranslational modifications include phosphorylation, glycosylation, acetylation, methylation, ubiquitination, and nitrosylation).

[179] *Id.* at 2 ("By changing protein conformation, activity, charges and stability and interactions with DNA, RNA, and other proteins within and between cells, [posttranslation modifications] ultimately alter the phenotypes and biological functions of cells.").

TABLE 2: PER-BIOLOGIC PATENTS COUNTS AND FREQUENCIES, BY PATENT TYPE

Patent Type	Mean Number of Patents of Indicated Type Per Biologic (Standard Deviation)	Percentage of Biologics with at Least One Patent of Indicated Type
Any Patent Type	22.8 (35.3)	-
Main Compound	2.9 (4.9)	60.1%
Method of Treatment	6.2 (9.2)	80.7%
Formulation	4.3 (12.3)	72.1%
Device	3.6 (12.9)	37.7%
Manufacturing	5.7 (10.8)	76%

Note. Data are organized at the biologic level, focusing on the sample of 509 FDA-approved biologics with at least one patent

Table 2 provides the percentage of biologics that have at least one patent of the five different patent types. Approximately 60% of FDA-approved biologics have a main compound or primary patent. Over 80% of biologics are associated with a method of treatment patent, 76% have a manufacturing patent, 72% have a formulation patent, and 38% are associated with a device patent.

A. Background of the Categories of Patents that Lead to Patent Evergreening versus Patent Thicketing

With these overview statistics of our database, we now turn to a quick exposition on patent examination to help illuminate patents that will likely contribute to patent evergreening versus patent thicketing. To obtain a patent, a patent applicant must file an application with the USPTO. Every patent application contains claims, which are a set of statements within the application that define the legal boundaries of an invention, specifying what the patent protects and preventing others from making, using, or selling the invention.[180] The Patent Office may allow some claims in an application that meet the patentability requirements and reject others that fail to meet the

[180] Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. REV. 63, 64–66 (2004).

patentability standards.[181] In this scenario, a patent will issue containing the allowable claims in the original application and a patent applicant may elect to file a continuation application to pursue patent claims that were rejected in the original application.[182] A continuation application is based on the same disclosure as a previously filed "parent" application while retaining the original application's filing date.[183] As a result, a continuation application will expire on the same date as the original application, making the patent portfolio thicker but not necessarily longer. In contrast, an original application that issues will likely expand the monopoly period of a drug.

As noted above, pharmaceutical companies often obtain a series of patents associated with a single drug product.[184] Importantly, pharmaceutical firms are not necessarily obtaining patents on unique patentable aspects associated with the development of a biological drug.[185] It is possible that firms are obtaining patents that have substantial overlap with their previous patents, contributing to patent thickets. A patent applicant can claim an invention that is considered so similar to a previously issued patent, also owned by the same applicant, that the new claims are deemed obvious and therefore not patentable.[186] The patent does not have to claim the exact same invention as the earlier patent but only an obvious variant, meaning a skilled person would readily see how to make the claimed invention based on the earlier patent.[187] In this scenario, the USPTO will issue an obviousness-type double patenting rejection, which is a judicially created doctrine. [188] Obviousness-type double patenting rejection stems from a statutory provision which provides that an inventor may obtain a patent—i.e., a single patent—for an invention.[189] If different entities own the early patent and the later-filed patent application, the later-filed patent application is rejected and no patent issues. However, if the same entity owns the early patent and the later-filed patent application, the patent holder can respond to such rejection by filing something called a terminal disclaimer.[190] A terminal disclaimer stipulates that the later-filed patent application will expire at the same time

[181] *Id.* at 66–67.

[182] *Id.* at 68.

[183] *Id.*

[184] Hemphill & Sampat, *supra* note [*79], at 328–29.

[185] *See* Carrier & Tu, *supra* note [*91], at 82.

[186] 35 U.S.C. § 103 (2012) ("A patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.").

[187] Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966) (describing the legal test for obviousness).

[188] *See* Gilead Scis., Inc. v. Natco Pharma Ltd., 753 F.3d 1208, 1212–13 (Fed. Cir. 2014).

[189] 35 U.S.C. § 101.

[190] *Gilead Scis., Inc.*, 753 F.3d at 1213.

as the earlier-issued patent.[191] The later-filed patent is then issued, making the patent portfolio thicker, although not longer.[192]

B. Patent Thicketing

Patent thickets refer to pharmaceutical companies obtaining numerous, often overlapping patent rights, on a drug.[193] The primary goal of patent thickets is not necessarily to extend the exclusivity period of a drug but instead to protect the drug with a dense web of patents that makes it almost impossible for a biosimilar firm to challenge these patents and gain FDA approval before they all expire.[194] Thus, patent thickets work to discourage competitors from entering the market by making it too costly and risky to do so.[195]

Table 2 has already begun to shed light on the patenting practices of biologic firms. Row 1 of Table 2 demonstrates that biologics are associated with a hefty average of approximately 23 patents per drug. In Column 1 of Table 3, we move beyond a mere demonstration of the mean and instead depict the full distribution of per-drug patent counts across all FDA-approved biologics. To offer a frame of reference, we show in Column 2 the corresponding distribution of per-drug patent counts across all small-molecule drugs represented in the FDA's Orange Book.[196] As evident from Column 1, large-molecule drugs tend to have substantially more patents than small-molecule drugs. Whereas virtually none—less than 1%—of the small-molecule distribution is beyond 20 patents per drug, a substantial portion of large-molecule drugs—roughly 36%—have over 20 patents. Nearly 9% of biologics have more than 50 patents, and nearly 3% have more than 100. The average patent-per-drug for small molecules is 3.8, far short of the 22.8 average for biologics.[197]

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[191] *Id.*; *See generally* Mark A. Lemley & Lisa Larrimore Ouellette, *Fixing Double Patenting*, 74 AM. U. L. REV. 1013, 1023–25 (2025) (discussing the rise of terminal disclaimers).

[192] *See* Lemley & Ouellette, *supra* note [*191], at 1023. Importantly, the later-filed patent application can comprise a continuation application or an original application. However, most terminal disclaimers are associated with the former.

[193] *See* Carrier & Tu, *supra* note [*91], at 82.

[194] *Id.* at 82–83.

[195] *Id.* at 83.

[196] For the Orange Book data, we used the small-molecule dataset compiled in Frakes &Wasserman, *supra* note [*118], and updated it to reflect the most recent Orange Book data from the FDA. These data amount to a series of snapshots of the Orange Book over time to ensure that we collect information from patents that were ever listed in the Orange Book (even if delisted at some point).

