PURPLE IS THE NEW ORANGE: A COMPARISON OF COMPETITIVE INFORMATION (?) IN GENERICS AND BIOLOGICS

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The Hatch-Waxman Act of 1984 ushered in a new era of affordable medicine, with 90% of all prescriptions today filled with generic drugs. Hatch-Waxman provided an expedited pathway for generic entry and mandated that the FDA publish up-to-date information on patent information related to non-biologic drugs. That publication is known as the Orange Book.

Roughly twenty-five years later, the Biosimilars Act similarly aimed to facilitate the entry of less-expensive versions of biologics, which are more complex drugs made by living systems. Information related to biologics and biosimilars is published in what is known as the Purple Book. Biosimilars, however, have captured less of the biologic market and have reduced prices to a lesser extent than generic non-biologic drugs.

To explore the biosimilars system's shortcomings, this Article uses the case study of insulin drugs, which are popular biologics. Insulin offers a natural experiment, given that these drugs were originally listed in the Orange Book before moving to the Purple Book, in 2020. Comparing the intellectual property data available for insulin in both books reveals the surprising dearth of patent information disclosed in the Purple Book.

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In fact, despite taking inspiration from the Hatch-Waxman regime, the biosimilars system bears little resemblance to its muse. Indeed, the Purple Book is missing intellectual property data for most biologics. Without this information, biosimilar companies are forced to dance in the dark, running into legal barriers made by the brand's patents. As a result, biosimilar hopefuls may be deterred or delayed from entering the market.

The Article concludes with proposals to improve the regulatory pathway for licensing biosimilars and remedy the lack of patent transparency in the Purple Book. With these reforms, biosimilars are better poised to follow in the footsteps of generic drugs, increasing access to life-saving biologic medicines.

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I. INTRODUCTION

In 1984, President Ronald Reagan signed into law the Hatch-Waxman Act, which provides a pathway for generic, non-biologic drugs[1] to enter the market rapidly once patent protection has expired.[2] The goal of the Act was to inject competition into pharmaceutical markets, giving patients access to less-expensive versions of medication.[3] The Hatch-Waxman Act has been enormously successful. Today, 90% of prescriptions are filled with generic drugs, and the price of a drug can drop as much as 50% when even a single generic competitor enters the market.[4]

A key element of the Hatch-Waxman system involves the open exchange of information about intellectual property protections, particularly patent information. When a non-biologic company receives FDA approval to market a drug, the company must identify all patents it owns that could be reasonably asserted in protection of the drug.[5] The FDA makes that information publicly available by publishing what is known as the Orange Book, named for the fact that in the days of paper records, the cover of each volume was orange.[6] The transparency elements available in the Orange Book provide potential competitors with notice and the opportunity to plan competitive entry. With the Orange Book, potential competitors can determine the range of intellectual property protection that might be deployed against them, consider whether some of that protection is weak and could likely be overturned in court, decide whether they could design a product to avoid existing protection,[7] and know when that protection will expire. The Hatch-Waxman system, however, applies only to drugs whose structure is less complex—non-biologics such as Tylenol, Adderall, Lyrica, and Crestor.[8]

1. The drugs covered by the Hatch-Waxman system are versions of what are frequently called "small molecule" or "chemical" drugs. This Article uses the term "non-biologic" drugs, instead, to distinguish Hatch-Waxman system drugs from those covered by the biosimilars system. *See infra* note 8.

2. Orrin G. Hatch, *The 30th Anniversary of the Hatch-Waxman Act: Foreword*, 40 WM. MITCHELL L. REV. 1194, 1198 (2014).

3. Meeting Notice, 82 Fed. Reg. 28,493 (June 22, 2017).

4. U.S. FOOD & DRUG ADMIN., OFF. OF GENERIC DRUGS, 2021 ANNUAL REPORT ii (2022); RYAN CONRAD & RANDALL LUTTER, U.S. FOOD & DRUG ADMIN., GENERIC COMPETITION AND DRUG PRICES: NEW EVIDENCE LINKING GREATER GENERIC COMPETITION AND LOWER GENERIC DRUG PRICES 9 (2019).

5. 21 U.S.C. § 355(b)(1)(A)(viii).

6. *See* Kendra Stewart, *From Our Perspective: The Orange Book at 40: A Valued FDA Resource Continually Enhanced by User Input*, U.S. FOOD & DRUG ADMIN. (Oct. 26, 2020), https://www.fda.gov/drugs/news-events-human-drugs/our-perspective-orange-book-40-valued-fda-resource-continually-enhanced-user-input [https://perma.cc/MR2E-X264].

7. Some protection, for example, extends only to "skinny labels." Thanks to the Hatch-Waxman system, drug manufacturers can bring a generic drug to market as long as they remove any patented methods of use or treatment from the drug label, turning it into a label that covers less—in other words a slimmer label. In this way, the generic drug manufacturer can avoid infringing upon pre-existing patents and enter the market more easily to compete with their brand-name counterparts. *See* Garrett T. Potter, Note, *Beefing up Skinny Labels: Induced Infringement As a Question of Law*, 97 NOTRE DAME L. REV. 1707, 1708 (2022).

8. George Dranitsaris, Eitan Amir & Kristine Dorward, *Biosimilars of Biological Drug Therapies: Regulatory, Clinical and Commercial Considerations*, 71 DRUGS 1527, 1527 (2011); Paul Declerck, Romano Danesi, Danielle Petersel & Ira Jacobs, *The Language of Biosimilars: Clarification, Definitions, and Regulatory Aspects*, 77 DRUGS 671, 672 (2017).

Roughly twenty-five years later, President Barack Obama signed into law an additional pathway for rapid licensing of follow-on versions of the more complex medications known as biologics. Biologic medicines are made by living systems and include substances such as proteins and antibodies.[9] The mRNA vaccines available for COVID-19 are biologic drugs.[10] Humira, the blockbuster treatment for rheumatoid arthritis, is also a biologic, as are many oncology drugs.[11] Although the new pathway is commonly called the BPCIA,[12] this Article will use the term "Biosimilars Act" to avoid the confusion of alphabet soup.

The Biosimilars Act slipped into the Affordable Care Act package at the eleventh hour, bypassing much of the normal route of congressional hearings and debate that might have smoothed out the rough edges.[13] Commentators rained criticism on the puzzling language and awkward processes created by the legislation,[14] and the FDA labored for years to produce a workable set of regulations. In 2015, five years after passage of the Act, the first biosimilar won licensing in the United States;[15] by 2023, the FDA had licensed forty-five medicines through the Biosimilars Act pathway.[16]

9. *See* 42 U.S.C. § 262; *see also* Thomas Morrow & Linda Hull Felcone, *Defining the Difference: What Makes Biologics Unique*, 1 BIOTECHNOLOGY HEALTHCARE 24, 25 (2004).

10. *See, e.g.*, *Pfizer and BioNTech Receive U.S. FDA Approval for 2023-2024 COVID-19 Vaccine*, PFIZER (Sept. 11, 2023, 1:50 PM), https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-us-fda-approval-2023-2024-covid [https://perma.cc/VEG4-URLV]; *Moderna Receives Full U.S. FDA Approval for COVID-19 Vaccine Spikevax*, MODERNA (Jan. 31, 2022), https://investors.modernatx.com/news/news-details/2022/Moderna-Receives-Full-U.S.-FDA-Approval-for-COVID-19-Vaccine-Spikevax/default.aspx [https://perma.cc/62DC-FZB3].

11. *Biologic Therapies for Cancer*, UVA HEALTH, https://uvahealth.com/services/cancer/biologics (last visited Apr. 7, 2024) [https://perma.cc/N4YN-FN2T].

12. The acronym stands for the Biologics Price Competition and Innovation Act—the name of the bill eventually enacted as part of the Patient Protection and Affordable Care Act in 2009. *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, tit. VII, subtit. A, §§ 7001–03, 124 Stat. 119, 804–21 (2010) (enacting, among other things, Biologics Price Competition and Innovation Act of 2009).

13. In 2007, Senate Health, Education, Labor, and Pensions ("HELP") Committee members—Senators Kenney, Clinton, Hatch, and Enzi—drafted a biosimilars bill known as S. 1695, whose language largely parallels that of the later enacted Biosimilars Act. *See* Erika Lietzan, Krista Hessler Carver & Jeffrey Elikan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 746 (2010). The following year, the Senate HELP committee reported S. 1695, but "[n]o committee report accompanied the reported bill, which was considered unusual." *See id.* at 776–77. The timing of this action was also considered "curious" by many, including the trade press—who "speculated that there might be some interest in attaching the bill to the automotive bailout package in December 2008, or that it might be attached to the health care reform [the Affordable Care Act] in the following Congress, which ultimately proved to be correct." *See id.*

14. *See* Yaniv Heled, *Follow-on Biologics Are Set Up to Fail*, 2018 U. ILL. L. REV. ONLINE 113, 114–15 (criticizing the Biosimilars Act for creating "an Industry-favorable, obstructed pathway for the approval of follow-on biologics"); *see also* Robin Feldman & Jason Kanter, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L.J. 57, 60–70 (2012) (asserting that the Biosimilars Act lacked sufficient incentives for biosimilar development).

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

16. *Biosimilar Product Information*, U.S. FOOD & DRUG ADMIN. (Dec. 11, 2023), https://www.fda.gov/drugs/biosimilars/biosimilar-product-information [https://perma.cc/9BJ4-LL36]. For an explanation of the difference between biosimilar and interchangeable medicines under the Biosimilars Act, see *infra* Section III.B.2.a.

Although inspired by Hatch-Waxman, the biosimilars system bears little resemblance to its muse. In particular, the biosimilars process does not require the brand drug to disclose any intellectual property protection information at the outset.[17] Rather, the system anticipates that relevant patents will emerge down the line, when a biosimilar drug begins the process of resolving any patent rights disputes as part of trying to enter the market.[18] The portion of the emerging information that becomes publicly released is available in what is known as the Purple Book, again named for the color of the cover page on the printed version.[19]

On the one hand, one could argue that a system in which information emerges as it is needed saves time and energy for everyone. Companies provide information only when it becomes relevant for a drug because a follow-on hopeful has knocked on the door. From that perspective, the FDA need not bother recording and publishing information, until and unless it becomes relevant. On the other hand, one could argue that insufficient information emerges under the Purple Book system, and that this insufficiency could hobble those *considering* entering the market. This dampens the very competitive forces that Congress intended to unleash through the Biosimilars Act.

Testing any hypotheses about the sufficiency of information that is—or is not—released in the Purple Book faces a challenging hurdle. It is difficult to reach conclusions about sufficiency of disclosure without knowing the universe of information that might be disclosed, and one cannot measure a quantity of information when that information is unknown. In other words, how could one say that the Purple Book does not provide enough disclosure if there is no way to know what remains undisclosed? The Biosimilars Act, however, provides a precious and rare opportunity to observe a natural experiment.

Natural experiments are opportunistic moments when a change in circumstances, unrelated to anything the researcher controls, allows for a comparison. In social science research, however, the conditions ripe for natural experiments that answer questions of interest are few and far between. Life and law do not offer up interventions targeting the right subjects at the right time so easily, and one is normally left trying to cobble together inferences from partial or related information, or engage in theoretical analysis at a high level of abstraction.[20] And yet, the winding pathways through which the FDA has treated approval of one particular set of products provide such a rare opportunity: Insulin.

Insulin has always been a strange cousin in the pharmaceutical family. Despite being a large and complex molecule, insulin did not follow the approval pathway set forth for biologics by the Public Health Service Act.[21] As one of the

17. *See infra* Subsection IV.B.1.

18. *See infra* Subsection IV.B.1.

19. *See infra* Subsection IV.B.2.

20. Scott T. Leatherdale, *Natural Experiment Methodology for Research: A Review of How Different Methods Can Support Real-World Research*, 22 INT'L J. SOC. RSCH. METH. 19, 30–31 (2019).

21. Jonathan J. Darrow, Mengdong He & Kristina Stefanini, *The 505(b)(2) Drug Approval Pathway*, 74 FOOD & DRUG L.J. 403, 426 (2019) ("[I]nsulins have the unusual status of biologic drugs that for historical

few biologics approved under the Federal Food, Drug, and Cosmetic Act ("FD&C Act") of 1938,[22] insulin instead was subject to non-biologic regulation under the Hatch-Waxman regime,[23] with the result that the Orange Book contained full, historic, patent information on insulin drug products. Following language in the Biosimilars Act, however, the FDA in 2020 reclassified insulin drug products, moving them from the realm of Hatch-Waxman's Orange Book to the domain of the Biosimilars Act's Purple Book.[24]

This historic change offers the perfect observational opportunity for studying the types of information theoretically available under each regime, as well as the types of information that emerge on the ground. Thus, this Article looks at the natural experiment provided by the historic insulin shift. Part II of the Article describes insulin and the evolution of insulin drug products in the United States. Part III traces the FDA's regulatory treatment of insulin across time. Part IV describes the Biosimilars Act and the Hatch-Waxman Act, including the compromises within both legislative systems. With both pieces of legislation, Congress provided additional patent or other intellectual property protections to brand companies in exchange for establishing rapid-entry pathways for generics or biosimilar versions of the medicines.[25]

Part V examines the categories of information available through the Purple Book and compares them to the categories available through the Orange Book. This section analyzes at a highly granular level the types of patent information that, theoretically, could be found in both books. Part VI compares what has happened in reality—that is, what patent information related to insulin products was available to the public in the Orange Book and what patent information related to insulin products is now available to the public in the Purple Book.

The results are anything but subtle. The final version of the Orange Book[26] listed 19 unique NDAs for insulin products; 17 of those NDAs contained patent

reasons have been approved under the NDA process," which typically regulates only non-biologics, rather than "under the biologics license application process of the Public Health Service Act").

22. John White & Jennifer Goldman, *Biosimilar and Follow-on Insulin: The Ins, Outs, and Interchangeability*, 35 J. PHARM. TECH. 25, 28 (2019).

23. *See id.*:

> [Insulin products were] eligible for abbreviated approval under Section 505(b)(2), the paper New Drug Application (NDA) route . . . . Under this pathway, the follow-on biologics . . . have to be shown to be bioequivalent to the reference biologic, and can rely on safety and efficacy data from published studies for the reference biologic to support their application.

See also Darrow, He & Stefanini, *supra* note 21, at 404 (explaining that the 505(b)(2) pathway as codified by the Hatch-Waxman Act "requires the submission of 'full reports' of safety and efficacy investigations, but . . . allows the applicant to rely in part on previous studies conducted by an unrelated party, such as another drug manufacturer, which could help to satisfy the requirement to submit full reports").

24. *See* 42 U.S.C. § 262(k)(7)(D); *see also* U.S. FOOD & DRUG ADMIN., THE "DEEMED TO BE A LICENSE" PROVISION OF THE BPCI ACT 6 (2020).

25. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984); *see generally* Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, 124 Stat. 804 (Mar. 23, 2010).

26. That final version comprises the Orange Book Data Files available in October 2019. *Orange Book Data Files*, U.S. FOOD & DRUG ADMIN. (Dec. 12, 2019), https://web.archive.org/web/20191212235609/https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-data-files [https://perma.cc/LW5H-RCUS].

disclosures, identifying 101 unique patents.[27] In addition, five of those nineteen NDAs also disclosed non-patent exclusivities (which we will refer to simply as "exclusivities").[28] In contrast, no patent or exclusivity information at all is available now for any of the thirty insulin products listed in the Purple Book, even though many of those same thirty products were listed in the Orange Book *with* such information.[29] This complete lack of information exists, despite the fact that two biosimilar insulin drugs have emerged under the Biosimilars Act and gained FDA licensing.[30] In other words, even if one hypothesizes that the relevant information will emerge as biosimilar versions of biologic drugs emerge, that has not proven true in the case of insulin. Nor does insulin appear to be a complete outlier. More than a decade after passage of the Biosimilars Act, the Purple Book contains no information for 98% of the biologic drugs licensed for use in the United States.[31] For just one of these drugs, Humira, courts and commentators have documented that the company holds at least 132 patents.[32]

In designing this project two years ago, shortly after the transition, we hypothesized that less information about the patents protecting insulin products would become available in the Purple Book. Nevertheless, the complete lack of *any* patent information is both startling and troubling.

27. *Id.*

28. *Id.*

29. *Id.*

30. The two biosimilars are Semglee and Rezvolgar. *See* Skylar Jeremias, *Lilly Plans to Launch Insulin Biosimilar at 78% Discount to Lantus*, AJMC CTR. FOR BIOSIMILARS (Mar. 2, 2023), https://www.centerforbiosimilars.com/view/lilly-plans-to-launch-insulin-biosimilar-at-78-discount-to-lantus [https://perma.cc/R758-P6R8] ("[Rezvolgar] was originally approved by the FDA in December 2021 and was the second insulin biosimilar to receive the interchangeability label, following the approval of Semglee (insulin glargine-yfgn) in July 2021."). It is difficult to determine whether the parties fully engaged in the exchange of patent information known as the patent dance, given that parties are able to maneuver around the Act. *See* Robin Feldman, *Dance of the Biologics*, 38 BERKELEY TECH. L.J. (forthcoming 2024). But, it is clear that the two biosimilars have completed the approval process and still, no patent information has reached the Purple Book.