[197] We acknowledge there is a comparability challenge inherent in Table 3 in that Congress did not require that manufacturers list certain patents in the Orange Book, mainly manufacturing patents. Unfortunately, we are not aware of a comprehensive database in the small-molecule context that was

TABLE 3: DISTRIBUTION OF PATENTS PER DRUG ACROSS FDA-APPROVED BIOLOGICS AND SMALL-MOLECULE DRUGS

	(1) Large-Molecule Drugs	(2) Small-Molecule Drugs
Percentage of Drugs with Less than 10 Patents	34.5%	92.6%
Percentage of Drugs with 10–20 Patients (Cumulative: % Up to 20)	29.9% (64.4%)	6.4% (99%)
Percentage of Drugs with 20–30 Patents (Cumulative: % Up to 30)	15.3% (79.8%)	0.9% (100%)
Percentage of Drugs with 30–40 Patents (Cumulative: % Up to 40)	5.9% (85.7%)	0% (100%)
Percentage of Drugs with 40–50 Patents (Cumulative: % Up to 50)	5.5% (91.2%)	0% (100%)
Percentage of Drugs with 50–60 Patents (Cumulative: % Up to 60)	1.9% (93.1%)	0% (100%)
Percentage of Drugs with 60–70 Patents (Cumulative: % Up to 70)	1.9% (95.1%)	0% (100%)
Percentage of Drugs with 70–80 Patents (Cumulative: % Up to 80)	0.8% (95.9%)	0% (100%)
Percentage of Drugs with 80–90 Patents (Cumulative: % Up to 90)	0.6% (96.5)	0% (100%)
Percentage of Drugs with 90–100 (Cumulative: % Up to 100)	0.8% (97.2%)	0% (100%)
Percentage of Drugs with 100+ Patents (Cumulative: % All)	2.8% (100%)	0% (100%)

Note. Reported distributions in Column 1 are from our hand-collected and coded data on biologics patents across all 509 large-molecule drugs with at least one patent. Reported distributions in Column 2 are from a sample of 2,032 small-molecule drugs, using data from Frakes and Wasserman's 2023 analysis, which drew from the FDA's Orange Book. In each case, each observation represents a given trade-name as registered with the FDA.

constructed through a search process similar to that taken in this paper. Nonetheless, we do not believe the omission of small-molecule manufacturing patents from the FDA's Orange Book impacts the effective comparison we are attempting to make in Table 3. After all, manufacturing processes are simply less critical in small-molecule contexts in the first place. For further validation, we turn to the I-MAK database, which provides patent information on the top four selling small-molecule drugs, including those listed and not listed in the Orange Book. There are 59 Orange Book patents collectively across these four drugs, and I-MAK finds that these drugs are associated with 16 method-of-production (process) patents. Accordingly, the small-molecule patents missing from the Orange Book are unlikely to account for the over five-fold difference in mean patents depicted in Table 3 between small- and large-molecule drugs. Moreover, considering our aim in this paper of assessing the degree to which drug patents may block competitive entry, we note that the Orange Book patents identified in the I-MAK data were nearly eight times more likely to be asserted in litigation than the non-Orange Book patents.

How many of these patents are continuation applications? That is, how many patents share a priority date with an earlier-filed patent and hence make the patent portfolio thicker but not necessarily longer? A whopping 55% of patent-drug pairs are continuation patents, suggesting that over half of patent-drug pairs stem from applications based on the same disclosure as a previously filed "parent" application and contribute to the thicketing of patents. This percentage is higher than that for all patents, wherein approximately 20% are continuation applications.[198]

Finally, how often are pharmaceutical firms obtaining patents that have substantial overlap with their previous patents associated with the development of a biological drug? As noted above, a patent applicant can claim an invention that is considered so similar to a previously issued patent, also owned by the same applicant, that the new claims are deemed obvious and therefore not patentable.[199] In this scenario, the USPTO will issue an obviousness-type double-patenting rejection.[200] A patent applicant can file a terminal disclaimer to overcome this type of rejection.[201] Thus, terminal disclaimers can be utilized by pharmaceutical firms to obtain new patents that offer only trivial changes over existing inventions and expire at the same time as an earlier filed patent, again making the patent portfolio thicker but not necessarily longer.

To examine how many of the patents in our biologics database are associated with an obviousness-type double-patenting rejection and a terminal disclaimer, we used the PatEx database produced by the Office of the Chief Economist at the USPTO.[202] Our analysis suggests that 31% of the patents in our biologic database are associated with a terminal disclaimer, indicating that close to a third of the patents associated with biologic drugs may represent trivial advances over prior patenting activity.

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[198] Cesare Righi, Davide Cannito & Theodor Vladasel, *Continuing Patent Applications at the USPTO*, 52 RSCH. POL'Y 1, 1 (2023).

[199] 35 U.S.C. § 103.

[200] *See* MPEP § 804(II)(B) (9th ed. Rev. 7, Feb. 2023).

[201] MPEP § 804.02(II)((9th ed. Rev. 7, Feb. 2023).

[202] Sean Tu, Aaron Kesselheim, and Bernard Chao recently found that of the over 7,000 patents listed in the Orange Book, 45% of small molecule drug patents included an obviousness-type double patenting rejection and a terminal disclaimer. Tu, Kesselheim & Chao, *supra* note [*143], at 837. Tu, Kesselheim, and Chao also analyzed biologics patents but utilized the Purple Book which at the time listed less than 250 patents. *Id.* The authors found approximately 30% of the patents listed in the Purple Book included an obviousness-type double patenting. *Id.* Sean Tu, Rachel Goode, and William B. Feldman recently found that of the 271 patents they identified in biologics litigation, approximately 48% included a terminal disclaimer. Tu, Goode & Feldman, *supra* note [*156], at 355. Again, this is a highly select sample and may not accurately reflect the full world of patents associated with FDA approved biologics.

C. Evergreening

To demonstrate the extent to which biologics manufacturers may be evergreening through their secondary patenting practices, it is helpful as a starting point to imagine that manufacturers only receive one patent per biologic. Now, imagine that a manufacturer is considering receiving a secondary patent—e.g., a formulation patent—and is considering doing so years after receiving the first patent for the drug to achieve evergreening goals. The most straightforward way to characterize the evergreening potential of this secondary patent is to calculate the additional years of patent life conferred to the drug as a result of this secondary patent, which equals the difference in years between when the first patent associated with the relevant drug is set to expire and when the secondary patent in question is set to expire. Accordingly, we calculate this value for each drug-patent pair in our database (remember that some patents may be represented across multiple drugs). In Column 1 of Table 4, we show a distribution of this patent-extension value across each of the patents in the database. To provide a frame-of-reference, we show the corresponding distribution for small-molecule patents in Column 2.

There are several important conclusions to draw from Table 4. First, the mean number of years by which a given biologic patent extends the period when a patent protects the relevant drug is considerable—i.e., roughly 12.8 years. Second, there is considerable heterogeneity across biologics patents in the degree to which they expire after the drug's first patent expires, with a standard deviation of this extension measure of roughly nine years. Nearly 24% of biologics patents expire within five years of the expiration of the drug's first patent, but nearly 22% of biologics patents expire at least twenty years after the first patent's expiration. Third, we find that the degree of these patent extension levels (along with the degree of across-patent heterogeneity in these extensions) is considerably greater for biologics relative to small-molecule drugs. The average number of years of difference between a small-molecule drug's expiration and the expiration of the associated drug's first-expiring patent is four and a half years, nearly a third of the associated metric for biologics.

All told, our evidence suggests that, in the process of building dense patent thickets, biologics manufacturers are also able to extend the duration over which patents protect biologics from biosimilar competition.

II. TABLE 4: EVERGREENING STATISTICS: DISTRIBUTION OF YEARS BETWEEN A GIVEN PATENT'S EXPIRATION AND EXPIRATION OF RELEVANT DRUG'S FIRST-EXPIRING PATENT

	(1) Large-Molecule Drugs	(2) Small-Molecule Drugs
Percentage of Patents Expiring Within 5 Years of Expiration of Relevant Drug's First-Expiring Patent	23.6%	63.7%
Percentage of Patents Expiring Between 5 and 10 Years of Expiration of Relevant Drug's First-Expiring Patent (Cumulative: Up to 10 Years)	18.3% (42.0%)	19.6% (83.3%)
Percentage of Patents Expiring Between 10 and 15 Years of Expiration of Relevant Drug's First-Expiring Patent (Cumulative: Up to 15 Years)	19.0% (61.6%)	11.5% (94.8%)
Percentage of Patents Expiring Between 15 and 20 Years of Expiration of Relevant Drug's First-Expiring Patent (Cumulative: Up to 20 Years)	16.9% (77.9%)	4.0% (98.8%)
Percentage of Patents Expiring Between 20 and 25 Years of Expiration of Relevant Drug's First-Expiring Patent (Cumulative: Up to 25 Years)	12.6% (90.5%)	0.7% (99.5%)
Percentage of Patents Expiring Between 25 and 30 Years of Expiration of Relevant Drug's First-Expiring Patent (Cumulative: Up to 20 Years)	5.7% (96.2%)	0.3% (99.8%)
Percentage of Patents Expiring Beyond 30 Years Following Expiration of Relevant Drug's First-Expiring Patent (Cumulative: All)	3.8% (100.0%)	0.2% (100.0%)
Mean Years Between Expiration of Given Patent and Expiration of Relevant Drug's First Expiring Patent (Standard Deviation)	12.78 (9.08)	4.47 (5.47)

Note. Reported distributions in Column 1 are from our hand-collected and coded data on biologics patents, with the unit of observation at the drug-patent pair level (N=11,595). Reported distributions in Column 2 are from a sample of 2,032 small-molecule drugs, using data from Frakes and Wasserman's 2023 analysis, which drew from the FDA's Orange Book.[203] The unit of observation in Column 2 is also a drug-patent pair (N=7,772).

A. Welfare Implications

We concede a critical question: are these findings necessarily problematic? After all, it is possible that all of the statistics just set forth surrounding biological drug patent portfolios could be the product of a normal, justified process by which biological drug manufacturers truly innovate over secondary drug features. Such innovations may produce an

[203] Frakes & Wasserman, *supra note* 118, at 151.

associated portfolio of patents. Those patents, in turn, may be necessary to allow the manufacturers to recoup the research and development costs associated with the assumed justified secondary innovations—after all, such recoupment is the traditional justification of the patent system.[204] Is a story of this benign nature responsible for the findings in Tables 3 and 4? Or, on the other hand, are those findings—or, at least, some portion of them—attributable to a story in which manufacturers are not using biologics patents for their traditional purposes? That is, are biologics manufacturers using patents on secondary drug features for reasons that go beyond justifying the innovations associated with those features in an attempt to strategically "game" the system and excessively block competition?

Answering that question goes beyond the scope of this paper. However, we tackle that especially challenging question in a companion paper.[205] Employing various causal-inference methodologies, we find evidence in this companion paper suggestive of motivations of biologics manufacturers to receive secondary patents that indeed go beyond simply recouping the research and development expenses associated with those particular secondary drug features.[206] For instance, among other empirical exercises, we probe the exact timing of secondary-patent filings and find evidence suggesting that manufacturers are deliberately trying to maximize evergreening goals.[207] Markers of deliberate evergreening are inconsistent with a normal, benign secondary-drug-feature development process that produces later-expiring patents.[208]

Though this companion piece does find evidence suggestive of strategic gaming, an assessment of the full welfare implications of these practices confronts other challenges. Mainly, a complete welfare analysis would also require an assessment of the underlying patent system itself. For instance, consider a strategic evergreening tactic based on receiving a secondary drug patent, which is potentially problematic insofar as it aims to prolong the exclusivity period of the whole drug, not just a version of the drug with the features associated with that secondary patent. In the face of an optimally designed patent system, that evergreening tactic might be welfare-reducing. However, in the face of an underlying patent system with certain suboptimal

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[204] KEVIN J. HICKEY & ERIN H. HARD, CONG. RSCH. SERV., R46679, THE ROLE OF PATENTS AND REGULATORY EXCLUSIVITIES IN DRUG PRICING 4–5, 46 (2024).

[205] Michael D. Frakes & Melissa F. Wasserman, *Strategic Patenting: Evidence from the Biopharmaceutical Industry,* 24 (Nat'l Bureau of Econ. Rsch., Working Paper No. 34024, 2025.), https://www.nber.org/papers/w34024 [https://perma.cc/FAN8-BCKD].

[206] *Id.* at 9, 41.

[207] *Id.* at 24–30.

[208] Warren Grimes, *Perverse Results from Pharmaceutical Patents in the United States*, 52 INT'L REV. INDUS. PROP. & COPYRIGHT L. 596, 599 (2021).

components—e.g., sub-optimal patent term lengths—the hypothesized strategic evergreening tactic may be welfare-enhancing in that it allows firms to overcome those otherwise sub-optimal system features. In other words, a firm may need to strategically game the patent system using patents on secondary drug features to generate enough market rents to justify the research and development it put into the *entire* drug in the first place. The rents it would otherwise generate may be insufficient given the hypothesized inadequate term lengths.

Ultimately, the goal of this Article, and its companion, is not to fully resolve whether secondary patents are normatively desirable nor is it to identify the "right" number of patents that should be associated with a biological drug. As just implied, a full welfare analysis of secondary patents is extraordinary complex. Stating the challenge differently, the removal of some secondary patents would likely result in accelerated biosimilar entry and concomitantly consumer welfare gains. More specifically, welfare gains will result from consumers purchasing the drug at a lower price than before and from consumers who were originally priced out of the market now being able to afford the medication. However, importantly, accelerated biosimilar entry is not only associated with welfare gains. Earlier biosimilar entry will reduce the profits of biologic firms which may chill future efforts to produce new drugs. Whether consumer gains outweigh the costs of forgone drug innovation is unknown. Thus, we do not attempt to answer whether secondary patents are normatively desirable.

That being said, through the statistics set forth in Tables 3 and 4, and through the findings from our causal-inference exercises in our companion paper, our analysis has laid the groundwork to establish that the patenting practices of biologics manufacturers have the potential to produce deleterious welfare losses. That is, at least, our findings can rule out purely benign practices. This is likely to prove helpful to policymakers and emphasize the need for further scrutiny of the biologics industry.