31. *See* Robin Feldman, *Paucity of Intellectual Property Rights Information in the U.S. Biologics System a Decade After Passage of the Biosimilars Act*, 21 PLOS MEDICINE 1, 2 (2024) (documenting that the Purple Book lists patents for only ten drugs: Neulasta (pegfilgrastim), Humira (adalimumab), Avastin (bevacizumab), Lucentis (ranibizumab), Eylea (aflibercept), Actemra (tocilizumab), Herceptin (trastuzumab), Prolia and Xgeva (two brand names for denosumab), Stelara (ustekinumab), and Tysabri (natalizumab)); Judith Stewart, *What Biosimilars Have Been Approved in the United States?*, DRUGS.COM (Oct. 24, 2023), https://www.drugs.com/medical-answers/many-biosimilars-approved-united-states-3463281/ [https://perma.cc/5ABU-2VMK] (explaining that the FDA had licensed forty-four biosimilars in the United States through October 31, 2023); *see also supra* text accompanying note 16 (noting forty-five biosimilars licensed by FDA as of December 11, 2023).

32. *See* Mayor & City Council of Balt. v. AbbVie Inc., 42 F.4th 709, 711 (7th Cir. 2022) (proclaiming that "AbbVie, [Humira's] owner, obtained 132 additional patents related to the medicine"); *see also* Ryan Knox & Gregory Curfman, *The Humira Patent Thicket, the* Noerr-Pennington Doctrine *and Antitrust's Patent Problem*, 40 NATURE BIOTECHNOLOGY 1761, 1761 (2022) (noting that "AbbVie applied for at least 247 patents, of which 132 were granted"); *see also* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, OVER-PATENTED, OVERPRICED SPECIAL EDITION: HUMIRA 2 (2021), https://www.i-mak.org/wp-content/uploads/2021/09/i-mak.humira.report.3.final-REVISED-2021-09-22.pdf [https://perma.cc/7HMF-6DS5] (reaffirming that "247 patent applications have been filed on Humira in the U.S."). Recent reporting puts the number of Humira patents at 165. *See* Rebecca Robbins, *How a Drug Company Made $114 Billion by Gaming the U.S. Patent System*, N.Y. TIMES (Jan. 28, 2023), https://www.nytimes.com/2023/01/28/business/humira-abbvie-monopoly.html [https://perma.cc/VDW3-RYUG].

In short, the Biosimilars Act falls woefully short of the goal of providing information to current and potential competitors in the market. In response, Part VII advances a proposal for reforming the Biosimilars Act. The proposal follows the types of compromises struck in both Hatch-Waxman and the Biosimilars Act, in which brand biologic companies receive additional rights in exchange for additional transparency, and respects the understandable concerns that brand biologics harbor regarding the entry process for competitors.[33] Thus, this section suggests that brand biologics should receive assurance of no biosimilar entry until a certain, critical point in the patent dance—modeled after the thirty-month stay of a challenged patent provided by the Hatch-Waxman regime.[34] In light of this additional buffer of time—time on the market without a competitor and time to ensure enforcement of valid intellectual property rights—brand biologics would be required to list all patents and exclusivities in the Purple Book, giving up the ability to enforce those rights if the company fails to list them.

II. UNDERSTANDING INSULIN

Insulin, a frequent topic for health care reformers and policy makers, has been a foundational drug in the U.S. health care system for more than 100 years.[35] Discovered in 1921 by four scientists working in Canada, insulin provides a lifeline for 30 million people in the United States who suffer from diabetes.[36] Among these, more than 7 million people depend on insulin each day.[37] The four scientists who discovered insulin were adamant about ensuring that this life-saving discovery would be accessible to all.[38] Two of the pioneers, Frederick Banting and John Macleod, refused to patent the drug because they believed patenting it would violate the Hippocratic Oath.[39] The other two—biochemist James Collip and medical student Charles Best—obtained U.S. patents on insulin and sold these patents to the University of Toronto for $1 each.[40] Banting famously proclaimed: "Insulin does not belong to me. It belongs to the world."[41]

A century has passed since the discovery of insulin, and yet its discoverers' dream—that insulin be accessible to all—remains unrealized. The insulin market remains fraught with patents and exclusivities that render the drug unaffordable

33. *See supra* note 25 and accompanying text.

34. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1589 (1984) (amending Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) by inserting new subsection (j)(4)(B)(iii)).

35. *See* Jeremy A. Greene & Kevin R. Riggs, *Why Is There No Generic Insulin? Historical Origins of a Modern Problem*, 372 NEW ENG. J. MED. 1171, 1171 (2015).

36. *Id.*; Mallory Locklear, *Insulin Is an Extreme Financial Burden for Over 14% of Americans Who Use It*, YALE NEWS (July 5, 2022), https://news.yale.edu/2022/07/05/insulin-extreme-financial-burden-over-14-americans-who-use-it [https://perma.cc/43PU-QAMW].

37. Locklear, *supra* note 36.

38. Greene & Riggs, *supra* note 35, at 1171.

39. *See* Robert A. Hegele, *Insulin Affordability*, 5 LANCET DIABETES & ENDOCRINOLOGY 324, 324 (2017).

40. *Id.*

41. Gary F. Lewis & Patricia L. Brubaker, *The Discovery of Insulin Revisited: Lessons for the Modern Era*, J. CLINICAL INVESTIGATION 6 (2021).

to many who need it. This situation is partly attributable to improvements in the drug that allow insulin manufacturers to receive new patents and thereby extend their monopoly period. The triumvirate of insulin manufacturers—Eli Lilly, Novo Nordisk, and Sanofi, also known as the Big Three—have been able to retain control of the market for decades.[42] During this time, insulin has undergone an evolution of sequential improvements that make the drug more akin to a "family of products" than to a single medicine.[43] Some of these developments have increased the drug's safety and efficacy over time.[44] Others have involved shifting from animal-derived insulin, to so-called recombinant human insulin, to what is known as analog insulin. In recent decades, most of the developments relate to the devices used to deliver the insulin, rather than the insulin itself. With each generation of new changes, older insulin products have fallen into disuse, and in some cases have disappeared from the market, even if they provide the same clinical results at lower costs.[45]

A. Human Insulin Versus Insulin Analogs

Animal insulin was the only treatment for diabetes until the late 1970s, when scientists genetically engineered human insulin.[46] This innovation made animal insulin obsolete in the United States, although it remained available in Canada until 2019, and a small number of patients continue to use it in the United Kingdom today.[47] The genetically engineered human insulin required scientists to extract the human insulin gene, insert it into bacteria, and then induce the bacteria to produce insulin in large quantities.[48] Compared with animal insulin, this human insulin significantly reduced the development of anti-insulin antibodies

42. *See* Ryan Knox, *Insulin Insulated: Barriers to Competition and Affordability in the United States Insulin Market*, 7 J.L. & BIOSCIENCES 1, 7 (2020).

43. Greene & Riggs, *supra* note 35, at 1173.

44. For example, in the early 1970s, scientists developed a refining process that significantly reduced the impurities inherent in animal insulins, which were the only insulins then available. *See id.* at 1172. But, most of the patents on the drug—including both animal insulins and their successors, human insulins (*see infra* Section II.A)—have expired, and most of the remaining patents cover delivery devices. *See* Knox, *supra* note 42, at 11.

45. *See* Robin Feldman, *Leading with the Trailing Edge: Facilitating Patient Choice for Insulin Products*, 10 J.L. & BIOSCIENCES 1, 2–3 (2023).

46. This Article refers to the genetically engineered human insulin as "human insulin."

47. *See* Anders Kelto, *Why Is Insulin So Expensive in the U.S.?*, NPR (Mar. 19, 2015, 3:06 AM) https://www.npr.org/sections/health-shots/2015/03/19/393856788/why-is-u-s-insulin-so-expensive [https://perma.cc/XD2M-NQP5]; *see also* Ahmed Iqbal, Peter Novodvorsky & Simon R. Heller, *Recent Updates on Type 1 Diabetes Mellitus Management for Clinicians*, 42 DIABETES & METABOLISM J. 3, 4 (2018) (noting that bovine insulin was discontinued in the U.K. only in 2017, and that porcine insulin continues to be produced and used by a minority of patients); *Hypurin Porcine Isophane Vials*, ELEC. MEDS. COMPENDIUM (Sept. 10, 2020), https://www.medicines.org.uk/emc/product/1670/smpc#SHELF_LIFE [https://perma.cc/CDC7-8A6U] (providing a summary of product characteristics of one of multiple porcine insulin products available in the U.K.). Porcine insulin also remained available in Canada well past its discontinuation in the U.S. *See* Agnes V. Klein, Elaine Taylor, Carole Legaré, Duc Vu & Emma J. Griffiths, *The Role of Animal-Sourced Insulin in the Treatment of Type 1 Diabetes and Its Availability*, 34 CHRONIC DISEASE & INJ. IN CAN. 169, 170 (2014) (noting the availability in Canada of the same porcine insulin used in the U.K. and advocating for continued access to animal insulin for the minority of patients who achieve better glycemic control using animal insulin).

48. *100 Years of Insulin*, U.S. FOOD & DRUG ADMIN. (June 8, 2022), https://www.fda.gov/about-fda/fda-history-exhibits/100-years-insulin [https://perma.cc/JW38-MQGP].

that cause lipoatrophy and insulin resistance.[49] Human insulin also could be mass produced, which made diabetes treatment more globally accessible, given that sources of animal insulin were scarce in many parts of the world.[50]

In the face of this technological advance, animal insulin was withdrawn from the U.S. market.[51] The withdrawal was not mandated by the FDA, but rather was voluntary on the part of insulin manufacturers.[52] That voluntary withdrawal began a key trend, in which insulin manufacturers, having created new products, promptly remove existing products from the market.[53] The trend has consequences for patients and the healthcare economy, given that the newer products are typically more expensive, yet not necessarily more therapeutic, than what came before.[54]

During the 1990s, the trend continued when the human insulin that replaced animal insulin was itself replaced by insulin analogs. These analogs now dominate the market and are significantly more expensive than human insulin.[55] To create an insulin analog, scientists alter the structure of the amino acid in a human insulin molecule in order to alter various properties of the drug—such as how quickly the drug takes effect and how long the effect lasts.[56] While the entry of insulin analogs into the body more closely resembles the physiological secretion of insulin by the non-diabetic body after a meal,[57] there is heated debate about the relative benefits of insulin analogs as compared to human insulin, particularly for individuals with type 2 diabetes.[58] One comparative study found "no population-level evidence that the extra expenditure [for insulin analogs] is warranted for most people with type 2 diabetes."[59]

The type 2 market is the larger market by far: Of Americans with diagnosed diabetes who use insulin, at least two-thirds, and perhaps even three-fourths, are type 2.[60] The cost differential has ramifications beyond the financial: With a drug

49. Irl B. Hirsch, Rattan Juneja, John M. Beals, Caryl J. Antalis & Eugene E. Wright, Jr., *The Evolution of Insulin and How It Informs Therapy and Treatment Choices*, 41 ENDOCRINE REVS. 733, 735 (2020).

50. *Id*. at 736.

51. *Id.*

52. *See* Warren A. Kaplan & Reed F. Beall, *The Global Intellectual Property Ecosystem for Insulin and Its Implications: An Observational Study*, 10 J. PHARM. POL'Y & PRAC. 1, 2 (2017).

53. Feldman, *supra* note 45, at 4–5.

54. *Id.*

55. Karen N. Peart, *Human Insulin as Safe and Effective to Treat Type 2 Diabetes as Costlier Insulin Analogs*, YALE NEWS (June 26, 2018), https://news.yale.edu/2018/06/26/human-insulin-safe-and-effective-costlier-insulin-analogs [https://perma.cc/4FNG-K3YV] (showing that a vial of insulin analog costs approximately ten times more than a vial of human insulin).

56. Hirsch et al., *supra* note 49, at 738.

57. *Id.*

58. Kasia J. Lipska, *Insulin Analogues for Type 2 Diabetes*, 321 J. AM. MED. ASS'N 350, 350 (2019).

59. Peart, *supra* note 55.

60. In 2018, approximately 26.9 million American adults had diagnosed diabetes. *See* CTRS. FOR DISEASE CONTROL & PREVENTION, NATIONAL DIABETES STATISTICS REPORT: 2020 3 (2020), https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf [https://perma.cc/LL4Y-483B]. From 2016 to 2017, 91.2% of American adults with diagnosed diabetes had diagnosed type 2 diabetes while 5.6% had diagnosed type 1 diabetes, and the balance of 3.2% had what is referred to collectively herein as "other-type diabetes." *See Current Rates of Diagnosed Type 1 and Type 2 Diabetes in American Adults*, SCIENCEDAILY (Sept. 17, 2018), https://www.sciencedaily.com/releases/2018/09/180917191843.htm [https://perma.cc/KT2M-X4EB].

like insulin, a high price tag can lead to a reduced ability to purchase treatment, with potentially fatal consequences.[61]

B. Patents and Extensions of Market Control

In a practice known as evergreening, drug manufacturers that have already patented a drug's base compound obtain additional patents covering different

Notwithstanding the slight difference in time periods for the total and percentage data (2018 vs. 2016/2017), it is reasonable to conclude that, by the start of 2018, the numbers of American adults with diagnosed type 2, type 1, and other-type diabetes were 24.4 million, 1.5 million, and 0.85 million, respectively. *Cf.* CTRS. FOR DISEASE CONTROL & PREVENTION, *supra*, at 4 (in 2018, 1.4 million American adults self-reported having type 1 diabetes and using insulin). Of the 7.4 million diabetics in America who used insulin in 2018, 1.5 million were type 1 (as *all* type 1 diabetics use insulin). *See* William T. Cefalu et al., *Insulin Access and Affordability Working Group: Conclusions and Recommendations*, 41 DIABETES CARE 1299, 1299–1300 (2018); Serena Gordon, *A Young Life Lost to High Insulin Prices*, HEALTHDAY, https://www.healthday.com/health-news/diabetes/a-young-life-lost-to-high-insulin-prices-734118.html (May 28, 2018, 11:15 PM) [https://perma.cc/DCT8-H3A7] (discussing Dr. William Cefalu's testimony before Congress in May 2018 that approximately 7.4 million Americans with diabetes use insulin, including "approximately 1.5 million individuals with type 1 diabetes"). Assuming conservatively (and counter-factually) that all other-type diabetics used insulin, the number of Americans with type 2 diabetes who used insulin in the same period was at least 5.1 million. *See What Is Monogenic Diabetes?* BEYOND TYPE 1, https://beyondtype1.org/what-is-monogenic-diabetes/ (last visited Apr. 7, 2024) [https://perma.cc/U3K7-EQHT] (noting that some of those with monogenic diabetes require sulfonylurea agent medication while others require insulin). Thus, in 2018, at least 68.9% of American insulin-using diabetics (5.1/7.4) were type 2. There is no reason to think that the percentage currently is any different. For this reason, it is safe to conclude that type 2 diabetics represent at least two-thirds, and perhaps as much as three-fourths, of the insulin market in America. Nor does the proportion appear to be lowered by any differences in per-capita insulin consumption as between type 1 and type 2 diabetics: Type 1 diabetics typically require 0.5 to 1.0 unit of insulin per kg; many type 2 diabetics, while starting with a dosage as low as 0.15 unit per kg, eventually require 1 to 2 units of insulin per kg. *See* Irl B. Hirsch, *Type 1 Diabetes Mellitus and the Use of Flexible Insulin Regimens*, 60 AM. FAM. PHYSICIAN 2343, 2343 (1999); David M. Tridgell, *Insulin Is Too Expensive for Many of My Patients. It Doesn't Have to Be*, WASH. POST (June 22, 2017, 11:43 AM), https://www.washingtonpost.com/outlook/insulin-is-too-expensive-for-many-of-my-patients-it-doesnt-have-to-be/2017/06/22/c5091c42-56cf-11e7-a204-ad706461fa4f_story.html [https://perma.cc/P5R4-NUE6] ("Patients with Type 1 diabetes typically require two or three vials of insulin per month, but patients who are more resistant to insulin, such as those with Type 2 diabetes, may require six or more.").

61. *See* Bram Sable-Smith, *Insulin's High-Cost Leads to Lethal Rationing*, NPR (Sept. 1, 2018, 8:35 AM), https://www.npr.org/sections/health-shots/2018/09/01/641615877/insulins-high-cost-leads-to-lethal-rationing [https://perma.cc/22DK-QMGL]; *see also* Darby Herkert et al., *Cost-Related Insulin Underuse Among Patients with Diabetes*, 179 J. AM. MED. ASS'N INTERNAL MED. 112, 112–13 (2019). Advocacy groups for *type 1* diabetics warn against the "Walmart insulin" solution, which offers diabetics who cannot afford analog insulin the opportunity to purchase affordable over-the-counter human insulin at Walmart. But, in relying on these insulins sold at Walmart, those type 1 patients would be obtaining a treatment that is inappropriate and ineffective for their variant of the disease, resulting in higher costs and worsening health in the long term. *See T1International Statement on Walmart Insulin*, T1INT'L (June 1, 2018, 9:34 AM), https://www.t1international.com/blog/2018/06/01/t1international-statement-ada-insulin-access-paper/ [https://perma.cc/PPC5-9N4P]; *see also* Nicki Nichols, *Why Walmart Insulins Aren't the Answer to High Insulin Prices*, INSULIN NATION (Sept. 16, 2016), https://insulinnation.com/treatment/why-walmart-insulins-arent-the-answer-to-high-insulin-prices/ [https://perma.cc/3E4T-GUHL]. The warning is presumably due to the belief that, for type 1 diabetics, insulin analogs have benefits that justify the higher cost. Some studies have shown that insulin analogs are associated with reduced risk of nocturnal hypoglycemia for those with type 1 diabetes. *See* Fernanda O. Laranjeira, Keitty R. C. de Andrade, Ana C. M. G. Figueiredo, Everton N. Silva & Mauricio G. Pereira, *Long-Acting Insulin Analogues for Type 1 Diabetes: An Overview of Systematic Reviews and Meta-Analysis of Randomized Controlled Trials*, 13 PUB. LIBR. SCI. ONE 1, 1, 10 (2018). Nothing in this Article advocates for the use of human insulin by those diabetics who clinical research shows cannot manage their condition as effectively with human insulin as with analog insulin.

aspects of the drug in an effort to prolong their market control for that drug.[62] Academic literature on the topic of evergreening categorizes patents as "primary," "secondary," and "tertiary."[63] These terms are not statutory, and there are no precise definitions for what constitutes a primary, secondary, or tertiary patent.[64] Nevertheless, the following general understandings are commonly accepted. A patent on a drug's base compound is referred to as a "primary patent."[65] A patent that makes claims on aspects other than the base compound is called a "secondary patent."[66] And a patent on a drug device is termed a "tertiary patent."[67] Many secondary and tertiary patents are criticized for not being therapeutically innovative, and their accumulation is viewed as a way for brand manufacturers to create barriers to biosimilar entry.[68] In particular, the pileup of patents makes it more difficult for biosimilars to enter the market, thereby helping shield brand manufacturers from financial losses that may occur when the initial patent expires and competitors enter.[69] The three categories of patents are demonstrated by Novo Nordisk's Novolog. United States Patent and Trademark Office data show that the first Novolog patent covered the drug's rapid-acting, insulin analog formula.[70] The second patent, granted in 1999, was for a formulation with "superior chemical stability."[71] The latest patent, granted in 2018, covers the injection device.[72] By such accumulation of patents, the Big Three insulin manufacturers delay the entry of less-expensive competitors and thereby create a barrier protecting the Big Three's own monopolistic pricing.

62. *See* Robin Feldman, *May Your Drug Price Be Evergreen*, 5 J.L. & BIOSCIENCES 590, 596, 601–02 (2018).

63. *See infra* notes 64–67 and accompanying text.

64. *See, e.g.*, María José Abud Sittler, Christian Helmers & Bronwyn Hall, *Study on Pharmaceutical Patents in Chile*, *in* WORLD INTELL. PROP. ORG., COMM. ON DEV. & INTELL. PROP., at 1, 1 n.5 (2015).

65. *See* Amy Kapczynski, Chan Park & Bhaven Sampat, *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents*, 7 PUB. LIBR. SCI. ONE 1, 3 (2012) (defining primary patent as patents with claims on the chemical compound); *see also* Michael S. Sinha, *Costly Gadgets: Barriers to Market Entry and Price Competition for Generic Drug-Device Combinations in the United States*, 23 MINN. J.L. SCI. & TECH. 293, 309 (2022) (defining primary patents as patents on a "new chemical entity"); *see also* Sittler et al., *supra* note 64, at 1 (defining primary patents as a patent protecting a drug's active ingredient).

66. *See* Feldman, *supra* note 62, at 632–34 ("'[S]econdary patents,' . . . instead of covering the active ingredient or base compound, cover modified forms of the active ingredient, associated uses of existing chemical compounds, new combinations of old chemical compounds, dosage regimens, and specific formulations . . . ."); Kapczynski et al., *supra* note 65, at 3 ("[W]e use the term 'secondary' to differentiate these claims/patents from primary (chemical compound) claims."); *see also* 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 AFFS. 2286, 2286 (2012) ("'[S]econdary' or 'later-issued' patents may protect peripheral features of the product (such as a tablet's coating), metabolites or alternative crystalline forms of the product, or methods of use (such as a method of treating disease).").

67. *See* Reed F. Beall & Aaron S. Kesselheim, *Tertiary Patenting on Drug-Device Combination Products in the United States*, 36 NATURE BIOTECHNOLOGY 142, 142 (2018).

68. Chie Hoon Song & Jeung-Whan Han, *Patent Cliff and Strategic Switch: Exploring Strategic Design Possibilities in the Pharmaceutical Industry*, 5 SPRINGERPLUS 692, 697 (2016).

69. *Id.*

70. U.S. Patent No. 5,618,913 (filed Aug. 29, 1986).

71. U.S. Patent No. 5,866,538 (filed June 20, 1996).

72. U.S. Patent No. 9,861,757 (filed Aug. 19, 2016).

Other evergreening examples abound. Take Sanofi's effort to protect its drug Lantus, an insulin analog. Of Sanofi's 74 patent applications for Lantus in the U.S., 69–or 95%–were filed *after* the drug launched in 2000.[73] Although Lantus' primary patent expired in 2015, additional patents on the product have extended Sanofi's patent protection until 2031.[74] Lantus is an insulin analog that differs from regular human insulin in chemical composition, allowing it to be longer acting than regular human insulin products such as Humulin R.[75] Though licensed in 1982, Humulin R has patent protection until 2024.[76] After the patent on Humulin R expired in 2002, Eli Lilly filed a patent application in 2004 on a Humulin injection device.[77]

Tertiary patents related to drug-device combination products[78] have become increasingly common. Of patents associated with drug-device combination products, the proportion represented by tertiary patents (as opposed to primary or secondary patents) jumped from 34% in 2000 to 57% in 2016.[79] Although in 2004, there were merely eight patents on devices for insulin products listed in the Orange Book, ten years later this number spiked to nineteen, constituting more than half of all active patents on insulin in the Orange Book.[80] A pair of Orange Book studies published in 2016 found that, out of twenty-one total insulin products (which includes all dosage variations),[81] fourteen were drug-medicine/device combination products containing insulin.[82] Of patents associated with drug-device combination products in the insulin market, a significant proportion were device patents, as opposed to patents on the drug itself.[83] In

73. INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, OVERPATENTED, OVERPRICED SPECIAL EDITION: LANTUS (INSULIN GLARGINE) 2–4 (2018), http://www.imak.org/wp-content/uploads/2018/10/I-MAK-Lantus-Report-2018-10-30F.pdf [https://perma.cc/67JR-FDKC].

74. *Id.* at 4.

75. Hirsch et al., *supra* note 49, at 741 ("Insulin glargine differs from human insulin in that the amino acid asparagine in position A21 was substituted with glycine, and 2 arginine (glargine) residues were added at positions B31 and B32.").

76. Robin Feldman, *Evergreening Drug Patent Search*, CTR. FOR INNOVATION, UNIV. OF CAL. S.F. COLL. OF L., https://sites.uchastings.edu/evergreensearch/#.YbPGrS-B1-V (last visited Apr. 7, 2024) [https://perma.cc/7XB8-WJD7].

77. U.S. Patent No. 7,291,132 (filed Aug. 9, 2004).

78. Drug-device combination products are defined by 21 C.F.R. § 3.2(e) as "[t]wo or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products." *Combination Product Definition Combination Product Types*, U.S. FOOD & DRUG ADMIN. (Feb. 15, 2018), https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types [https://perma.cc/QR98-DULA].

79. *See* Beall & Kesselheim, *supra* note 67, at 142.

80. Jing Luo & Aaron S. Kesselheim, *Evolution of Insulin Patents and Market Exclusivities in the USA*, 3 LANCET 835, 836 (2015).

81. WARREN KAPLAN & REED BEALL, HEALTH ACTION INT'L, INSULIN PATENT PROFILE 14, 18 (2016) (defining a product as including "any formulation or strength by any manufacturer listed").

82. Reed F. Beall, Jason W. Nickerson, Warren A. Kaplan & Amir Attaran, *Is Patent "Evergreening" Restricting Access to Medicine/Device Combination Products?*, 11 PUB. LIBR. SCI. ONE 1 (2016).

83. *Id.* at 5–6 (finding that, of patents on drug-device combination products in insulin market, proportion of those patents that were device patents, as opposed to patents on drug itself, ranged from 32% to 100%).

addition, the patent protection added by the device patents ranged from 1.2 years to 9.8 years, with an average of 4.89 years.[84]

The insulin pen provides an example of the dominance of tertiary patents in insulin. Replacing the traditional vial-and-syringe form of injection, the first insulin pen, the NovoPen, was released in 1985.[85] Since then, countless different versions of the insulin pen have been released onto the market, including different versions within a single company's product history.[86] Each pen in Novo Nordisk's line of insulin Aspart pens, for example, was phased out with a new adaptation to the pen's mechanical features.[87] The insulin pen offers no clinical benefits (in terms of efficacy and safety) relative to the vial-and-syringe system,[88] but patients strongly prefer pen delivery over vial-and-syringe delivery, meaning that the pen delivery system could increase patient compliance.[89]

Insulin pen products are sold in disposable pens prefilled with the active ingredient or in cartridges designed to fit only the manufacturer's particular pen device. Given that there is no way to access the medication without also buying the manufacturers specific device and refills, any patents on pen devices create barriers to entry for biosimilar competitors. Potential market entrants cannot simply make and sell insulin once the patent on insulin has expired. They must also incur the costs of designing and manufacturing a pen device and/or related cartridge that does not infringe on any patent for any existing pen device or cartridge.[90] In addition, potential competitors may be deterred from entering given that consumers have already developed preferences for their current devices.[91] The difficulty of overcoming these preferences—also known as switching costs—helps maintain monopolies.[92]

Lars Kellberg, the Corporate Vice President of Novo Nordisk, acknowledges that "the most profitable part of the business in this sector is the refill

84. *Id.*

85. Jothydev Kesavadev, Banshi Saboo, Meera B. Krishna & Gopika Krishnan, *Evolution of Insulin Delivery Devices: From Syringes, Pens, and Pumps to DIY Artificial Pancreas*, 11 DIABETES THERAPY 1251, 1254 (2020).

86. *See id.* at 1254–55.

87. Beall et al., *supra* note 82, at 11.

88. Andrew Ahmann, Sheryl L. Szeinbach, Jasvinder Gill, Louise Traylor & Satish K. Garg, *Comparing Patient Preferences and Healthcare Provider Recommendations with the Pen Versus Vial-and-Syringe Insulin Delivery in Patients with Type 2 Diabetes*, 16 DIABETES TECH. & THERAPEUTICS 76, 82 (2014) (detailing a randomized study that demonstrated efficacy and safety outcomes were similar among patients who used the pen devices and those who used vial-and-syringe delivery).

89. *Id.*

90. *See* Markus Reitzig, *Strategic Management of Intellectual Property*, 45 MIT SLOAN MGMT. REV. 35, 39 (2004).

91. *See* Sinha, *supra* note 65, at 312–13.

92. *See* Paul Klemperer, *Competition When Consumers Have Switching Costs: An Overview with Applications to Industrial Organization, Macroeconomics, and International Trade*, 62 REV. ECON. STUD. 515, 519 (1995) (stating that the "effect of switching costs is to give firms some market power over their existing customers, and thus to create the potential for monopoly profits"); *see also* Jing Shao, Huanhuan Chen & Jinke Li, *Price-Rising Competition: A Higher Market Price When a Monopoly Faces a Small Entrant*, 22 J. INDUS., COMPETITION & TRADE 481, 510–11 (2022) (creating a model to demonstrate that larger competitors are able to outcompete their smaller counterparts and maintain their customers due to switching costs, maintaining monopolies as a result).

business—selling insulin cartridges that fit the base delivery device."[93] The patent-protected, cartridge-pen interface raises the costs for competitors, impeding their entry into the market by making it difficult for competitors to produce cartridges that match the NovoPen.[94] At the same time, the patent raises switching costs,[95] which are the consumer's financial and learning barrier costs of changing from one product to another.[96] Consumers who want to purchase another supplier's cheaper cartridge would have to incur full switching costs, *i.e.*, the cost of the new device plus the cost of the other supplier's cartridge, as well as learn how to use a new device.[97] This accumulation of costs allows insulin manufacturers to create what is known as an "intellectual property rights (IPR)-based technologic incumbency."[98] Such strategies have caused some to call for the standardization of insulin pens to allow biosimilar competitors a realistic opportunity of entering the market.[99]

Furthermore, the recent advances towards insulin pill development by an MIT-led research team that included Novo Nordisk scientists[100] could render obsolete all insulin pen products, which would further prolong market control of the Big Three insulin manufacturers. At this point, the insulin pill has been studied only in animals, and it is still far from ready to enter the market.[101] Such a delivery method would be less invasive for individuals with diabetes, and a major advancement in the treatment.[102] Nevertheless, it is important to ensure that any new treatments leave room for generic versions of older-technology options—ones that may be more appealing to some consumers, particularly those who would struggle to afford the latest treatment technology.[103] While self-driving cars are an innovative technological advancement, not all drivers can pay the hefty price tag, or even desire this new alternative. Like the autopilot vehicles, auto-injecting insulin pills are a luxury not all patients want or can afford. If manufacturers stopped making insulin products other than the expensive pill, many patients who need insulin would no longer be able to afford the treatment.

93. Reitzig, *supra* note 90, at 38.

94. *Id.* at 39.

95. *Id.* at 37–38.

96. Mitchell Grant, *Switching Costs: Definition, Types, and Common Examples*, INVESTOPEDIA (Dec. 22, 2020), https://www.investopedia.com/terms/s/switchingcosts.asp. [https://perma.cc/ASK5-GQBZ].

97. Reitzig, *supra* note 90, at 39.

98. *Id.* at 38.

99. Sinha, *supra* note 65, at 354.

100. *See* Anne Trafton, *New Pill Can Deliver Insulin*, MIT NEWS (Feb. 7, 2019), https://news.mit.edu/2019/pill-deliver-insulin-orally-0207 [https://perma.cc/B3K4-DTMB].

101. *Id.*

102. *Id.*

103. *See supra* notes 51–54 and accompanying text (asserting that the discontinuation of older yet effective insulins from the market denies patients who cannot afford the costly new insulins access to perfectly effective treatments at more affordable prices).

C. Capping Out-of-Pocket Payments for Insulin

Rising insulin prices have prompted state and federal governments to implement regulatory counter-measures.[104] Over the past two years, eight states, led by Nevada and Colorado, have enacted bills that cap insulin prices.[105] On the federal level, the Inflation Reduction Act of 2022 capped insulin prices at $35 per month for all Medicare recipients starting in 2023.[106] The Act did not, however, generally affect the prices that Medicare plans themselves will pay for insulin unless particular insulin products are selected for the price negotiation elements of the legislation.[107] Thus, although insulin patients will pay less at the pharmacy counter, all patients, including those who use insulin, will continue to feel the impact of high insulin prices as those costs flow through to the amount each patient pays in the form of an annual premium.

Despite structural barriers to entry, the net price of one insulin product, insulin glargine, decreased significantly when the first biosimilar entered the market. The net price of even the brand-name insulin dropped upon facing biosimilar competition.[108] This example hints at the potential for biosimilars to reduce prices in the biologics market.[109]

III. CHALLENGES IN CREATING BIOLOGICS AND BIOSIMILARS

Despite the passage of twelve years since the Biosimilars Act's enactment, academics continue to observe significantly slower rates of biosimilar entry into biologic markets compared to rates of generic entry when Hatch-Waxman created an abbreviated pathway for non-biologic markets.[110] Less competition necessarily entails less competitive price reductions in biologic markets. Thus, the

104. *See* Julia Belluz, *The Absurdly High Cost of Insulin, Explained*, VOX (Nov. 7, 2019, 6:00 AM) https://www.vox.com/2019/4/3/18293950/why-is-insulin-so-expensive [https://perma.cc/KUC9-7UUD].

105. Joshua Cohen, *To Reduce Diabetics' Out-of-Pocket Costs for Insulin, States Fill the Void Left by Federal Government Inaction*, FORBES (July 8, 2021, 4:09 PM), https://www.forbes.com/sites/joshuacohen/2021/07/08/to-reduce-diabetics-out-of-pocket-costs-for-insulin-states-fill-the-void-left-by-federal-government-inaction/?sh=18b1cc337db3 [https://perma.cc/N4JW-WM7F].