On this policy point, whether or not secondary drug patenting is welfare-reducing, policymakers seem to be taking an affirmative stance in the underlying debate. As we discuss in Part VII below, policymakers are actively considering proposals to limit the scope of biologics patent portfolios and to accelerate biosimilar entry. With this in mind, a more modest aim of our analysis is to aid policymakers in this endeavor and to at least give them information on how certain patenting mechanisms may delay biosimilar entry. Tables 3 and 4 are helpful in this regard in showing the bulkiness of the portfolios that biosimilars have to navigate and in showing the time periods over which biosimilars may need to wait. Those findings demonstrate the potential for biologics patenting practice to delay biosimilar

entry. To further aid policymakers, we now turn to a discussion of whether this potential will materialize. Do biologics patenting practices actually delay biosimilar entry?

VI. EFFECTIVE MARKET LIFE OF BIOLOGICS

In this section, we aim to explore the extent to which patents are effective at keeping biosimilars off the market.[209] To enter the market, a biosimilar must first be approved by the FDA.[210] That is, the FDA must find that the biosimilar applicant's product is "highly similar to the reference product" with "no clinically meaningful differences" in "safety, purity, and potency."[211] Regulatory approval is not enough to guarantee biosimilar competition because the maker of a biologic may hold patents that can prevent the biosimilar from entering the market. A biosimilar company must analyze each patent associated with a biologic to determine its legitimacy. A patent that is invalid or is drawn so specifically to the biological product that the biosimilar falls outside the patent's ambit—i.e., non-infringed—should not prevent biosimilar entry. Only if the biosimilar company successfully challenges patents in litigation, that is, the patents turn out to be invalid or non-infringed, can the biosimilar enter the market before the patents expire. Such success in litigation, however, is neither guaranteed nor easily achieved.

Why may biosimilar companies struggle to clear invalid patents? Patent litigation is extremely expensive. Recent studies have found that biological drug companies assert, on average, over 20 patents during patent litigation.[212] A legal opinion on the validity of a patent can run over $100,000, meaning the attorney costs may be millions before litigation even begins.[213] When

[209] Our analysis in this Part draws heavily from a corresponding discussion in our companion paper exploring the strategic-gaming nature of biologics manufacturers. *See* Frakes & Wasserman, *supra* note [*204], at 36–38. Mainly, Figure 1 is a reproduction from this companion piece. *Id.* at 37. The contributions of the present Article regarding this discussion over our companion piece come in a deeper discussion over the legal foundations behind a delaying effect on biosimilar entry stemming from biologics patents.

[210] *Biosimilar and Interchangeable Biologics: More Treatment Choices*, FDA, https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices [https://perma.cc/6E4Y-JJCB] (last updated Aug. 17, 2023).

[211] The Biologics Price Competition and Innovation Act (BPCIA) was enacted as part of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001–7002, 124 Stat. 119 (2010) (codified as amended in scattered sections of 42 U.S.C. and 21 U.S.C.).

[212] Huiya Wu & Michael Siekman, *Are Reference Product Sponsors Asserting More Patents in BPCIA Litigation?*, BIG MOLECULE WATCH (Dec. 31, 2024), https://www.bigmoleculewatch.com/2024/12/31/are-reference-product-sponsors-asserting-more-patents-in-bpcia-litigation/ [https://perma.cc/C8FZ-8A2W].

[213] Matthew D. Powers & Steven C. Carlson, *The Evolution and Impact of the Doctrine of Willful Patent Infringement*, 51 SYRACUSE L. REV. 53, 102 (2001).

over $25 million of damages are at risk, which will almost always be the case in biologics litigation, the median cost of patent litigation is $1.5 million for each side through the end of discovery and $3.625 million for each side through trial and appeal.[214]

It is unclear how successful biosimilar companies are at identifying and clearing invalid patents. In this section, we examine the ability of biosimilars to successfully challenge patents and enter the market before all the patents associated with a biologic expire. To conduct this exercise, we focus on the 20 biological drugs with at least one biosimilar receiving FDA approval thus far. Out of these 20 drugs, four have experienced actual market entry by a biosimilar. For each biologic, we identify four pieces of information: (1) the approval date of the biologic; (2) the expiration date of the first patent associated with the biologic; (3) the first biosimilar approval date; and (4) the first biosimilar launch date, if any. Importantly, while a biologic's approval and launch date are almost always within a month of each other, the time between the approval and launch date of a biosimilar can include a lengthy delay.[215] The BPCIA provides for a streamlined path to litigation

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[214] AM. INTELL. PROP. LAW ASS'N, 2023 REP. OF THE ECON. SURVEY 41 (2023). Some biosimilar companies have opted not to litigate patents in federal court but instead challenge the validity of patents before the adjudicatory body at the USPTO—the Patent Trial and Appeal Board (PTAB). Erik Paul Belt & Maria Laccotripe Zacharakis, *Wallflowers: Biosimilars Don't Dance — They Go to the PTAB*, IAM (June 18, 2021), https://www.iam-media.com/global-guide/global-life-sciences/2021/article/wallflowers-biosimilars-dont-dance-they-go-the-ptab [https://perma.cc/8JVL-RBUG]. PTAB offers a streamlined process to challenge patents that are less costly than federal litigation. Kevin J. Hickey & Christopher T. Zirpoli, *The Patent Trial and Appeal Board and Inter Partes Review*, CONG. RSCH. SERV. (May 28, 2024), https://www.congress.gov/crs-product/R48016 [https://perma.cc/N7TD-5FK5]. However, this is not always possible and the majority of patents challenged at PTAB are also subject to parallel federal patent litigation, racking up litigation costs. *See* USPTO, *Patent Trial and Appeal Board Parallel Litigation Study* 3 (June 2022), https://www.uspto.gov/sites/default/files/documents/ptab_parallel_litigation_study_20220621_.pdf [https://perma.cc/6KRW-23TV] (reporting that "[t]he vast majority of petitioners (about 80% or higher) have been sued by patent owners in another venue prior to filing their petitions").

A biosimilar company is unlikely to launch at risk, meaning they are unlikely to launch before they have certainty on whether the patents associated with the biologic are invalid or non-infringed. Once a patent is found to be valid and infringed, its owner is entitled to infringement damages. The governing statute provides for "damages adequate to compensate for the infringement, but in no event less than a reasonable royalty." 35 U.S.C. § 284 (2015). Courts have interpreted this language to conclude that patent damages come in two primary measures: lost profits and reasonable royalties. Biologics drug companies would almost certainly seek lost profits, which provide the patentee with a damage award of the profits the patentee would have made but for the infringing sales. Because biosimilars are priced substantially below the price of biologic drug, the lost profits of the biologics drug company will almost certainly be more than the profits made by the biosimilar. Things get even worse if we take into account willful infringement, which provides for treble damage awards when someone intentionally infringes the patent of another.

[215] *See, e.g.*, Jinoos Yazdany, *Failure to Launch: Biosimilar Sales Continue to Fall Flat in the United States*, 72 ARTHRITIS & RHEUMATOLOGY 870, 871 (2020) (finding that several FDA-approved biosimilars remained unlaunched for years after approval).

which results in a biologic manufacturer asserting a series of patents against the biosimilar before the biosimilar is approved by the FDA.[216] If the two companies settle the patent litigation before the patents are litigated to finality, the settlement often contains an agreed-upon biosimilar launch date.[217] This agreed-upon launch date is typically after the FDA approval date of the biosimilar, in part because of the timing of patent litigation required by the BPCIA.[218]

In an attempt to shed light on whether biologic patent portfolios actually delay biosimilar entry, we utilize our novel patent database to make several observations about these twenty biological drugs associated with biosimilar approval to date. First, we observe the difference between the timing of a biologic's first-expiring patent and the timing of biosimilar approval. Second, we observe the difference in time between when a biosimilar is approved and when it is launched. Third, we compare the biosimilar entry date to the approval date of the reference biologic. The years between when the biologic enters the market and the biosimilar enters the market is referred to as the effective market length. This effective market length illuminates the period of time over which patents effectively prevent biosimilar competition.

Figure 1 contains the results of our analysis. The twenty biologics with a biosimilar approved by the FDA are on the y-axis, and the year is on the x-axis. The blue diamond represents the FDA approval date of the biologic, which we treat as synonymous with the biologic's launch date. The red circle represents the expiration of the first patent associated with the biologic, the green triangles represent the date the first biosimilar is approved by the FDA, and the yellow squares represent the launch date of the biosimilar.

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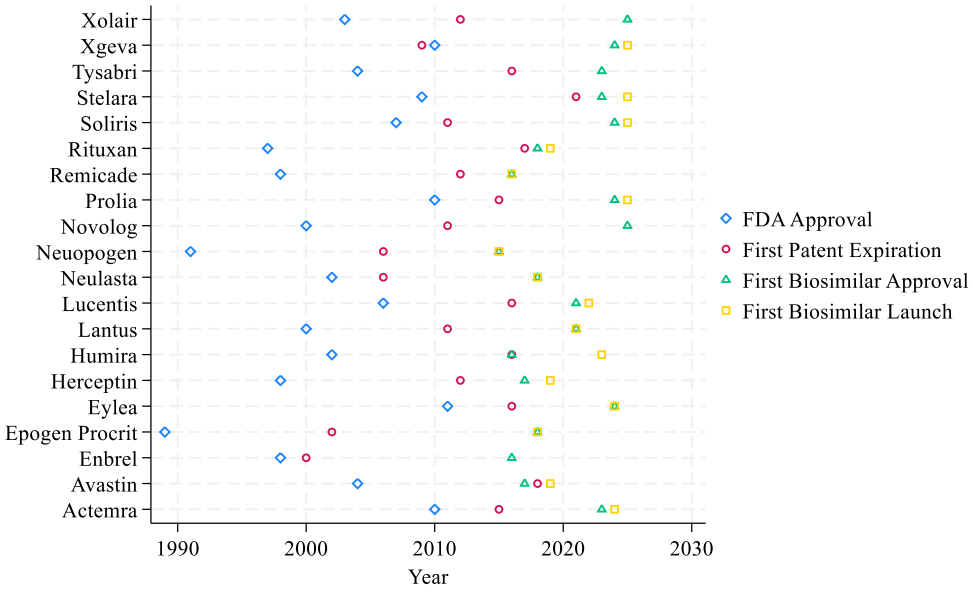
[216] *See* Belt & Zacharakis, *supra* note [*213].

[217] Eastern Research Group, U.S Biosimilar Market Entry Challenges and Facilitating Factors, Final Report (Aug. 18, 2025) at tbl.6, *available at* https://aspe.hhs.gov/sites/default/files/documents/2d5c0a194c180b52d1c760d3bb09f70a/Biosimilars%20Final%20Report_250825_v508.pdf.

[218] *Id*.

FIGURE 1: EFFECTIVE MARKET LIFE OF BIOLOGICS



Notes. This figure is a reproduction of a corresponding figure from our companion working paper exploring whether biologics manufacturers' patenting practices are reflective of strategic gaming.[219]

The biologics in Figure 1 were approved by the FDA over a range of approximately 15 years. Epogen Procrit was approved the earliest in 1988 and Eylea was approved the latest in 2011. The BPCIA was signed into law on March 23, 2010, and created an abbreviated pathway for biosimilars to be approved by the FDA.[220] Therefore, it is not surprising that we do not see biosimilar entry until several years after the BPCIA was enacted. In fact, the first biosimilar that was approved by the FDA was Zarxio in 2015.[221] Zarxio is a biosimilar of Neuopogen, which decreases the risk of infection after cancer treatment.[222]

The first result is that all biosimilars have entered after the expiration of the first expiring patent. This result suggests that secondary patents are performing some blocking effect. Second, a number of drugs evidence a gap in time beyond a year between when a biosimilar is approved and when it

[219] Frakes & Wasserman, supra note 205 at 37.

[220] BPCIA, Pub. L. No. 111-148, 124 Stat. 119 (2010).

[221] Lisa A. Raedler, *Zarxio (Filgrastim-sndz): First Biosimilar Approved in the United States*, 9 AM. HEALTH & DRUG BENEFITS 150 (2016).

[222] *Id.*

launches, including Herceptin, Stelara, and Avastin. As seen above, this gap is reflective of the delaying effects of patents as it is generally the result of agreements made in connection with patent lawsuits.[223] Third, the average effective market life of these biologics is 18.6 years but there is substantial variation. The smallest effective market life was 13 years for Eylea, and the largest effective market life was 29 years for Epogen Procrit. As a comparison, the average effective market life of a small-molecule drug is 13 to 14 years.[224] Thus, our results suggest that, on average, a biological drug enjoys a longer period of exclusivity than a small-molecule drug.

There are a couple of caveats with respect to these data. First, BPCIA is associated with twelve years of data exclusivity, which refers to the period of time when only the original developer of the biologic can use the clinical trial data submitted for market approval.[225] In other words, data exclusivity prevents other companies from relying on that data to bring a biosimilar to market during that time.[226] Thus, the smallest effective market life associated with a biologic would be a dozen years. For several biologics listed in Figure 1, the first patent expired within this twelve-year data exclusivity period, confounding our ability to state whether the first expiring patent had any blocking effect at all. That being said, we do not see a cluster of biosimilar entry at the twelve-year period, preserving the possibility that some portion of the biologics patent portfolios are blocking entry. Second, biologics approved substantially before 2010 will likely have a longer effective market life, as there was no abbreviated pathway for biosimilars to enter before 2010.[227] Third, our 18.6 years of effective market life is likely a lower bound. That is, we can only calculate this number for biologics that have had at least one biosimilar approved by the FDA. The vast majority of biologics in our data set have not yet had any biosimilar approval or entry.

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[223] CONG. RSCH. SERV., R44620, BIOLOGICS AND BIOSIMILARS: BACKGROUND AND KEY ISSUES 11–12 (2019). Eastern Research Group, U.S Biosimilar Market Entry Challenges and Facilitating Factors, Final Report (Aug. 18, 2025) at tbl.6, *available at* https://aspe.hhs.gov/sites/default/files/documents/2d5c0a194c180b52d1c760d3bb09f70a/Biosimilars%20Final%20Report_250825_v508.pdf.