106. Inflation Reduction Act of 2022, Pub. L. No. 117-169, § 11406, 136 Stat. 1818, 1902–04.

107. The Inflation Reduction Act provides that certain drugs are eligible for price negotiation in Medicare, with the results of those negotiations taking effect in 2026. *See id.* § 11001(a), 136 Stat. at 1837, 1839 (amending Title XI of Social Security Act by adding, among other things, new section 1192(d)(1), (e)(1)(B)(iii), to be codified at 42 U.S.C. § 1320f-1(d)(1), (e)(1)(B)(iii)). On August 29, 2023, the government announced that Novo Nordisk's suite of insulin products (Fiasp, Fiasp FlexTouch, Fiasp PenFill, NovoLog, NovoLog FlexPen, NovoLog PenFill) were among the first ten drugs selected for that price negotiation. CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE DRUG PRICE NEGOTIATION PROGRAM: MANUFACTURER AGREEMENTS FOR SELECTED DRUGS FOR INITIAL PRICE APPLICABILITY YEAR 2026 (2023). Novo Nordisk has filed suit challenging the selection of its insulin products. Novo Nordisk Inc. v. Becerra, No. 3:23-cv-20814 (D.N.J. Sept. 29, 2023).

108. *See* Joseph Levy, Zahra M. Chowdhury, Mariana P. Socal & Antonio J. Trujillo, *Changes Associated with the Entry of a Biosimilar in the Insulin Glargine Market*, 181 J. AM. MED. ASS'N INTERNAL MED. 1405, 1405–06 (2021).

109. *Id.* at 1406.

110. *See* Ariel Dora Stern et al., *Biosimilars and Follow-On Products in the United States: Adoption, Prices, and Users*, 40 HEALTH AFFS. 989, 989–90, 997 (2021).

legislation lags behind Hatch-Waxman's ability in creating competitive markets and improving consumer welfare.

Limited market entry of biosimilars is due, in part, to the difficulty of developing biologic drugs at all. In this context, it is important to understand just how biologics differ from non-biologic drugs and how these differences drive some of the idiosyncrasies of the biologic regulatory framework.

A. The Science of Biologics—The Process Is the Product

Understanding the regulatory framework begins with understanding the difference between biologic and non-biologic drugs. Non-biologic drugs are organic compounds that typically consist of tens of atoms.[111] They are sometimes referred to as "small-molecule" drugs or "chemical" drugs.[112] The follow-on medications are called "generics."[113]

As the descriptor "small-molecule" implies, these drugs are small enough to cross cell membranes and target intracellular activities.[114] Encompassing medicines such as aspirin and antihistamines, non-biologics have simple structures that can be fully analyzed, with the result that they can be chemically synthesized and replicated with relative ease.[115] Once the chemical structure of the drug is known, a manufacturer can reverse-engineer a chemical "pathway," or sequence of chemical reactions, through which the compound can be created.[116] The selection of the particular sequence of chemical reactions does not affect the final product. Multiple chemical reactions involving different processes or different chemicals may yield the same molecule, and two companies using different pathways can be confident, nevertheless, that their products will be chemically indistinguishable.[117] A "generic" version of a non-biologic, therefore, can be considered to have an active ingredient that is substantially identical to the active ingredient of the "brand" drug.[118]

Biologics, on the other hand, include proteins, nucleic acids, sugars, whole cells, and other biologically derived therapeutic products, each consisting of thousands or even tens of thousands of atoms.[119] These products target sites

111. W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1033 (2016).

112. *See, e.g.*, Price II & Rai, *supra* note 111, at 1023 (using the term "small-molecule drugs"); Brian R. Bouggy, *Follow-on Biologics Legislation: Striking a Balance Between Innovation and Affordability*, 7 IND. HEALTH L. REV. 367, 369 (2010) (using the term "chemical drugs").

113. Alyssa Billingsley, *How Are Biologic and Small Molecule Drugs Different?*, GOODRX HEALTH (Jan. 12, 2022), https://www.goodrx.com/drugs/biologics/vs-small-molecule-drugs [https://perma.cc/VCY7-7TRR].

114. *About Small Molecules*, GENENTECH, https://www.genentechoncology.com/development-platforms/small-molecules.html (last visited Apr. 7, 2024) [https://perma.cc/G9BR-Z8CW].

115. *Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN. (July 7, 2015), https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products [https://perma.cc/CN39-RJYR].

116. *See* Price II & Rai, *supra* note 111, at 1033–34.

117. *Id.* at 1034.

118. *See id.*

119. *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN. (Feb. 6, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-

outside the cell membrane because they tend to be too large to pass through cell membranes. In addition, they cannot be chemically synthesized.[120] Instead, they are developed in, and harvested from, living systems through means such as genetic modification.[121]

Consider, for example, the complexity of the process for making a biologic drug product that is a protein. First, an edited segment of DNA containing the instructions for creating the protein is inserted into a microorganism, plant cell, or animal cell. The cell is then induced to "read" the edited segment and produce the appropriate protein.

Unlike the simple compounds that constitute non-biologics, proteins and other forms of biologic drugs have complex multilayered structures.[122] Current methods are often incapable of fully identifying the composition, structure, and function of a biologic.[123] In addition, the cell line in which the biologic is synthesized, the environment in which the cell line is cultured, and the methods with which a manufacturer isolates, purifies, and stores the final products each affect the structure, purity, and efficacy of the drug.[124] Biologics, in other words, are

answers [https://perma.cc/4BYV-U33H]; *see also Biological Product Definitions*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf (last visited Apr. 7, 2024) [https://perma.cc/9UYZ-D7KH].

120. Thomas Morrow & Linda Hull Felcone, *Defining the Difference: What Makes Biologics Unique*, NAT'L CTR. FOR BIOTECHNOLOGY INFO. (Sept. 4, 2004), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564302/ [https://perma.cc/M5N8-77SW]; Par Matsson & Jan Kihlberg, *How Big Is Too Big for Cell Permeability?*, 2017 J. MED. CHEMISTRY 1662, 1662–64.

121. *Differences Between Biologics and Small Molecules*, UNIV. COLL. LONDON, https://www.ucl.ac.uk/therapeutic-innovation-networks/differences-between-biologics-and-small-molecules (last visited Apr. 7, 2024) [https://perma.cc/3Z2P-EJYQ].

122. A protein's final configuration (also called its "conformation") depends on three to four structural "levels." Proteins consist of molecular units known as amino acids, each of which is made up of an identical "backbone" unit and a unique "R group" unit. A length of DNA encoding a protein directs the cell to assemble a chain of amino acids in a particular order. The sequence of amino acids is known as the protein's "primary structure." Atoms in the protein's backbone interact with each other to generate the protein's "secondary structure." The R groups then interact with each other to produce the protein's "tertiary structure." Some proteins consist of more than one amino acid chain; these have a "quaternary structure," which is formed when multiple subunits in their tertiary conformations come together. While it is often possible to determine which amino acids constitute a protein's primary structure, it is much more difficult to ascertain how chemical interactions produce its tertiary structure. Variations between proteins also arise when carbohydrates and other molecules attach to the proteins' surfaces and from other "post-translational" modifications. Differences between batches of proteins can arise by chance, through purposeful manipulation of various elements in the manufacturing process, or from uncontrollable disparities between cellular and/or culture environments.

123. *See* Steven A. Berkowitz, John R. Engen, Jeffrey R. Mazzeo & Graham B. Jones, *Analytical Tools for Characterizing Biopharmaceuticals and the Implications for Biosimilars*, 11 NATURE REVS. DRUG DISCOVERY 526, 527 (2012) (noting that for many "larger and more complex" biologics, "the extent to which existing analytical technologies can be used to support the likelihood of clinical comparability between a follow-on version and the original product is much more limited than for small-molecule drugs, and it is not possible to demonstrate that the two products are absolutely identical"). "Characterization" is the process by which the composition, structure, and function of a molecule are determined. The characterization of a protein may include uncovering which amino acids make up its primary structure, the order in which the amino acids are linked, the way in which the amino acid chain folds, how and where external molecules attach, how heavy the protein is, and more. *See Protein Characterization, Identification, & Purification*, JORDI LABS, https://jordilabs.com/blog/protein-characterization-identification-purification/ (last visited Apr. 7, 2024) [https://perma.cc/Y43S-PMEH].

124. Price II & Rai, *supra* note 111, at 1033–36.

path dependent and the process through which a biologic is created is considered to be as important as its chemical makeup.[125] As is frequently said in the biologics world, the process is the product.[126]

To appreciate the impact of the manufacturing process on biologic production, consider a 2011 study by Martin Schiestl and other researchers.[127] The study examines how the market versions of three different protein biologics, Aranesp (darbepoetin alfa), Rituxin/Mabthera (rituximab), and Enbrel (etanercept), changed between 2007 and 2010.[128] Comparing analyses of the sugars attached to each of these proteins across the three-year period, Schiestl and his colleagues found that all three biologics experienced a measurable shift in their chemical compositions.[129] None of the drugs were rebranded or relabeled over the studied period, and the authors concluded that the compositional shifts resulted from alterations in how each biologic was manufactured.[130] Although "the observed changes were predicted to result in no altered clinical profile," such occurrences of "product drift"[131] speak to the difficulty of maintaining the chemical identity of just the brand drug—to say nothing about the difficulty of guaranteeing commensurability between a brand biologic and its biosimilar. It is for this reason that when a drug-maker other than the brand biologic maker attempts to recreate the brand biologic, its product is considered a "biosimilar" rather than a substantially identical "generic."

In short, technical hurdles prevent scientists from fully identifying the chemical composition, structure, and function of biologics, with the result that it is not always possible to determine whether two biologic products are true duplicates of each other.[132] Furthermore, although some features of proteins produce known therapeutic effects,[133] the clinical ramifications of others are not so well known.[134] This makes it difficult to ascertain—even with structural analysis—whether two similar molecules will produce similar therapeutic outcomes, be they products of separate batches by the same drug-maker or a brand biologic

125. Arnold G. Vulto & Orlando A. Jaquez, *The Process Defines the Product: What Really Matters in Biosimilar Design and Production?*, 56 RHEUMATOLOGY iv14, iv15 (2017).

126. *See, e.g.*, Raj K. Puri, *FDA's Perspectives on Quality and Non-Clinical Evaluation of Cell/Tissue-Based Products*, CTR. FOR BIOLOGICS EVALUATION & RSCH., U.S. FOOD & DRUG ADMIN. (Aug. 26, 2010), https://www.pmda.go.jp/files/000153661.pdf [https://perma.cc/BEV5-K89X] (presenting at the Pharmaceuticals and Medical Devices Agency 5th International Symposium on Biologics in Tokyo); *see also NCI Initiative Aims to Boost CAR T-Cell Therapy Clinical Trials*, NAT'L CANCER INST. (Apr. 23, 2020), https://www.cancer.gov/news-events/cancer-currents-blog/2020/car-t-cell-nci-manufacturing-clinical-trials [https://perma.cc/Q7V8-4VJN]; H.R. REP. NO. 106-556, at 41 (2000); Yaniv Heled, *The Case for Disclosure of Biologics Manufacturing Information*, 47 J.L., MED. & ETHICS 54, 56 & n.40 (2019).

127. Martin Schiestl et al., *Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals*, 29 NATURE BIOTECHNOLOGY 310, 310 (2011).

128. *Id.*

129. *Id.* at 312.

130. *Id.*

131. *See also* Sundar Ramanan & Gustavo Grampp, *Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing*, 28 BIODRUGS 363, 368–69 (2014).

132. *See* Schiestl et al., *supra* note 127, at 310.

133. *Id.*; Berkowitz et al., *supra* note 123, at 537–38.

134. *See* Schiestl et al., *supra* note 127, at 310.

and a proposed biosimilar. To get around the characterization problem, the FDA uses the manufacturing process as a proxy measure of consistency: In addition to clinical trial data, drug companies seeking licensing must submit information about how the biologic is produced.[135] The FDA then evaluates this information for scalability, reproducibility, and controllability.[136] Drug-makers, in turn, have sought to protect their methods from competitors by patenting those methods, in addition to obtaining patents for the biologic molecules themselves,[137] and by enshrouding the methods as trade secrets.

B. Hurdles for Creating a Biosimilar

The fact that biologic drugs are process dependent[138] makes all details of the manufacturing process tremendously important. Even when patent information detailing the biologic's chemical makeup is available, other crucial information about the manufacturing process is currently withheld under a claim of trade secrecy.[139] As such, biosimilar manufacturers must painstakingly reverse engineer the biologic to develop a biosimilar[140]—a process that is both costly and lengthy.[141]

1. Costs of Developing a Biosimilar

The triple opacities of biologic structure, function, and production render biosimilar creation a far costlier endeavor than generic creation. An analysis from Pfizer in 2018 suggests that while a generic drug costs $1 to $2 million and two years to develop, a biosimilar costs over $100 million and five to nine years to develop.[142] Not only do biosimilars cost more to develop, they also cost more to manufacture. A 2017 analysis from Morgan Stanley estimates that biologic

135. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES 3–5 (2011).

136. *Id.* at 4.

137. Arti K. Rai & W. Nicholson Price II, *An Administrative Fix for Manufacturing Process Patent Thickets*, 39 NATURE BIOTECHNOLOGY 20, 21 (2021); Laura Karas, *Pharmaceutical Patents on Manufacturing Methods: Groundless or Well-Supported?*, BILL OF HEALTH BLOG (Feb. 16, 2021), https://blog.petrieflom.law.harvard.edu/2021/02/16/method-patents-biologics-patent-thicket/ [https://perma.cc/N9M5-W8F4].

138. Favour Danladi Makurvet, *Biologics vs. Small Molecules: Drug Costs and Patient Access*, 9 MED. DRUG DISCOVERY 1, 2 (2021).

139. Robin Feldman, *Trade Secrets in Biologic Medicine: The Boundary with Patents*, 24 COLUM. SCI. & TECH. L. REV. 1, 33 (2022); Price II & Rai, *supra* note 111, at 1028.

140. Charlotte Geaghan-Breiner, Note, *The Patent Trap: The Struggle for Competition and Affordability in the Field of Biologic Drugs*, 54 COLUM. J.L. & SOC. PROBS. 589, 595 (2021).

141. *See* Allison Inserro, *Comparing the Economics of Biosimilars and Generics*, AJMC (June 25, 2019), https://www.centerforbiosimilars.com/view/comparing-the-economics-of-biosimilars-and-generics [https://perma.cc/9YAB-JPTW] ("[I]t may take $1 million to $2 million over 2 years to launch a generic. Meanwhile, biosimilar launches cost more than $100 million and take 5 to 9 years.").

142. PATIENTS AT OUR CENTER: PFIZER 2018 ANNUAL REVIEW, PFIZER 17 (2018).

drugs cost $95 to $225 to manufacture per gram;[143] non-biologics, in contrast, cost only tens of cents per gram to make.[144]

The difficulty and the high costs of development can deter potential biosimilar developers from pursuing development. As such, the pool of potential competitors is much smaller, with the result that the price-lowering effects of competition are more limited in biologics markets compared to non-biologic markets. For manufacturers that successfully undertake biosimilar development, regulatory differences present the next challenges that hobble competition between biologics and biosimilars.

2. Regulatory Hurdles

Some of the regulatory differences between non-biologic and biologic drugs arguably stem from the differences inherent in the chemical structure of these two types of drugs. For example, the molecular complexity of a biologic renders it impossible to perfectly replicate the brand drug, as one can with generics. Thus, follow-on biologics are considered *biosimilar* to the brand product, rather than *bioequivalent*.[145] That subtle difference in language has strong ramifications, with the first relating to the materials required for FDA licensing.

Although generic drug applicants can rely fully on the brand non-biologic drug's clinical trial data, biosimilar applicants must submit analytical studies, animal studies, and clinical studies to the FDA with the aim of developing an increasingly refined understanding of the proposed biosimilar and its likeness to the brand biologic product.[146] Although a biosimilar application calls for some additional studies and data, the purpose is to enable the biosimilar drug-maker to rely in part on the FDA's previous "determination of the safety and effectiveness of the reference product for [licensing]" so that it does "not need to conduct as many expensive and lengthy clinical trials."[147]

The difference between biosimilarity and bioequivalence has strong competitive ramifications, as well. The most important relates to whether pharmacists can substitute the biosimilar when the doctor's prescription lists the brand.

a. To Substitute or Not to Substitute

Understanding the competitive importance of substitutability begins with understanding the role substitution has played in development of the generics

143. Avik Roy, *Biologic Medicines: The Biggest Driver of Rising Drug Prices*, FORBES (Mar. 8, 2019, 8:20 PM), https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices/?sh=112aae1a18b0 [https://perma.cc/XS5P-WSYH].

144. Andrew M. Hill, Melissa J. Barber & Dzintars Gotham, *Estimated Costs of Production and Potential Prices for the WHO Essential Medicines List*, 3 BMJ GLOB. HEALTH 1, 4 (2018).

145. Anne Park Kim & Ross Jason Bindler, *The Future of Biosimilar Insulins*, 29 DIABETES SPECTRUM 161, 163 (2016); Ramsey Baghdadi, *Biosimilars*, HEALTH AFFS. (July 21, 2017), https://www.healthaffairs.org/do/10.1377/hpb20170721.487227/full/ [https://perma.cc/8JW9-8ZZ8].

146. *Biosimilars: Review and Approval*, U.S. FOOD & DRUG ADMIN. (Dec. 13, 2022), https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval [https://perma.cc/56J6-AYV6].

147. *Id.*

industry. Success of generic market entry was due, in part, to state laws that allow pharmacists to fill a prescription with the generic when a doctor prescribes a brand product—presumably to reduce the cost to patients and insurers.[148] States have based that decision on the FDA's determination that the generic is *bioequivalent* to the brand non-biologic drug.[149] In fact, most states allow generic substitution, and a few actually mandate the substitution of generic drugs for their brand-name counterparts.[150] The generics industry has relied on state substitution laws to drive business, reducing the need to advertise generic versions.[151] Lack of advertising spending in the generics industry helps keep the price of generics low.

In contrast, the Biosimilars Act distinguishes among biosimilars, categorizing biosimilars into two types: (1) interchangeable biosimilars and (2) non-interchangeable biosimilars.[152] To obtain the coveted interchangeable designation, a biosimilar must not only demonstrate that there are "no clinically meaningful differences . . . in terms of safety, purity, and potency" between its drug and the brand biologic,[153] but also conduct a switching study to show that there is no difference in a patient's clinical outcomes when switching from the biologic to the interchangeable biosimilar and vice-versa.[154] Such switching studies are costly;[155] only four biosimilars have been designated as interchangeable so far.[156]

The Biosimilars Act specifies that a pharmacist may substitute a biosimilar "without the intervention of the health care provider," only if that biosimilar has

148. Erwin A. Blackstone & Joseph P. Fuhr, Jr., *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS 469, 472 (2013); Benjamin P. Falit, Surya C. Singh & Troyen A. Brennan, *Biosimilar Competition in the United States: Statutory Incentives, Payers, and Pharmacy Benefit Managers*, 34 HEALTH AFFS. 294, 298 (2015).

149. *See* Feldman & Kanter, *supra* note 14, at 61.

150. Chana A. Sacks et al., *Assessment in Variation of State Regulation of Generic Drug and Interchangeable Biologic Substitution*, 181 J. AM. MED. ASS'N INTERNAL MED. 16, 18 (2021).

151. *Id.* at 17; *see also* Feldman & Kanter, *supra* note 14, at 74 (noting that substitution laws can help generic drugs attain market success).

152. Sacks et al., *supra* note 150, at 17.

153. *See* 42 U.S.C. § 262(i)(2)(A)–(B) (using the language of "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency"); *see also id.* § 262 (k)(4)(A)(ii) (describing the requirement as producing "the same clinical result . . . in any given patient").

154. *See* 42 U.S.C. § 262(i)(2)(A)–(B) (explaining that to demonstrate biosimilarity, the manufacturer must submit data showing that the biosimilar is "highly similar" to the originator biologic and with "no clinically meaningful differences . . . in terms of . . . safety, purity, and potency"); Tony Hagen, *The Difference Between an Interchangeable Biosimilar and One That Isn't*, CTR. FOR BIOSIMILARS (May 5, 2021), https://www.centerforbiosimilars.com/view/the-difference-between-an-interchangeable-biosimilar-and-one-that-isn-t [https://perma.cc/3TZ3-SXCN].

155. Falit et al., *supra* note 148, at 296 (noting significant expense of conducting large-scale switching study: switching studies "can cost more than $50,000 per patient").

156. *See FDA Roundup: September 15, 2023*, U.S. FOOD & DRUG ADMIN. (Sept. 15, 2023), https://www.fda.gov/news-events/press-announcements/fda-roundup-september-15-2023 [https://perma.cc/9YVH-548V]; *Remarks by Commissioner Robert Califf to the 2023 Food and Drug Law Institute (FDLI) Annual Conference*, U.S. FOOD & DRUG ADMIN. (May 17, 2023), https://www.fda.gov/news-events/speeches-fda-officials/remarks-commissioner-robert-califf-2023-food-and-drug-law-institute-fdli-annual-conference-05172023 [https://perma.cc/6AMV-VSCN].

been designated with an interchangeable status.[157] Without the ability to rely on automatic substitution, non-interchangeable biosimilars, which constitute the majority of biosimilars, must rely on advertising to promote their products, adding costs that can flow through to the drug pricing.[158] The non-substitutability of biosimilar drugs has led some commentators to characterize them as "me-too" drugs, "standalone pharmaceutical products that are indicated for the same disease or condition but are not clinically fungible."[159]

Moreover, even interchangeable status does not guarantee automatic substitution at the state level.[160] Despite the Biosimilars Act's provision that an interchangeable can be "substituted without prescriber notification," forty-five states still require prescriber notification before interchangeable substitution can take place.[161] In addition, substitution laws for almost all states contain more requirements for interchangeable substitution than for generic substitution—such as mandating that pharmacists notify physicians about interchangeable substitution.[162] These additional requirements reduce the amount of substitution that takes place for biologic drugs compared to non-biologic drugs.[163]

In contrast to the U.S. system, Europe permits all biosimilars to be substituted for their biologic counterparts.[164] A review of studies encompassing 11,000 patients found that adverse effects from such substitutions, while not nonexistent, are rare.[165]

b. What's in a Name?

The FDA's mandated naming convention also hampers the uptake of biosimilars, creating stickiness in the market that makes it less likely for physicians and patients to switch, particularly in comparison to non-biologic drugs. With non-biologic drugs, federal regulations mandate that the drug's label include the generic name that the World Health Organization creates through its International Nonproprietary Name ("INN") process.[166] Biologics, however, are not treated that way. Given that biosimilars are not considered bioequivalent to the

157. 42 U.S.C. § 262(i)(3). Almost all states have adopted laws allowing automatic substitution of biosimilars that are interchangeable. *See* Heled, *supra* note 14, at 126–27.

158. Henry Grabowski & Erika Lietzan, *FDA Regulation of Biosimilars*, *in* FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 414, 419–20 (Holly F. Lynch & I. Glenn Cohen eds., 2015).

159. Yaniv Heled, *Biosimilars Are a Distraction*, HEALTH AFFS. (Apr. 8, 2019), https://www.healthaffairs.org/do/10.1377/forefront.20190328.523018/full/ [https://perma.cc/N6EJ-N23P].

160. Adriana Lee Benedict, *State-Level Legislation on Follow-on Biologic Substitution*, 2014 J.L. & BIOSCIENCES 190, 191–92 (noting that some states require "patient consent or physician notification of substitution").

161. Sacks et al., *supra* note 150, at 18.

162. *Id*.

163. *Id.*

164. Jacob S. Sherkow, *The Science of Substitution: A Response to Carrier and Minniti*, 2018 U. ILL. L. REV. ONLINE 81, 90–91.

165. *Id.*; Pekka Kurki et al., *Interchangeability of Biosimilars: A European Perspective*, 31 BIODRUGS 83, 86 (2017).

166. Jordan Paradise, *The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the United States Healthcare System*, 41 AM. J.L. & MED. 49, 55, 59 (2015).

brand biologics, some have argued that biosimilars should not be given the same nonproprietary name, on the grounds that for safety reasons, regulatory agencies must be able to distinguish between the biosimilar and the brand.[167] That argument is somewhat lacking, given that safety agencies do not need unique names to trace the origin of a product, and these agencies can already trace those origins with great precision through other coding methods.[168]

In 2017, however, the FDA adopted guidelines to give biosimilars, including interchangeable biosimilars, a random four-letter suffix added to the generic name of the drug.[169] The FTC opposed the policy because it suggests that the biosimilar and brand biologics differ in meaningful ways. This suggested difference would diminish physician and patient trust in the safety and efficacy of biosimilar products, making it more difficult for biosimilar manufacturers to compete against the brand biologics.[170] As such, the FTC has argued that assigning different names will negatively impact the cost-saving effect of biosimilar market entry.[171] Others have argued that naming conventions also can impact pharmacist confidence in substituting interchangeable biosimilars for originator biologics.[172] In a survey, pharmacists reported being most confident in substituting interchangeable biosimilars when they share the same nonproprietary name with their brand counterpart compared to when the names differ in any way.[173] Additionally, the inclusion of the four-letter suffix might signal to the patients that the biosimilar is different from the originator biologic in clinically meaningful

167. *Id.* at 72.

168. *See id.* at 74 (explaining that the FDA traces product origin using NDC codes, which are unique 10-digit numbers to identify each human drug and show the manufacturer, strength, dosage form, formulation, package size, and type of drug).

169. *See* FOOD & DRUG ADMIN., NONPROPRIETARY NAMING OF BIOLOGICAL PRODUCTS: GUIDANCE FOR INDUSTRY 1 (2017). In the context of naming drugs, generic names are also known as nonproprietary names, the names for the medicine's active ingredient. *See* Karan B. Thakkar & Gauri Billa, *The Concept of: Generic Drugs and Patented Drugs vs. Brand Name Drugs and Non-Proprietary (Generic) Name Drugs*, 4 FRONTIERS IN PHARMACOLOGY 1, 1 (2013).

170. Ameet Sarpatwari, Rachel Barenie, Gregory Curfman, Jonathan J. Darrow & Aaron S. Kesselheim, *The US Biosimilar Market: Stunted Growth and Possible Reforms*, 105 CLINICAL PHARMACOLOGY & THERAPEUTICS 92, 97 (2019). Not only were the FTC's concerns well-founded, but the FDA's expectations also have not panned out. When adopting the naming convention that mandates the four-letter suffix, the FDA argued that the suffix would facilitate the assessment and mitigation of adverse drug effects, especially when no other means to track a specific dispensed product are readily available. In practice, however, prescribers and pharmacists have found it difficult to track products using a random four-letter label that is devoid of meaning. One analyst noted, for example, that as of the second quarter of 2018, less than half a percent of biosimilar-related adverse drug reports ("ADRs") utilized the four-letter suffix to identify the biosimilar that caused the adverse effect. The rest of the ADRs simply used the biosimilar's brand name. *See* U.S. FOOD & DRUG ADMIN., NONPROPRIETARY NAMING OF BIOLOGICAL PRODUCTS: Update (2019); *see also* Stanton Mehr, *If Four Letter Suffixes Aren't Used in Biosimilar Tracking, What Use Are They?*, BIOSIMILAR DEV. (Nov. 6, 2018), https://www.biosimilardevelopment.com/doc/if-four-letter-suffixes-aren-t-used-in-biosimilar-tracking-what-use-are-they-0001 [https://perma.cc/PDP7-4QU2].

171. Paradise, *supra* note 166, at 73.

172. Sara Fernandez-Lopez, Denise Kazzaz, Mohamed Bashir & Trent McLaughlin, *Assessment of Pharmacists' Views on Biosimilar Naming Conventions*, 21 J. MANAGED CARE & SPECIALTY PHARMACY 188, 192 (2015).

173. *Id.* at 193.

ways,[174] further reducing the uptake of biosimilars. Thus, naming conventions also present a drag on competition between biosimilars and brand biologics.

c. Weaker Statutory Incentives

Substitution is not the only way in which the Biosimilars Act lags behind the Hatch-Waxman Act in encouraging competition. The Biosimilars Act also contains weaker statutory incentives for potential biosimilar manufacturers.[175] Specifically, the Hatch-Waxman Act gives the first generic manufacturer a 180-day exclusivity period in which no other generic can enter the market.[176] In contrast, the Biosimilars Act offers no exclusivity for the first biosimilar, providing an incentive only for the first successful interchangeable biosimilar.[177] Congress may have anticipated that the interchangeable status would provide a more viable pathway than history has shown. As noted above, however, the FDA has licensed only four interchangeable biosimilars since the passage of the Biosimilars Act in 2010.[178] Thus, the interchangeable pathway has proven a less-than-robust method of injecting competition into the market for biologic medicines.

In short, given statutory and regulatory impediments to competition, biosimilars that get licensed and successfully navigate the patent dance may still face challenges through state and federal laws that can dampen competition between biologics and biosimilars. As a result, biosimilars have captured less of the biologic market share and reduced prices to a lesser extent than generics.[179]

IV. ASSERTION OF INTELLECTUAL PROPERTY RIGHTS: COMPARING THE HATCH-WAXMAN AND BIOSIMILARS ACTS

In addition to the legislative and regulatory differences described above, the approval pathway for generics differs significantly from the licensing pathway for biosimilars. These contrasts are particularly strong in the realm of identifying the intellectual property rights that might be asserted in protection of a biologic drug. When a company contemplates producing a generic or biosimilar drug, part of the calculation will involve identifying what intellectual property

174. One study analyzed patient perception of the four-letter suffix by asking the participants a series of questions after showing them a print advertisement of a fictitious large molecule drug. It found that the four-letter suffix diminished the perceived similarity of a biosimilar to its reference brand biologic. Mariana P. Socal, Jace B. Garrett, William B. Tayler, Ge Bai & Gerard F. Anderson, *Naming Convention, Interchangeability and Patient Interest in Biosimilars*, 33 DIABETES SPECTRUM 273, 276 (2020).

175. Falit et al., *supra* note 148, at 295.

176. 21 U.S.C. § 355(j)(5)(B)(iv).

177. Falit et al., *supra* note 148, at 295; 42 U.S.C. § 262(k)(6)(A) (providing one-year marketing exclusivity for the first interchangeable biosimilar).

178. *See supra* note 156 and accompanying text.

179. *See After Sluggish Start, Is the Biosimilar Market Poised for Growth?*, ARNOLD VENTURES (Apr. 6, 2021), https://www.arnoldventures.org/stories/after-sluggish-start-is-the-biosimilar-market-poised-for-growth [https://perma.cc/N9B3-BYQT] (asserting that the "savings reaped by the swelling generics market have proven harder to tap in the biologics market"); *see also* Steven Kozlowski et al., *Uptake and Competition Among Biosimilar Biological Products in the US Medicare Fee-for-Service Population*, 37 J. GEN. INTERNAL MED. 4292, 4292 (2022) ("[B]iosimilar uptake was generally lower than that reported for generic drugs.").

rights protect the drug, whether those rights are likely to stand up if challenged in court, and when those rights expire.[180]

With the Hatch-Waxman framework for non-biologic drugs, companies must provide information about the patents and exclusivities they claim in relation to an approved drug. The FDA makes this information available in the Orange Book as a matter of course.[181] In contrast, biologic companies are not required to provide such information as a matter of course under the Biosimilars Act; any information that the FDA eventually publishes related to biologics will emerge only following a long and arduous sequence of litigation steps.[182] Those steps—and the information that emerges from those steps—are under the control of the drug manufacturers themselves. By granting drug companies this level of control over information disclosure in the biologic context, this framework erects additional barriers to market entry—both for any initial biosimilar product and for any later biosimilar companies. The following section describes strategic behaviors deployed by brand biologic companies (called "reference product sponsors" by the FDA) and their biosimilar counterparts that hamper the public dissemination of intellectual property information.

A. Intellectual Property Information in the Hatch-Waxman Process for Generics

Replicability and ease of characterization were both key to the construction of the approval pathway for non-biologic entry laid out in the 1984 Drug Price Competition and Patent Term Restoration Act, better known as the Hatch-Waxman Act. These attributes of non-biologic drugs made it possible to alleviate the financial burden on generic drug-makers of conducting clinical trials, which account for over 50% of non-biologic drug research and development costs.[183] Prior to the Act's passage, generic manufacturers were expected to complete their own trials, even though their products were the same as brand drugs, which had already been proven safe and effective.[184]

180. A brand company can create or authorize a generic or biosimilar version of its drug, in which case the calculation is different. The brand already holds any rights to the drug and has regulatory permission to produce it. Thus, the FDA does not require any additional approval process, and the Hatch-Waxman and Biosimilars Act provisions do not apply. *See* Robin Feldman, *Captive Generics: The Wolf in Sheep's Clothing*, 59 HARV. J. ON LEGIS. 378, 387 (2022) (using Medicare data to compare drug markets that host a captive generic with those that do not and finding that the presence of captive generics triples the magnitude of the brand price increases, boosts the growth of true generic prices, reduces true generic market share, and does not increase the total number of generics).

181. *Approved Drug Products with Therapeutic Equivalence Evaluations | Orange Book*, U.S. FOOD & DRUG ADMIN. (Nov. 17, 2023), https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book [https://perma.cc/7RWY-JXE8].

182. *See* 42 U.S.C. § 262(l); Robin Feldman, *Dance of the Biologics*, 38 BERKELEY TECH. L.J. 101, 146–47 (forthcoming 2024).