[224] Emily Michiko & Joshua Kresh, *Pharmaceutical "Nominal Patent Life" Versus "Effective Patent Life," Revisited*, Ctr. For Intell. Prop. X Innovation Pol'y (May 20, 2024), https://cip2.gmu.edu/2024/05/20/pharmaceutical-nominal-patent-life-versus-effective-patent-life-revisited/ [https://perma.cc/F2CR-SAHW].

[225] 42 U.S.C. § 262(k)(7)(A).

[226] *Id.*

[227] *See* Jacqueline Wright Bonilla, *Biosimilars – the View from the US*, SCIENCE|BUSINESS (Apr. 6, 2011), https://www.sciencebusiness.net/news/74945/Biosimilars-%E2%80%93-the-view-from-the-US [https://perma.cc/F6U6-MK5J].

VII. ANALYSIS OF POLICY SOLUTIONS

Lawmakers on both sides of the aisle are committed to tackling high prescription drug prices, but finding the right solution has proven to be difficult. This section evaluates several recent proposals that attempt to lower drug spending by targeting patent thickets. In evaluating these proposals, we utilize our novel patent database to provide much-needed empirical guidance on how these proposals would impact the biological patenting landscape. By doing so, our hope is to provide policymakers with critical data on how effective these proposals will be in practice at limiting biologic patent thickets.[228]

The first proposal is the Affordable Prescriptions for Patients Act of 2025 (APPA), which addresses high prescription drug prices by limiting the number of patents that a biologics manufacturer can assert in litigation.[229] The second is a set of prescriptions that encourages biosimilar competition by diminishing the value of patent thickets formed by patents associated with a terminal disclaimer.

A. Affordable Prescriptions for Patients Act of 2025

The APPA, which was unanimously passed by the U.S. Senate in the summer of 2024 and reintroduced to the U.S. Senate in spring of 2025, addresses high drug prices by targeting patent practices like thicketing, which raise entry barriers for competitor biosimilar manufacturers.[230] More specifically, the APPA limits the number of patents that may be litigated in a patent infringement lawsuit between a biologic manufacturer and a biosimilar applicant.[231] The APPA has attracted several bipartisan sponsors as well as the support of patient groups and other constituents advocating for lower prescription drug prices.[232] According to Senator Cornyn, a sponsor of

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[228] Because our data does not include biologic-agnostic manufacturing patents, the percentages discussed in this Part likely represent lower bounds of patents that could not be asserted in litigation or held unenforceable.

[229] Affordable Prescriptions for Patients Act, S. 1041, 119th Cong. (2025); Affordable Prescriptions for Patients Act of 2023, S. 150, 118th Cong. (2023).

[230] Affordable Prescriptions for Patients Act, S. 1041, 119th Cong. (2025).

[231] *Id* § 2(a)(2).

[232] *See, e.g.*, Shira Stein, *Cornyn, Running for Re-Election, Gets in Pharma's Crosshairs*, BLOOMBERG LAW (June 12, 2019) https://news.bloomberglaw.com/health-law-and-business/cornyn-running-for-re-election-gets-in-pharmas-crosshairs-2 [https://perma.cc/GAK8-NTTG] (demonstrating long-standing bipartisan support for prior versions of the APPA); Letter from David Certner, AARP, to John Cornyn and Richard Blumenthal, United States Senate, AARP (June 18, 2019) https://www.aarp.org/content/dam/aarp/politics/advocacy/2019/06/061819-endorsement-letter-for-cornyn-blumenthal-patent-bill-final.pdf [https://perma.cc/HF8C-48GL] (showing the support of patient constituencies for prior versions of the APPA).

the bill, its purpose is to "resolve patent issues faster and focus on those patents that really matter the most."[233]

The APPA divides patents into three categories. The first category consists of patents filed with the USPTO within four years of the biological drug's approval.[234] The APPA imposes no limits on asserting this first type of patent as long as any methods of manufacturing the biologic covered by the patents are actually used by the biologics firm.[235] The second category includes patents granted after the biologic manufacturer submits its 3A list to the biosimilar applicant.[236] The bill allows up to ten such patents to be litigated.[237] The third category encompasses litigated biologics patents that do not fall into the first two categories.[238] The bill limits the number of patents that may be asserted in an action to twenty total across the second and third categories.[239] Courts may relax these limits upon appropriate showing of cause, and the limits only apply if the biosimilar applicant completes every step of the patent dance.[240]

Limiting the number of patents that can be litigated is not a new phenomenon. District court judges have long advocated for litigants to narrow the number of patents they assert in court.[241] The United States Courts of Appeals for the Federal Circuit (Federal Circuit), the appellate court that hears appeals of patent cases, has welcomed these limitations. For example, consider *In re Katz Interactive Call Processing Patent Litigation*, wherein a district court ordered a patent litigant to reduce the number of asserted patent claims from 1,975 to 64.[242] The Federal Circuit approved the procedure, noting that since the district court judge permitted the patent holder to show cause for a more extensive set of patent claims, there was no wrongful deprivation of rights.[243]

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[233] Bruce M. Wexler et al., *Senate Judiciary Committee Passes Bill Limiting the Number of Patents for BPCIA Litigation*, PAUL HASTINGS LLP (July 3, 2019) https://www.lexology.com/library/detail.aspx?g=5e87f92a-017e-437d-9b07-95bd343a2712 [https://perma.cc/HGN5-RJHC].

[234] Affordable Prescriptions for Patients Act, S. 1041, 119th Cong. § 2(a)(2).

[235] *Id.*

[236] *Id.*

[237] *Id.* This limit only applies to patents issued after enactment.

[238] *Id.*

[239] Affordable Prescriptions for Patients Act, S. 1041, 119th Cong. § 2(a)(2).

[240] *Id.*

[241] *See* PETER S. MENELL, LYNN H. PASAHOW, JAMES POOLEY, MATTHEW D. POWERS, STEVEN C. CARLSON, JEFFEREY G. HOMRIG, GEORGE F. PAPPAS, CAROLYN CHANG, COLETTE REINER MAYER & MARC DAVID PETERS, PATENT CASE MANAGEMENT JUDICIAL GUIDE 2-11–2-12 (3d. ed. 2016).

[242] 639 F.3d 1303, 1309 (Fed. Cir. 2011).

[243] *Id.* at 1312.

Although the APPA limits the number of patents that can be asserted in biologics litigation, it is unclear whether these limits increase competition and lower drug prices. We apply the APPA limits to the biologics database to examine the extent to which the APPA would limit biologics litigation.[244] Table 5 contains the results of this exercise and depicts the percentage of biological drugs with the indicated number of patents implicated by the APPA.[245] We find that 13.7% of biological drugs have at least one patent that could not be asserted under the APPA, 10.6% of biological drugs have more than five patents that could not be asserted under the APPA, 8.3% of biological drugs have more than ten patents that could not be asserted under the APPA, and 5.5% of biological drugs have more than twenty patents that could not be asserted under the APPA.[246]

TABLE 5: PERCENTAGE OF BIOLOGICS DRUGS IMPACTED BY THE APPA

	At Least 1 Patent	**More than 5 Patents**	**More than 10 Patents**	**More than 20 Patents**
Percentage of Biologics with the Indicated Number of Patents Implicated by the APPA	13.7%	10.6%	8.3%	5.5%

Note. Results are from a sample of 515 FDA-approved biologics.