183. Steven Simoens & Isabelle Huys, *R&D Costs of New Medicines: A Landscape Analysis*, 8 FRONTIERS MED. 1, 2 (2021).

184. ROBIN FELDMAN & EVAN FRONDORF, DRUG WARS: HOW BIG PHARMA RAISES PRICES AND KEEPS GENERICS OFF THE MARKET 21–22 (Cambridge Univ. Press 2017).

For a brand drug, patent protection and the possibility of recouping clinical trial costs by charging monopoly prices create the incentive for engaging in those studies. For generic companies, which would be making copies of drugs for which the patents have expired, no such patent protection would be available. Additional clinical trials, moreover, would be a waste of societal resources, given that the safety and efficacy of the drug was already established.

The cost of conducting new clinical trials, coupled with the low profit potential given the lack of patent protection, discouraged manufacturers from entering the generics market. Generic companies also have been deterred from market entry until after the brand non-biologic companies' patents had expired to avoid potential infringement lawsuits.[185] Thus, brand manufacturers could continue to reap monopoly profits for months or even years after their patent terms ended while the generic manufacturers waited for FDA approval.

The Hatch-Waxman Act addressed these issues and other impediments to generic market entry by creating a simplified pathway for generic market entry. Applicants for approval of a generic non-biologic no longer had to submit their own clinical trial data. They could rely on the safety and efficacy data presented by the brand company and simply demonstrate that their products were bioequivalent to the brand.[186]

The Act also created a method by which the generic could artificially infringe on the brand non-biologic's patents prior to the patents' expiration.[187] This allows generic companies to resolve potential intellectual property rights issues ahead of time without the risk of hefty infringement damages.[188] Normally, damages in patent litigation are based on the production of a product.[189] This artificial infringement occurs, however, before any product is produced so that no damages accrue.

To initiate the artificial infringement, generic companies can file what is known as a "Paragraph IV certification," which gives the brand company the opportunity to commence patent litigation.[190] If the brand company's patents are found to be invalid or not infringed, the generic company can enter the market as soon as its FDA application is approved, rather than waiting for the brand drug's patents to expire.

Engaging in any patent litigation is expensive, however, particularly with large pharmaceutical companies. To encourage generic companies to "do battle

185. *See* U.S. Fed. Trade Comm'n, Generic Drug Entry Prior to Patent Expiration: An FTC Study vii (2002) ("In most instances, generic applicants have waited to enter the market until at least a district court has held that the patent covering the brand-name company's drug product was invalid or not infringed by the generic applicant's ANDA."); *see also* Kerstin Vokinger, Aaron S. Kesselheim, Jerry Avorn & Ameet Sarpatwari, *Strategies That Delay Market Entry of Generic Drugs*, 177 J. AM. MED. ASS'N INTERNAL MED. 1665, 1665–66 (2017) ("When submitting their applications to the FDA, generic manufacturers must promise to wait to market their versions until these patents have expired or allege either that their versions do not infringe these patents or that the patents are invalid. The brand-name manufacturer usually challenges such claims in court.").

186. 21 U.S.C. § 355(j)(2)(A)(iv).

187. 35 U.S.C. § 271(e)(2).

188. Robin Feldman, *The Price Tag of "Pay-for-Delay,"* 23 COLUM. SCI. & TECH. L. REV. 1, 8 (2022).

189. *See id.*

190. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

with the big guns" by challenging improper patents, Hatch-Waxman rewarded the first generic drug-maker that filed a successful Paragraph IV certification with 180 days of market exclusivity.[191] During this period, only a first-filing generic and the brand are allowed on the market, a restriction that allows the first-filer to share in pricing above a competitive level.[192]

Resolving potential patent disputes under Hatch-Waxman includes three steps: The generic manufacturer submits its application and a Paragraph IV certification to the FDA; the generic company notifies the brand of its action; and the brand has forty-five days to sue the generic for infringement.[193]

Crucially, the Hatch-Waxman system institutes a high degree of rights transparency as part of the non-biologic approval process. When a brand company submits a new drug application ("NDA") for a non-biologic drug, the company must list any patents and exclusivities associated with the drug for which "a claim of patent infringement could be reasonably asserted."[194] If the brand company obtains additional patents or exclusivities, the company must amend its materials to include them.[195] The FDA, in turn, must maintain a public record of all such rights relevant to approved drugs and must update that record every thirty days.[196] The record is made available as an addendum to the FDA's list of all available non-biologic drugs in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the Orange Book.[197] Specifically, the Orange Book Transparency Act requires the FDA to publish drug product and method of use patents relating to approved products.[198]

The accessibility of relevant patent information is a huge boon to potential generic applicants. Generic hopefuls can easily discover what patents exist and when those patents will expire before beginning the process of generic drug development, allowing generics to better evaluate the risk of undertaking a particular generic venture. Patent rights disclosure and transparency have helped oil the machine of generic drug entry under the Hatch-Waxman regime. Prior to the Act, only 19% of prescriptions were filled with generics; 90% of prescriptions are filled with generics today.[199]

As a compromise with the pharmaceutical industry, the Hatch-Waxman Act enables the brand company to obtain a patent term extension, correlating with and compensating for any delays in regulatory approval. A patent term

191. Feldman, *supra* note 188, at 48.

192. *See* 21 U.S.C. § 355(j)(5)(B)(iv).

193. *Id.* § 355(j)(5)(B)(iii).

194. *Id.* § 355(b)(1)(A)(viii), (B).

195. *Id.* § 355(c)(2); 21 C.F.R. § 314.53.

196. *Id.* § 355(j)(7)(A)(ii).

197. *Orange Book Preface*, U.S. FOOD & DRUG ADMIN. (Jan. 25, 2023), https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface [https://perma.cc/AV3V-ZG9V]; Listing of Patent Information in the Orange Book, 85 Fed. Reg. 33,169, 33,170 (June 1, 2020).

198. Orange Book Transparency Act of 2020, Pub. L. No. 116-290, § 2, 134 Stat. 4889, 4889 (noting that the Orange Book includes drug product and method of *use* patents, but not method of *manufacture* patents).

199. *What is Hatch-Waxman?*, PHARM. RSCH. & MFRS. OF AM. (2018), https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/D-F/Fact-Sheet_What-is-Hatch-Waxman_June-2018.pdf [https://perma.cc/LVT8-VPBH].

extension is limited to a maximum of five years, and no patent term extension may extend the patent's expiration date beyond fourteen years after the drug's FDA approval.[200] That compromise is reflected in the formal title of the Hatch-Waxman Act: "The Drug Price Competition *and Patent Term Restoration* Act." In addition, the Hatch-Waxman Act also established certain exclusivities to incentivize pharmaceutical innovation. In particular, if the FDA approves a brand company's non-biologic drug containing a new chemical entity, the Hatch-Waxman Act gives the brand company either four or five years in which no other company can file a generic drug application relying on the brand company's data.[201] These so-called "data rights" apply even if all patents on the drug have expired or if the courts have rejected the patents as invalid. This legislative language gave brand manufacturers the potential to extend the length of their protection on a drug, at least if that drug is a new active ingredient.[202]

B. Intellectual Property Information in the Biosimilars Act Process for Biosimilars

The United States lacked a pathway for licensing biosimilars until 2010, five years after Europe had created such a pathway.[203] As noted above, Congress inserted the Biosimilars Act into the Affordable Care of 2010 last-minute, without undergoing the usual route of congressional hearings, markups, and debate that might have improved the system.[204]

For those who love complexity, the Biosimilars Act is "a garden of delights,"[205] full of short-hand language and meaningless numerical names. For mere mortals, the process is daunting to understand. The following section should provide a helpful guide.

1. Steps of the Patent Dance

In the same mold as the Hatch-Waxman Act, the Biosimilars Act followed a compromise between brand biologics and biosimilars: Biosimilars would be able to use the clinical trial data that the biologic company developed as part of licensing its drug, and the biologic company would receive regulatory rights in

200. 35 U.S.C. § 156(c)(3).

201. *See* 21 C.F.R. § 314.108(b)(2) (implementing new chemical entity exclusivity, which limits the simplified drug-approval pathways created by Hatch-Waxman Act, see 21 U.S.C. § 355(c)(3)(E)(ii), (j)(5)(F)(ii)); *see also* Robin Feldman, *Regulatory Property: The New IP*, 40 COLUM. J.L. & ARTS 53, 70–72, 103, Appendix A, n.** (2016) (describing the relevant data right and explaining that the length is shortened to four years if a generic hopeful files for FDA approval certifying its intent to challenge the patent on the drug as invalid, unenforceable, or not infringed).

202. *See supra* note 25 (citing Hatch-Waxman Act, which added new chemical entity exclusivities, *see supra* note 201); *see* U.S. FOOD & DRUG ADMIN., NEW CHEMICAL ENTITY EXCLUSIVITY DETERMINATIONS FOR CERTAIN FIXED-COMBINATION DRUG PRODUCTS: GUIDANCE FOR INDUSTRY 2–4 (2014).

203. Ioana Gherghescu & M. Begoña Delgado-Charro, *The Biosimilar Landscape: An Overview of Regulatory Approvals by the EMA and FDA*, 13 PHARMS. 48, 49 (2021).

204. *See supra* note 13 and accompanying text.

205. FELDMAN & FRONDORF, *supra* note 184, at 643.

return.[206] Those rights are stronger for biologics than for non-biologic drugs, perhaps in response to the greater effort and expense necessary to develop a biologic. For four years after the FDA approves a biologic, no biosimilar may even apply for licensing.[207] This bar holds even if the biosimilar uses its own data and the patents on the biologic have expired.[208] For an additional eight years, a biosimilar company cannot rely on the biologic company's data but can apply for and receive a license only if using its own data.[209] In other words, in exchange for allowing a biosimilar to use the brand's original clinical data, the Act gave biologic companies four years of complete protection and twelve years of data protection.

In contrast to the Hatch-Waxman regime, the Biosimilars Act does not require that biologic companies provide information about their intellectual property rights related to a particular drug as soon as the biologic receives licensing.[210] Instead, intellectual property information is doled out as part of a complicated sequence of negotiations between the brand and the biosimilar when the *biosimilar* applies to become licensed—a sequence known as "the patent dance."[211] As a result, the biosimilar must decide whether to invest in developing its own version of the drug without knowing what rights exist or what other barriers might be thrown their way. That knowledge gap is particularly burdensome for the *first* biosimilar, as subsequent biosimilars may obtain at least some of that knowledge from the first biosimilar's own patent dance with the biologic. Moreover, the complexity of the Act has invited companies to engage in strategic behaviors to prevent their intellectual property information from ever becoming public.

One should note that although patents are intended to provide notice to all of the boundaries one claims as one's own, there is wide acknowledgment that the system falls woefully short of that goal.[212] Patents asserted against a drug will not necessarily mention the drug; searching the millions of patents in the USPTO data base is a tricky and difficult process. Thus, the decision of whether to launch a biosimilar is like dancing in the dark.

The full patent dance, set forth by the Biosimilars Act, begins when the FDA notifies the biosimilar company that its application has been accepted for review.[213] The biosimilar then must send its application and manufacturing

206. *See infra* notes 207–09 and accompanying text.

207. *See* 42 U.S.C. § 262(k)(7)(B).

208. *See* Feldman, *supra* note 201, at 84.

209. *See id.* (noting that although the Act's language is ambiguous regarding whether the full twelve years should provide only data rights or, rather, should block a biosimilar from even applying for approval with its own data, the FDA, following letters from Congress, has interpreted the language as providing only data rights for the full twelve years); *see also* JOHN R. THOMAS, CONG. RSCH. SERV., R42890, THE ROLE OF PATENTS AND REGULATORY EXCLUSIVITIES IN PHARMACEUTICAL INNOVATION 8–9 (2014) (describing the controversy and providing excerpts from the Congressional letters).

210. Michael J. Schellhous, *Improving Access to Emerging Lifesaving Drugs: Solving the Disclosure Problem Within the Patent Dance*, 15 ST. LOUIS U. J. HEALTH L. & POL'Y 201, 208–09 (2021).

211. *Id.* at 209–10.

212. ROBIN FELDMAN, RETHINKING PATENT LAW 52 (Harv. Univ. Press 2012).

213. 42 U.S.C. § 262(l)(2).

information to the brand company.[214] In exchange, the brand sends the biosimilar a list of the patents that it believes reasonably could be asserted against the biosimilar drug ("3A list").[215] The biosimilar company must respond with a "detailed statement" explaining why each listed patent is invalid or will not be infringed, or a statement promising that the biosimilar will not enter the market until the listed patents expire.[216]

The biosimilar company may then draw up its own list detailing any other patents that it believes that the brand biologic reasonably could assert against the new product ("3B list").[217] In other words, the biosimilar is saying to the brand: "We think you left some things out of your list that you might launch at us." The brand, in return, may share its own "detailed statement" explaining why each patent addressed in the biosimilar's "detailed statement" is, in fact, valid or will be infringed.[218]

If the brand receives a new patent that could be asserted against the biosimilar after giving its 3A list to the biosimilar, it must draw up a list containing any new patents ("7AB list").[219] The biosimilar must respond with another statement explaining why each listed patent is invalid or will not be infringed.[220] Theoretically, the brand could use the 7AB list as an opportunity to obtain or amend patents covering the biosimilar's manufacturing process, which was disclosed to the brand earlier in the patent dance. To prevent such opportunism, the biosimilar can protect its disclosure by having the brand first enter into a confidentiality agreement in which the brand company agrees not to prosecute patents on the basis of the biosimilar company's disclosure.

Once the biosimilar receives the brand's response to its statement, the parties must decide which patents from the 3A and 3B lists belong on a "final and complete list" of patents that will be the subject of an action for infringement ("4AB list").[221] If the two cannot agree, they each draw up a list of patents that should be the subject of an infringement action (collectively, "5B lists") and exchange those lists.[222] The number of patents on the brand list ("5BiII list") cannot exceed the number of patents on the biosimilar list ("5BiI list"),[223] a limitation apparently designed to empower the biosimilar to control the scale of the patent litigation and prevent the brand from drowning the biosimilar in litigation claims.

The brand biologic has thirty days to bring an infringement action covering the patents on the 4AB list or, if they have failed to agree on the 4AB list, the 5B

214. *Id.* § 262(1)(2)(A).
215. *Id.* § 262(l)(3)(A).
216. *Id.* § 262(l)(3)(B).
217. *Id.* § 262(l)(3)(B)(i).
218. *Id.* § 262(l)(3)(C).
219. *Id.* § 262(l)(7).
220. *Id*.
221. *Id*. § 262(l)(4)(A)–(B).
222. *Id.* § 262(l)(5)(B)(i).
223. *Id.* § 262(l)(5)(B)(ii)(I). There is one exception to this rule, however: If the biosimilar's 5BiI list does not contain any patent, the brand may include one patent in its own 5BiII list. *Id.* § 262(l)(5)(B)(ii)(II).

lists.[224] The biosimilar must give the complaint to the FDA, which then publishes notice of the complaint in the Federal Register.[225]

The second phase of the dance allows the parties to deal with first-phase patents whose validity and/or infringement status was not addressed at the time, as well as new patents that the brand company received after the initial exchange of lists.[226] The statute creates two phases apparently to enable the parties to isolate and litigate key patents in phase one, and leave other patents to be litigated, if at all, in the later, second phase.[227] With the second phase, the biosimilar company must give the brand advance notice of the biosimilar drug's first commercial marketing.[228] Before the biosimilar enters the market, the brand may seek a preliminary injunction staying manufacture or sale of the biosimilar until a court has evaluated any patents included in the 3A, 3B, and 7AB lists that did not make it onto the 4AB or 5B lists.[229] Note that the statute's patent dance provisions authorize a preliminary injunction only in phase two, not phase one, though other parts of the Biosimilars Act may authorize injunctive relief in both phases.[230]

Nothing in the Biosimilars Act requires the first phase to finish before the biosimilar company initiates the second phase.[231] Thus, if the brand company loses (or never files) its preliminary injunction motion in the second phase, the biosimilar company can, consistent with the Act, "launch at risk" upon obtaining FDA approval.[232] By launching at risk, the biosimilar company starts selling its drug but incurs the risk that the brand company will seek damages and a jury trial. Nor is there reason to believe that the FDA will withhold approval pending completion of any part of the patent dance; no statutory provision requires the FDA to wait for the dance to finish in whole or in part, and nothing indicates that the FDA is even inclined to wait. And if the second phase starts before the parties have negotiated the 4AB list or exchanged their 5B lists, then the first phase

224. *Id.* § 262(l)(6)(A)–(B).

225. *Id.* § 262(l)(6)(C)(i)–(ii).

226. *Id*. § 262(l)(8)(A).

227. While the statute creates these two separate phases, the two phases may be collapsed together in practice. For a practitioner's perspective, see Thomas J. Sullivan, *The Patent Dance*, EUR. BIOPHARMACEUTICAL REV. 70, 74 (2018):

> A second mechanism to shorten a suit under the BPCIA would be to collapse the two phases of litigation into a single action in a scenario where the biosimilar applicant provides its 180-day notice of commercial marketing contemporaneously with its notification to the reference product sponsor of its [biosimilar application].