[244] Given that the vast majority of biologics in our database have faced no biosimilar competition, we focus only on the limits of asserting twenty patents that have a filing date four years after the biological drug has been approved. More specifically, for each biologic we identify the number of patents filed more than four years after the biologic was approved by the FDA. If this number is more than twenty, we subtract twenty from this number as the biologic manufacturer is limited to only asserting twenty such patents. If this number is less than twenty, we zero this number out. We then divide this number by the total number of patents associated with the biologic to obtain the percentage of patents that the biologic manufacturer would not be able to assert under the APPA.

[245] Table 5 is a reproduction of a table from the Online Appendix of our companion paper exploring the strategic-gaming nature of biologics manufacturers patenting practices. Frakes & Wasserman, *supra* note [*204], at A24. In this Article, we expand upon the APPA analysis of this companion paper by offering greater legal details surrounding the APPA. Importantly, in this Article, we also situate the APPA analysis within a broader policy-analytical framework by engaging in a novel simulation analysis of other reforms aimed at curbing thicketing and evergreening practices, including the terminal-disclaimer reforms discussed below.

[246] We note that there is an inherent assumption in interpreting these numbers the way we have stated it, mainly that firms will not alter patenting practices in response to the passage of the APPA (e.g., if firms respond to the APPA by making sure that they have no patents implicated by the law, then naturally the figures indicated in Table 5 would be inaccurate). Even if one relaxes this assumption, there is still an inherent value in this simulation exercise, as these numbers still speak to the potential impact of the APPA. In this light, one can view the findings from Table 5 as a way of parameterizing the stringency of the APPA.

The most difficult aspect of the APPA is setting proper limits on the number of patents that can be asserted in pharmaceutical litigation. As a result, we also examine a range of parameters that alternative legislation could instead adopt. We then calculate the percentage of an average biologic patent portfolio that cannot be asserted in patent litigation with these hypothesized restrictions. We consider three different potential bills. The first two track the current APPA structure by providing no limits on the number of patents that can be asserted if filed within four years of the biologic's approval. However, our first two proposed bills differ from the APPA on the number of patents that can be asserted if filed four years after the date the biologic's approval. In proposed bill 1, we limit the latter to ten patents instead of twenty. In proposed bill 2, we prohibit the assertion of patents filed four years after the biologic's approval altogether. In proposed bill 3, we restrict assertions to patents filed before the biologic's approval. The results of this new exercise are reported in Table 6.[247]

TABLE 6: PERCENTAGE OF AVERAGE DRUG PORTFOLIO THAT CANNOT BE ASSERTED IN LITIGATION UNDER ALTERNATIVE POLICIES

	APPA: Can assert any patents filed within 4 years of biologic's approval and up to 20 patents thereafter	**Proposed Bill 1: Can assert any patent filed within 4 years of biologic's approval and up to 10 patents thereafter**	**Proposed Bill 2: No limits on asserting patents filed within 4 years of biologic's approval**	**Proposed Bill 3: Can assert any patent filed before biologic's approval**
Percentage of Average Drug Portfolio that Cannot be Asserted in Litigation	4.8%	9.9%	37.3%	55.4%

Note. Results are from a sample of 515 FDA-approved biologics.

We find that 4.8% of the average biologic patent portfolio could not be asserted in patent litigation under the APPA. This percentage steadily increases with each proposed bill. In proposed bill 1, 9.9% of the average biologic patent portfolio could not be asserted in patent litigation. In proposed bill 2, 37.3% of the average biologic patent portfolio could not be asserted in patent litigation. Finally, in proposed bill 3, over half of the average biologic patent portfolio could not be asserted in patent litigation.

[247] One should also interpret the results from this table following the same assumption discussed *supra* note [*242].

Setting the proper limits on the APPA will depend upon the social welfare consequences of secondary biologics patents. As discussed in Part V.D, this Article does not attempt to resolve that difficult question, though we begin to engage with this question more directly in a companion paper.[248] In practice, policymakers will choose among competing approaches to the APPA limits in light of their priors. Those who view most secondary biologic patents as reducing social welfare are likely to favor proposed bill 3, under which more than half of the average biologic patent portfolio would be unavailable for assertion in litigation. By contrast, policymakers who assume that only a small subset of secondary biologic patents diminish welfare may instead prefer the APPA as currently drafted or as revised in proposed bill 1.

B. Targeting Terminal Disclaimers

Another set of policy prescriptions seeks to encourage biosimilar competition by targeting a specific type of patent thicketing: biologics patents with terminal disclaimers. Patent thickets associated with terminal disclaimers may appear more vulnerable to invalidation through litigation. The reasoning is that if a patent serving as the basis for an obviousness-type double patenting rejection is invalidated, one would think that any patent linked to it by a terminal disclaimer would also be invalidated by the courts. However, the Federal Circuit has held otherwise.

In *Ortho Pharm. Corp. v. Smith,* the patentee, Smith, owned two patents: the U.S. Patent No. 3,959,322 ('322 patent) and the U.S. Patent No. 3,850,911 ('911 patent).[249] Both patents were directed toward compounds that were related to oral contraceptives.[250] The '911 patent was issued first, and Smith filed a terminal disclaimer on the '322 patent, presumably because the '322 patent was rejected due to obviousness-type double patenting in light of the '911 patent.[251] Ortho Pharmaceutical filed a declaratory judgement action against Smith, seeking to invalidate both the '322 patent and the '911 patent.[252] Ortho Pharmaceutical argued that if the '911 patent was invalid, then so was the '322 patent given its terminal disclaimer.[253] The lower court rejected this contention, stating "[t]he terminal disclaimer . . . of the '322 patent merely fixe[d] an earlier date certain upon which the patent expires" and that "the disclaimer does not operate to tie the validity of the

[248] Frakes & Wasserman, *supra* note [*204], at 39–41.

[249] 959 F.2d 936, 937, 939 (Fed. Cir. 1992).

[250] *Id*. at 937.

[251] *Id.* at 940–41.

[252] *Id.* at 937–38.

[253] *Id.* at 941.

'322 patent to the validity of the '911 patent."[254] The Federal Circuit upheld the lower court holding, noting that "the filing of a terminal disclaimer simply serves the statutory function or removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection."[255] As a result, biosimilar firms must individually invalidate every patent connected by a terminal disclaimer. The patents related via a terminal disclaimer do not necessarily rise and fall together. This legal stance, however, has been controversial and has prompted various proposed reforms, to which we now turn our discussion.