228. 42 U.S.C. § 262(l)(8)(A).

229. *Id.* § 262(l)(8)(B).

230. *Id*. § 262(l)(6), (8); AbbVie Inc. v. Alvotech hf., 582 F. Supp. 3d 584, 591–92 (N.D. Ill. 2022) (holding that because Biosimilars Act permits brand to bring artificial infringement claim under 35 U.S.C. § 271(e)(2) in both phases, Act also permits brand to obtain injunctive relief under 35 U.S.C. § 271(e)(4) in both phases); Carl J. Minniti III, Sandoz v. Amgen*: Why Current Interpretation of the Biologic Price Competition and Innovation Act of 2009 Is Flawed and Jeopardizes Future Competition*, 97 J. PAT. & TRADEMARK OFF. SOC'Y 172, 177, 179 (2015) (discussing Biosimilars Act's amendments to Patent Act).

231. *See generally* 42 U.S.C. § 262(l)(6), (8); Feldman, *supra* note 30, at 140.

232. Feldman, *supra* note 30, at 139–41.

effectively ends and the second phase simply proceeds as an infringement litigation concerning the patents on the 3A, 3B, and 7AB lists.[233]

2. Public Disclosure of Patents During the Dance—Prior to 2020

On September 9, 2014, a year before the FDA licensed the first biosimilar, the FDA took the initiative to publish a compilation of patents and exclusivities associated with biologics—which the Agency entitled, "Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations."[234] Better known as the Purple Book, this compilation acted as the biologic analog to the Orange Book, which details non-biologic drugs.[235] The FDA explained its two main motivations for creating the Purple Book: enabling users to see whether a drug was determined to be biosimilar to or interchangeable with a biologic, and providing information on exclusivities that protect biologics.[236]

While the Hatch-Waxman regime statutorily mandated that the FDA publish a list of approved non-biologic drugs with monthly updates,[237] the Biosimilars Act did not similarly require the FDA to publish a list of licensed biologic drugs.[238] Without an act to govern its data, the Purple Book lacked a significant amount of information, often missing patent information.[239] And unlike the Orange Book, the Purple Book was not updated regularly.[240] These knowledge gaps became increasingly troublesome as more and more drug companies started biosimilar ventures without knowing what patent protections for brand biologics they may be infringing upon.

233. 42 U.S.C. § 262(l)(8) (authorizing brand company to seek preliminary injunction against biosimilar company's marketing or sale of drug pending court's determination of infringement with respect to any patent on 3A or 3B list that is not on 4AB list or 5B lists); *id.* § 262(l)(7) (providing that any patent on 7AB list "shall be subject to [§ 262(l)] paragraph (8).").

234. Kurt R. Karst, *The "Purple Book" Makes Its Debut!*, FDA L. BLOG (Sept. 9, 2014), https://www.thefdalawblog.com/2014/09/the-purple-book-makes-its-debut [https://perma.cc/8L3L-2XLC].

235. *Id.*

236. Renu Lal, *The Purple Book*, FDA/CBER SMALL BUS. CHRONS. (Nov. 18, 2014), https://www.fda.gov/media/90150/download [https://perma.cc/8BF4-UNR7].

237. *See* 21 U.S.C. § 355(j)(7); *see also* Joint USPTO-FDA Collaboration Initiatives: Notice of Public Listening Session and Request for Comments, 87 Fed. Reg. 67,019, 67,021 (Nov. 7, 2022) ("New drug application sponsors are statutorily required to submit certain patent information for listing, and the FDA is statutorily required to publish that information, which it does in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book).").

238. Karst, *supra* note 234.

239. David Wallace, *US Bill Aims to Increase Transparency on Biologics*, GENERICS BULL. (Mar. 15, 2019), https://generics.citeline.com/GB140140/US-Bill-Aims-To-Increase-Transparency-On-Biologics [https://perma.cc/PM9G-C4WW].

240. Prior to the 2020 Transparency Act (*see infra* next paragraph of text), the Purple Book was updated only when the FDA licensed a biological product, or when the FDA made a determination about the date of first licensure of a biologic. *See Background Information: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book)*, U.S. FOOD & DRUG ADMIN. (July 25, 2018), https://wayback.archive-it.org/7993/20180725235106/https:/www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm [https://perma.cc/CZH8-M96N].

In attempt to remedy the lack of patent transparency in the biologic landscape, Congress amended the Biosimilars Act with the Purple Book Continuity Act, also known as the Biological Product Patent Transparency Act (2020 Transparency Act), on December 27, 2020.[241] The 2020 Transparency Act formally instructed the Secretary of Health and Human Services to publish a list of all licensed biologic products and to update it every thirty days.[242] Most important, the 2020 Transparency Act required that the Purple Book record all patents included in any 3A and 7AB lists submitted during a patent dance, alongside the expiration dates of those patents.[243] This information must be published in the Purple Book no later than thirty days after the brand manufacturer provides each list to the biosimilar manufacturer.[244]

Thus, in theory, the Purple Book should contain significant data about biologics, at least where biosimilars have emerged. The 2020 Transparency Act also coincided with the transition of insulin products from the Orange to the Purple Book. These new regulatory policies should have especially paved the way for additional information to surface about insulin products.

V. COMPARING THE DISCLOSURE CATEGORIES OF THE ORANGE AND PURPLE BOOKS

A. Summary of the Orange and Purple Books' Comparison

On March 23, 2020, the FDA stopped categorizing insulin as a non-biologic drug appropriate for Orange Book disclosure and started categorizing insulin as a biologic drug appropriate for Purple Book disclosure.[245] This shift provides an opportunity to perform an apples-to-apples comparison of the disclosure provided by the Orange and Purple Books. The comparison demonstrates that both books contemplate collection and disclosure of largely similar types or categories of information, with most categories of information existing similarly or identically in both the Orange and Purple Books.[246] Placing both side by side also shows that despite the similarity of the informational categories in each Book, significantly more patent information is actually disclosed in the Orange Book than in the Purple Book.

241. *New Law Establishes Purple Book Patent Disclosure Requirement*, COOLEY LLP (Jan. 21, 2021) https://www.cooley.com/news/insight/2021/2021-01-21-purple-book-patent-disclosure-requirement [https://perma.cc/3L6C-5V5Z].

242. 42 U.S.C. § 262(k)(9).

243. *See also* Joint USPTO-FDA Collaboration Initiatives: Notice of Public Listening Session and Request for Comments, 87 Fed. Reg. 67,019, 67,021 (Nov. 7, 2022) (explaining that if a brand biologic "provides a list of patents to a biosimilar applicant within the context of patent litigation, then the FDA is statutorily required to publish that patent list . . . in the Purple Book"); *see also supra* notes 238–39 and accompanying text.

244. 42 U.S.C. § 262(k)(9)(A)(iii).

245. Amy Abernethy, *Insulin Gains New Pathway to Increased Competition*, U.S. FOOD & DRUG ADMIN. (Mar. 23, 2020), https://www.fda.gov/news-events/press-announcements/insulin-gains-new-pathway-increased-competition [https://perma.cc/BY48-7GLQ].

246. *See infra* Section V.C.

B. Methodology

We began by comparing the disclosure categories in the Orange and Purple Books in order to evaluate the way in which the information to be disclosed under the non-biologic regulatory regime, as reflected in the Orange Book, differs from the kind of information to be disclosed under the biologic regulatory regime, as reflected in the Purple Book. We say "to be disclosed" because the disclosure categories are essentially cubbyholes. Those cubbyholes may be empty, however, if nothing has been entered into them. That is, what data *could* be put into the cubbyholes and what data are *in fact* in the cubbyholes are two separate matters.

We undertook this evaluation by comparing the entries of every insulin product in the Orange Book at the end of February 2020 with the entries of every insulin product in the May 2020 and November 2021 updates to the Purple Book.[247] Thus, we compared the Purple Book information to the last, full information in the Orange Book that was current a few weeks before insulin's transition to the Purple Book. In other words, the study looked at what information existed "in the wild" and the extent to which the information carried over or disappeared.

For the Purple Book information, we looked at two updates to the Purple Book for comparison, in case any initial lack of information immediately post-transition could be attributed to FDA backlog or other bureaucratic delay. It would be understandable, for example, if it took the FDA more than a month or two to transfer all of the information on insulin products from the Orange Book to the Purple Book. But, if the November 2021 update is any indication, a backlog is not the likely reason for the lack of disclosure; little new information was added in the November 2021 update.

The lack of new information is especially notable in the case of patent information because all patents relating to insulin products were publicly listed in the Orange Book prior to the transition, per the Hatch-Waxman Act.[248] In the Purple Book, those same products are listed with *no* patent information, even though the Purple Book now lists biosimilar insulins–Semglee, for example.[249]

247. The study used the fortieth edition of the Orange Book, which was current as of December 31, 2019, along with the January 2020 and February 2020 Cumulative Supplements of the Orange Book and the May 2020 and November 2021 updates to the Purple Book. The fortieth edition of the Orange Book was selected because it was the last full edition released prior to insulin's transition to the Purple Book. The Cumulative Supplements were used to ensure that the evaluation would be current through the end of February 2020 (*i.e.*, a few weeks before the transition). The May 2020 update to the Purple Book was selected because it was the earliest edition of the Purple Book that contained insulin; the November 2021 update to the Purple Book was selected because it was the most up-to-date edition of the Purple Book available at the time of evaluation.

248. *See infra* Part VI.

249. *See infra* Part VI.

C. Functional Classification of Categories

Understanding the Purple Book is as complex as understanding the patent dance. Little information exists in any literature about the steps of the dance or the details of the book, which may partly explain why so little scholarly research exists. Thus, as part of the process of comparing information on insulin, the study analyzed changes in the categories between the two books. We hope that the information in this and the next few footnotes will help future researchers in their journeys.

Some of the categories were identical, meaning that the analogous categories in each Book are coded for exactly the same *kind* of information, although the categories may have different names.[250] Some of the categories were similar but not identical between the two books, collecting comparable types of information but differing in significant ways.[251]

250. Identical categories are: 1) whether the drug is prescription, over-the-counter, or discontinued; 2) the name of the active ingredient; 3) the name of the drug as it appears on the label; 4) available strengths of the drug; 5) the dosage form of the drug; 6) the route by which the drug is administered; 7) the name of the company that applied for the drug; 8) the identifying number assigned to the drug's application by the FDA (the NDA, ANDA, or BLA number); 9) the identifying number assigned to each strength of a drug product by the FDA (the product number); 10) the date that the application was approved; 11) the identifying numbers of patents related to the drug (the patent number); 12) the date when a listed patent expires; and 13) the date when a listed exclusivity expires. The names for these categories occasionally differ between the Orange and the Purple Books. For example, the active ingredient of the drug is termed the "active ingredient" in the Orange Book but the "proper name" in the Purple Book. But, these categories are functionally and definitionally identical in each book. The "identical" disclosure categories with identical names are: applicant; product number; approval date; patent number; patent expiration date; and exclusivity expiration date. The "identical" disclosure categories with different names are: type (Orange) or status (Purple); active ingredient (Orange) or proper name (Purple); trade name (Orange) or proprietary name (Purple); available strengths (Orange) or strength (Purple); application number (Orange) or BLA number (Purple); dosage form/route of administration (Orange) or split into two separate categories (Purple). *See Orange Book Data Files*, U.S. FOOD & DRUG ADMIN. (July 18, 2019), https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-data-files [https://perma.cc/3W6N-P32J]; *Purple Book: Database of Licensed Biological Products*, U.S. FOOD & DRUG ADMIN., https://purplebooksearch.fda.gov (last visited Apr. 7, 2024) [https://perma.cc/3ST2-5X3R].

251. Similar categories are: 1) whether the drug listed is a follow-on (*i.e.*, a generic or a biosimilar); 2) whether a listed brand drug serves as the basis for a follow-on; and 3) the active ingredient and label name of a listed brand drug. Although the concept of a "reference product" in the Purple Book functions similarly to the concept of the "reference listed drug" in the Orange Book, the two disclosure categories are populated differently. The Purple Book's disclosure category "reference product proper name" contains information only when the drug at issue is a biosimilar or interchangeable while the Orange Book's disclosure category "reference listed drug" contains information when the drug at issue is a brand drug. *See supra* note 250.

More specifically, in the Orange Book, a "reference listed drug" is a drug product approved under section 505(c) of the Food, Drug, & Cosmetic ("FD&C") Act for which the FDA has made a finding of safety and effectiveness. *See id*. When a generic applicant files an ANDA, the applicant must indicate which reference listed drug its proposed generic will duplicate. The reference listed drug serves as the basis for comparison for meeting the sameness requirements under section 505(j) of the FD&C Act, but not for in vivo bioequivalence testing; only the reference standard can be used for in vivo bioequivalence testing. In the Orange Book, the "reference standard" is the drug product selected by the FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval of an ANDA. *See id*. The reference standard is often but not always the reference listed drug indicated in the ANDA. For example, where the reference listed drug has been withdrawn from sale for reasons other than safety or effectiveness, the FDA may select an ANDA that is therapeutically equivalent to this reference listed drug as the reference standard. *See Orange*

Each book also has categories that are unique, meaning that they do not exist in the other book. Some of the unique categories are specific to the way in which each regulatory regime works.[252] For example, some unique categories of the Purple Book contain information ranging from an identification of the department of the FDA having jurisdiction over the process to an indication of whether the listed drug was newly approved or updated.[253]

Just as the Purple Book has unique categories that do not appear in the Orange Book, the Orange Book has two categories that do not appear in the Purple Book. These are patent codes—indicating the purpose of each listed patent—and patent delist requested—indicating that a sponsor has requested delisting a patent or that the patent was invalidated following a Paragraph IV challenge.[254]

Differences also exist with the way the patent information is listed in each. Both books list the patent information in a separate list, rather than alongside each drug. Nevertheless, in the Orange Book, the separate list is organized by

Book Preface, U.S. FOOD & DRUG ADMIN. (Jan. 25, 2023) https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface [https://perma.cc/AV3V-ZG9V].

In the Purple Book, the "reference product proper name" is the active ingredient of the biologic serving as that entry's reference product sponsor. A reference product sponsor is a biologic, already FDA-licensed, that serves as the basis for comparison with a proposed biosimilar; the "reference product proprietary name" is simply the trade name of the biologic serving as that entry's reference product sponsor. The biosimilar must be "highly similar" to the reference product in order to be licensed. In the Purple Book, reference products are *not* marked; if a drug *is* a reference product, this disclosure category remained unpopulated because the drug does not *have* a reference product. In other words, information in this disclosure category indicates that the listed drug is a biosimilar or interchangeable and indicates which biologic is its reference product.

252. The following categories appear exclusively in the Orange Book and have no counterpart in the Purple Book: 1) therapeutic equivalence code (*i.e.*, whether a listed generic drug is bioequivalent to its brand counterpart and whether any extant problems relating to bioequivalence have been resolved); 2) a Federal Register determination that a product was not withdrawn for safety or efficacy reasons; 3) a code indicating the purpose of a patent (the patent code); 4) an indication that the holder of the associated drug's NDA requested a particular patent to be delisted from the Orange Book; and 5) a code indicating the type of exclusivity granted by the FDA to the drug product. Similarly, the following categories appear exclusively in the Purple Book and have no discernible counterpart in the Orange Book: 1) the status of the product license; 2) the number assigned to the product license; 3) the first day that the product is licensed in the U.S.; 4) whether the license application is for a biologic, biosimilar, or interchangeable product; 5) whether the application submitted is original or supplemental; 6) the identifying number assigned to the drug's application by the FDA in the case that the application is supplemental; 7) the identifying number assigned to the drug's application by the FDA in the case that the application is a supplemental one submitted to prove that a biosimilar meets the qualifications for interchangeability; 8) the date that an application or supplement for an interchangeable was licensed; 9) the date when an interchangeable product's exclusivity granted to the first interchangeable product licensed expires; 10) the date, twelve years from first licensure, when an innovator biologic product's exclusivity expires; and 11) the date when a biologic product's exclusivity for being designated an "orphan drug" expires. In some cases, the same category exists in both books, though information belonging to that category may be missing in one book or the other. These cases are not classified as "unique" because the presence of the category in the book implies that the missing information will or can be added at a future date. *See supra* notes 250–51.

253. Specifically, these categories are: 1) the center (*i.e.*, whether the Center for Biologics Evaluation and Research ("CBER") or the Center for Drug Evaluation and Research ("CDER") has jurisdiction over the listed product); 2) whether the listed drug was newly approved (and coded as "N"), added in the current release (coded as "R"), or updated (and coded as "U"); and 3) the product presentation (*i.e.*, the form the drug takes when it is sold).