1. Bill to Address Patent Thickets (BAPT)

In 2024, the Bill to Address Patent Thickets (BAPT) was introduced in Congress and would permit patent holders to assert only one patent in a group connected by terminal disclaimers in pharmaceutical litigation.[256] Like the APPA, the BAPT attracted bipartisan sponsors and the support of policy groups advocating for more affordable prescription drugs.[257] Senator Welch, who sponsored the bill, stated that "[t]his bipartisan legislation will be a step forward in the fight to stop pharmaceutical companies from abusing the patent system."[258]

In Part V.A, we documented that 31% of biologic patents are associated with a terminal disclaimer. Given that the BAPT permits a patent holder to assert only one patent in a group connected by terminal disclaimer, it follows that the BAPT would prevent 31% of biologics patents from being asserted in biologics litigation. Notably, this figure is significantly higher than the number of patents that could not be asserted under the APPA. It is clear that the BAPT takes a more aggressive stance on clearing patent thickets and increasing biosimilar competition than the APPA.

2. Patent & Trademark Office Proposed Rule on Terminal Disclaimers

In 2022, a bipartisan group of Senators petitioned the USPTO to limit or eliminate terminal disclaimers for pharmaceutical patents.[259] In 2024, the

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[254] Ortho Pharm. Corp. v. Smith, 18 U.S.P.Q.2d 1977, 1982 (E.D. Pa. 1990).

[255] *Ortho Pharm. Corp.*, 959 F.2d at 941–43.

[256] A Bill to Address Patent Thickets, S. 3583, 118th Congress § 1(a) (2024).

[257] Press Release, Sen. Peter Welch, Welch, Braun, and Klobuchar Introduce Bipartisan Legislation to Streamline Drug Patent Litigation, lower Cost of Prescription Drugs, (Jan. 12, 2024), https://www.welch.senate.gov/welch-braun-and-lobuchar-introduce-bipartisan-legislation-to-streamline-drug-patent-litigation-lower-cost-of-prescription-drugs/ [https://perma.cc/G2CK-MCTX].

[258] *Id.*

[259] Letter to Kathi Vidal, Director of the U.S. Patent & Trademark Office, signed by US Senators Patrick Leahy, John Cornyn, Richard Blumenthal, Susan M. Colins, Amy Klobuchar, and Mike Braun

Patent & Trademark Office proposed a rule that if any claim in a patent is found invalid, all patents linked to it by terminal disclaimers would become unenforceable—i.e., could not be asserted in patent litigation.[260] The USPTO stated that the proposed rule "is intended to promote competition by lowering the costs of challenging groups of patents tied by terminal disclaimers, resulting in reduced barriers to market entry and lower costs for consumers."[261]

The proposed rule could potentially lower the costs of challenging multiple related patents. If a patent owner is enforcing a patent along with several other patents tied by one or more terminal disclaimers to that patent, a competitor could seek to have the court narrow a validity dispute to address only that patent. Narrowing validity disputes in litigation to only one such patent could reduce litigation expenses. The USPTO received over 300 comments regarding its proposed rule,[262] and notably, the Federal Trade Commission submitted comments in favor of it.[263] However, the USPTO ultimately rescinded the proposed rule in December 2024, citing "resource constraints."[264] Nevertheless, it is possible that the agency could readopt the rule, as the USPTO lacked the resources at the time to review and address all of the comments.

We simulate the effect that the proposed rule would have on the patent portfolio of biologics. In doing so, we must assume some number of biologic patents that are invalidated in litigation and then calculate the additional number of patents that would be held unenforceable under the USPTO proposed rule. To this end, we simulate the effect the proposed rule would have on a range of biologic patents being held invalid. Our results of this exercise are shown in Table 7.

(June 8, 2022), available at https://www.collins.senate.gov/imo/media/doc/patent_letter.pdf [https://perma.cc/BT4J-XRR8].

[260] Terminal Disclaimer Practice to Obviate Nonstatutory Double Patenting: Notice of Proposed Rulemaking, 89 Fed. Reg. 40,439, 40,439 (May 10, 2024). More specifically, the USPTO will not issue a patent to a common owner or inventor with a claim that conflicts with a claim of a second patent unless the terminal disclaimer includes an additional agreement that the patent with the terminal disclaimer will not be enforced if any claim in the second patent is invalidated by prior art. *Id.*

[261] *Id.*

[262] Terminal Disclaimer Practice to Obviate Nonstatutory Double Patenting; Withdrawal, 89 Fed. Reg. 96,152, 96,152 (Dec. 4, 2024).

[263] Press Release, Federal Trade Commission, FTC Submits Comment Supporting Proposed USPTO Terminal Disclaimer Rule, available at https://www.ftc.gov/news-events/news/press-releases/2024/07/ftc-submits-comment-supporting-proposed-uspto-terminal-disclaimer-rule [https://perma.cc/2JJL-TTF5].

[264] Terminal Disclaimer Practice to Obviate Nonstatutory Double Patenting; Withdrawal, 89 Fed. Reg. at 96,152.

TABLE 7: PERCENTAGE OF ADDITIONAL PATENTS HELD UNENFORCEABLE UNDER PROPOSED TERMINAL-DISCLAIMER RULE, ASSUMING DIFFERENT DEGREES OF BASELINE PERCENTAGES OF PATENT INVALIDATIONS

	10% of Biologic Patents Invalidated	**15% of Biologic Patents Invalidated**	**20% of Biologic Patents Invalidated**
Percentage of Additional Patents Held Unenforceable Assuming the Indicated Baseline Percentage of Patents Invalidated	8.5%	11%	12%

Note. Results are from a sample of 515 FDA-approved biologics.

If 10% of biologic patents are invalidated in litigation, then we simulate that the USPTO's proposed rule would hold an additional 8.5% of biologic patents unenforceable; bringing the total percentage of biologic patents that would be invalid or unenforceable to 18.5%. If 15% of biologic patents are invalidated in litigation, the proposed rule would hold an additional 11% of biologic patents unenforceable; bringing the total percentage of biologic patents that would be invalid or unenforceable to 26. Finally, if 20% of biologic patents are invalidated in litigation, then the USPTO's proposed rule would hold an additional 12% of biologic patents unenforceable; bringing the total percentage of biologic patents that would be invalid or unenforceable to 32.

The marginal effect of the proposed rule—that an additional 8.5%, 11% or 12% of patents could not be asserted in patent litigation—suggests the USPTO's proposed rule is more aggressive than the APPA, which affects 4.8% of biologic patents, and less aggressive than the BAPT, which affects 31% of biologics patents. However, the reach of the USPTO's proposed rule is more aggressive along one dimension, in that, unlike the APPA and the BPAT, the proposed rule is not limited to pharmaceutical patents.

CONCLUSION

Biologics drugs are increasingly driving the expenditure level of prescription drugs. Policymakers have proposed a host of policy proposals aimed at increasing biosimilar competition by targeting the patent practices of pharmaceutical firms. But, due to differences in law, we have long had a robust source of patenting information for small-molecule drugs and a woefully incomplete source of patenting information for biologics. To fill this gap, we built the first comprehensive patent database associated with all 515 FDA approved biologics, which comprises over 11,500 patents. We then utilized our novel database to examine the patenting practices of biologic manufacturers. We found that both patent thicketing and patent evergreening

are significantly more prevalent with biologics than small molecules. We also found that patents are more effective at delaying biosimilar entry in the biologic market than generics in the small-molecule market. Finally, we utilized our novel database to evaluate various policy proposals to decrease patent thickets and provide much needed empirical evidence of how many biological patents these proposals would affect.