254. *See Orange Book Data Files*, U.S. FOOD & DRUG ADMIN. (July 18, 2019), https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-data-files [https://perma.cc/3W6N-P32J].

drug product[255] while in the Purple Book, the separate list is organized by patents.[256] Digging more deeply into the types of patent or regulatory rights listed, the separate patent lists of the two books share much of the same information.[257] Nevertheless, there are differences. Although the Orange Book's separate patent list contains codes that indicate the type of regulatory exclusivity granted by the FDA to the drug product and expiration dates for the exclusivity, the Purple Book's exclusivity information is not located in its separate patent list. The Purple Book features exclusivity expiration dates elsewhere but lacks exclusivity codes entirely.[258] The Purple Book includes expiration dates specifically for first interchangeable exclusivity, reference product exclusivity, and orphan drug exclusivity.[259]

VI. THE DISAPPEARANCE OF INSULIN INFORMATION

As demonstrated by the previous section, the Orange and Purple Books both collect largely similar kinds of data, but there are certain key differences. For example, each book has unique categories that the other does not have, and the two separate patent lists are organized in divergent ways. Crucially, the patent and exclusivity data in the Purple Book is much less comprehensive than its counterpart. The most striking example is the complete disappearance of information about insulin drugs when they moved from the Orange to the Purple Book in March 2020.[260]

Specifically, immediately prior to the transition,[261] the Orange Book included nineteen unique NDAs for insulin products. Of those nineteen NDAs, seventeen contained patent disclosures while five disclosed exclusivities. In sum, the last version of the Orange Book containing insulin products disclosed 101 unique patents and ten exclusivities covering the listed insulin products.[262]At the time of designing the project, we hypothesized that less data on insulin drugs would become available in the Purple Book than in its counterpart. Despite this hypothesis, we did not expect to see complete radio silence on information relevant to insulin products. That, however, is what has transpired: The Purple Book

255. The Orange Book patent list is organized by each drug product's application and product numbers, followed by information for each associated patent. *See id.*

256. *See Purple Book: Database of Licensed Biological Products*, U.S. FOOD & DRUG ADMIN., https://purplebooksearch.fda.gov (last visited Apr. 7, 2024) [https://perma.cc/DK2L-6PG5]. In the Purple Book patent list, each patent receives its own entry, but each entry includes the application number of the associated drug product; the product number is not included.

257. *See supra* notes 250–51. Within the patent information specifically, the following categories can be classified as identical: patent number; patent expiration date; and exclusivity expiration date. One similar category exists: other exclusivity-related data.

258. *See supra* note 252.

259. *See supra* note 252.

260. In accordance with the Biosimilars Act, insulin products moved from the non-biologic regulatory framework to the biologic one after March 23, 2020. *See* Abernethy, *supra* note 245.

261. This analysis used data from the Orange Book Data Files available in October 2019. *Orange Book Data Files*, U.S. FOOD & DRUG ADMIN. (Dec. 12, 2019), https://web.archive.org/web/20191212235609/https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-data-files [https://perma.cc/8CGC-CLB5].

262. *See supra* notes 27–28 and accompanying text.

now houses absolutely no patent or exclusivity information at all on any insulin product.[263]

Insulin products still exist, and those products are still patented. In fact, the December 2022 Purple Book lists thirty insulin products on the market, although those listings do not include any patent or exclusivity information.[264] Over half of those current insulin products were ones for which there were patents listed in the old Orange Book,[265] and many of those patents have not expired.[266]

The absence of patent or exclusivity information is particularly striking given that two biosimilars have come to market since insulin products moved to the Purple Book. In other words, two insulin biosimilars have emerged under the Biosimilars Act without any such information coming to light. Thus, to the extent one was expecting such information to become public through the processes spelled out in the Biosimilars Act, that has not been the case with insulin so far.[267]

In addition to the radio silence around insulin products, the Purple Book contains little patent information for most biologics. Specifically, the Purple Book lists no patent information for 98% of the biologics licensed for human use in the United States.[268] Thus, more than a decade after passage of the Biosimilars Act, and almost a decade after the Purple Book began, the Purple Book contains minimal patent and exclusivity information.

The fact that insulin has no patent information is within the norm for the Purple Book as a whole. With insulin, however, we know that patent information exists, and we know much of what that information is, given the prior Orange Book listings.

In short, to the extent Congress intended that the Purple Book provide meaningful information on patents and exclusivities held in relation to biologics, the Purple Book has failed. Even if one expected information to emerge during the biosimilar patent dance, the Purple Book falls woefully short.

VII. RETURNING TO THE ROOTS OF THE COMPROMISE

As described in the sections above, the Purple Book fails to provide more than a minimal amount of information on the patents and exclusivities held in relation to biologic medicines.[269] With that gap, society forgoes an important pathway for encouraging competitive biosimilar entry, a pathway that would bring downward pressure to bear on pricing and improve access to medicine. Specifically, the public listing of patent rights and exclusivities has the potential to help would-be biosimilar competitors understand the intellectual property

263. *See supra* note 29 and accompanying text.

264. *Purple Book: Database of Licensed Biological Products*, U.S. FOOD & DRUG ADMIN. (Nov. 8, 2023), https://purplebooksearch.fda.gov/patent-list [https://perma.cc/M4SC-H6FW].

265. Crossmatching the thirty insulin products listed in the Purple Book with those listed in the Orange Book demonstrates that over half of them have patents listed in the Orange Book. *See supra* note 30.

266. *See supra* note 261.

267. *See supra* notes 29–30 and accompanying and following text.

268. *See* Feldman, *supra* note 31.

269. *See* discussion *supra* Part VI.

landscape they might be facing, allowing them to better evaluate the risk of undertaking a particular biosimilar venture. Without that information, potential biosimilars must go through a lengthy process of guessing what rights might be asserted against them, whether those rights might be valid, and when they might expire. The Purple Book, however, fails in that regard.

The most effective method of providing notice to potential biosimilars would be to mirror the workings of the non-biologic world. As with non-biologic medicines, biologic companies could be required to provide and update the patents and exclusivities relevant to a particular drug product from the time of licensure going forward. The issue of whether the FDA would need a new grant of statutory authority to effect this proposed change, or whether existing grants of statutory authority would be sufficient, depends on two sub-issues. The first, which is complex, is whether the FDA has sufficient existing authority to *collect* information from drug applicants. The second, which is straightforward, is whether, having collected that information, the FDA has sufficient existing authority to *publish* it.

As to the second sub-issue, it is likely that the FDA already has sufficient existing authority to publish. The FDA began publishing the Orange Book years before the Hatch-Waxman Act of 1984 specifically authorized its publication.[270] When publishing the first edition of the Orange Book in 1980, the FDA cited four existing (albeit non-specific) grants of statutory authority for the publication.[271] Similarly, the FDA began publishing the Purple Book years before the 2020 Transparency Act specifically authorized its publication.[272] Although the

270. *Compare* Therapeutically Equivalent Drugs, 45 Fed. Reg. 72,582 (Oct. 31, 1980) (to be codified at 21 C.F.R. pt. 20) (final rule amending FDA's public information regulations to include Approved Prescription Drug Products List [*i.e.*, the Orange Book] in list of available information), *and Approved Prescription Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN. (Aug. 31, 1980), https://thefdalawblog.com/wp-content/uploads/2020/06/OB-Annual-1980-1st-Ed.pdf (first edition of Orange Book, published in 1980) [https://perma.cc/TQP9-A6NQ], *and* Listing of Patent Information in the Orange Book, 85 Fed. Reg. 33,169, 33,170 (June 1, 2020) (noting that the list published per 45 Fed. Reg. 72,582 was "the first Orange Book"), *with* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1591 (1984) (Hatch-Waxman Act, as originally enacted, amending Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355, by adding new section 505(j)(6)(a)(i)(I), which requires publication of a "list . . . of the official and proprietary name of each drug which has been approved for safety and effectiveness . . . .").

271. *See* Therapeutically Equivalent Drugs, 44 Fed. Reg. 2936 (Jan. 12, 1979) (citing Public Health Service Act §§ 310 (directing Secretary to issue "information related to public health, in the form of publications or otherwise, for the use of the public"), 311(a) (directing Secretary to advise the several States on matters relating to the preservation and improvement of the public health); Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, §§ 705(b), 306, 52 Stat. 1040 (1938) (authorizing Secretary to "disseminate . . . information regarding . . . drugs . . . in situations involving . . . imminent danger to health, or gross deception of the consumer'" in § 705(b) and "authoriz[ing] FDA to use written notices in lieu of formal enforcement actions when the public interest will be adequately served by such notices" in § 306).

272. *Compare* Karst, *supra* note 234 (observing that because Biosimilars Act of 2009 does not require the FDA to publish a list of licensed biologic products, the FDA's decision in 2014 to publish the Purple Book "is not unlike FDA's initial, pre-Hatch-Waxman decision to create the Orange Book"), *with* Consolidated Appropriations Act, 2021, Pub. L. No. 116-260, div. BB, tit. III, subt. C, § 325(a), 134 Stat. 2936–37 (2020) (2020 Transparency Act, as originally enacted, amending Public Health Service Act, 42 U.S.C. § 262(k), by adding new section 351(k)(9), which requires publication of "list of each biological product, by nonproprietary name (proper name), for which . . . a biologics license under subsection (a) or this subsection is in effect . . . .").

FDA did not publish any notice or rule in the Federal Register when it published the first edition of the Purple Book, presumably the same four sources of authority that it cited when first publishing the Orange Book applied in 2014 when it first published the Purple Book.[273]

As to the first sub-issue, it is unclear whether the FDA needs a new grant of statutory authority to collect patent and exclusivity information on biologics from the time of licensure going forward. On the one hand, the FDA did not collect patent information from NDA filers (and thus, arguably, could not include patent information in the Orange Book) until Hatch-Waxman specifically required such collection.[274] Similarly, the FDA did not collect patent information from BLA filers (and thus, arguably, could not include patent information in the Purple Book) until the 2020 Transparency Act specifically required such collection.[275] On the other hand, the FDA collected all manner of information from generic applicants—by creating and mandating the ANDA—years before Hatch-Waxman specifically required such collection and specifically authorized the ANDA.[276] Thus, while it would appear that the FDA could, with existing grants of statutory authority, collect patent and exclusivity information on biologics from the time of licensure going forward, the safer course may be to wait for specifically authorizing legislation.

In any event, both the Hatch-Waxman and Biosimilars Acts offer a model for the type of compromise that could be successful, providing brand companies with additional powers in the form of data or marketing rights. For the Hatch-Waxman Act, these included not only the thirty-month stay in which the FDA

273. *See* Therapeutically Equivalent Drugs, 44 Fed. Reg. 2932, 2936 (Jan. 12, 1979).

274. *Compare* 21 U.S.C. § 355(b)–(c) (Supp. II 1984) (requiring applicant to submit specified patent information with application), *with* 21 U.S.C. § 355(b)–(c) (1982) (not so requiring); *compare* FOOD & DRUG ADMIN., APPROVED PRESCRIPTION DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS v, 1–4 (5th ed. 1984) (stating that "information provided by the List is not intended to reflect the patent status of any of the drug products on the List"), *with* FOOD & DRUG ADMIN., APPROVED PRESCRIPTION DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS Addendum D (5th ed. Supp. 2 1984) (noting enactment of Hatch-Waxman and stating that Orange Book will "provide information on the current patent status of the listed drugs"); *see also* Elizabeth H. Dickinson, *FDA's Role in Making Exclusivity Determinations*, 54 FOOD & DRUG L.J. 195, 195 (1999) ("The Hatch-Waxman Act introduced the requirement that new drug applications (NDAs) include patent information . . . ."); Listing of Patent Information in the Orange Book, 85 Fed. Reg. 33,169, 33,170 (June 1, 2020) ("Following the enactment of the Hatch-Waxman Amendments, FDA provided NDA applicants and application holders with advice on how to comply with these new amendments, including *the new requirements for submission of patent information*, via letters to industry (see, e.g., [l]etter . . . [dated] March 26, 1985). . . ." (emphasis added)).

275. *Compare* 42 U.S.C. § 262(k)(9)(A)(iii) (Supp. II 2020) (requiring applicant to submit specified patent information to Secretary), *with* 42 U.S.C. § 262(k) (2018) (not so requiring).

276. *See* Erika Lietzan, *ANDAs Before Hatch-Waxman*, OBJECTIVE INTENT (Aug. 19, 2017), https://objectiveintent.blog/2017/08/19/andas-before-hatch-waxman/ [https://perma.cc/4FC6-QLF6] (noting that the ANDA was originally created by the FDA through a rulemaking: "In the late 1960s, FDA developed the 'abbreviated new drug application' ("ANDA") pathway through a rulemaking. The final rule was published in April 1970. This application—like today's ANDA—was supposed to prove the generic drug was the same as and bioequivalent to a reference product."); Abbreviated Applications, 35 Fed. Reg. 6574, 6574–75 (Apr. 24, 1970) (final rule amending new-drug regulations to create abbreviated new-drug application); Abbreviated Applications, 34 Fed. Reg. 2673 (Feb. 27, 1969) (to be codified at 21 C.F.R. pt. 130) (proposed rule amending new-drug regulations to create abbreviated new-drug application and citing as authority 21 U.S.C. § 355 (governing "New drugs"), § 371(a) (authorizing Secretary to "promulgate regulations for the efficient enforcement of this chapter")).

could not approve the generic drug for market,[277] but also the four- or five-year period in which no other company could use the brand's clinical data.[278] With the Biosimilars Act, these included the twelve years of data exclusivity.[279] Each of these compromises gave brand companies assurance of certain periods without direct competition, in exchange for public transparency of data or intellectual property information.

Passage of the Biosimilars Act itself provoked intense opposition from the pharmaceutical industry,[280] and one might expect similar opposition with any attempts to create greater industry obligations. In particular, given the importance of processes for biologic drugs,[281] there may be large numbers of patents on different parts of the drug production process. If the 132 patents mentioned in the 7th Circuit *Humira* case is any guide,[282] the sheer number of rights per drug for biologics is likely to be quite high. Thus, biologics companies are likely to view additional obligations as burdensome. Nor would any company in any industry welcome government procedures that are likely to enhance the potential for competitive entry.

In addition, companies may view litigation with a jaundiced eye. Each side has the potential to use litigation filings to increase costs and hamper the other. In particular, brand companies have complained that some generic companies have filed so-called "strike suits" under Hatch-Waxman—that is, meritless suits designed to do nothing more than force a settlement payment.[283]

With concerns such as these in mind, Congress could provide that brand biologics receive assurance of no biosimilar entry until a certain, critical point in the patent dance, perhaps a period mirroring the thirty-month stay of litigation in the Hatch-Waxman Act. In light of this additional buffer of time—time on the market without a competitor and time to ensure enforcement of valid intellectual property rights—brand biologics would be required to list all patents and exclusivities in the Purple Book, on pain of waiving enforcement of those rights.

As an alternative proposal, one could consider streamlining the process by asking companies to focus on key rights. Biologic companies may amass large numbers of rights on the pathway to licensing, but one must wonder whether all 132 patents are necessary for the protection of the single drug, Humira, for example.[284] Biologics companies might be asked to list a limited number of rights,

277. *See supra* note 34 and accompanying text.

278. *See supra* notes 201–02 and accompanying text.

279. *See supra* note 209 and accompanying and following text.

280. Heled, *supra* note 14, at 116.

281. *See supra* notes 124–25 and accompanying text.

282. *See supra* note 32.

283. For instance, the CEO of a brand drug company called the lawsuits filed by generic manufacturers under Hatch-Waxman "'strike suits' filed by opportunists seeking a quick pay-off from companies." *See* AMGEN PROPOSAL TO RESTRICT HATCH-WAXMAN SECTION 271(E)(1) SAFE HARBOR WOULD STIFLE INNOVATION, IMPEDE COMPETITION AND ENCOURAGE COSTLY AND UNNECESSARY LITIGATION, 106th Cong. 205 (1999).

284. 89% of the total patent applications for Humira were filed *after* the drug was approved in 2002. Indeed, almost 50% of the patent applications were filed after 2014, over two decades after the initial scientific research started. Thus, it does not seem credible that there are 132 distinct inventions associated with Humira that each need to be patented. *See* INITIATIVE FOR MEDS., ACCESS & KNOWLEDGE, *supra* note 32, at 3–4.

perhaps ten or fifteen, in the Purple Book. Any other rights would not be enforceable against the drug. Other patent rights would still exist but would not be enforceable as a protection against that drug, although the rights might be used to protect other biologics.[285] One might ask what would be done if the company acquires new rights to the drug after licensing. In theory, a drug company ought to know the universe of appropriate rights by the time a medicine is licensed. The FDA licensing process takes some time, and companies cannot make changes to the process after licensing without the FDA's knowledge.[286] To the extent later-acquired rights are of concern, however, the concern could be assuaged by requiring that the company replace a listed patent with the later-acquired right, perhaps providing that the end-point of the later-acquired right would remain the same as that of the replaced patent.[287]

Proposals such as these would go a long way towards improving the functioning of the Purple Book and the biosimilars system. They have the benefit of providing additional protection for brand biologics, streamlining biologic patents, and smoothing the way for increased competitive entry in the market for biologic medicine.

VIII. CONCLUSION

In 2010, President Obama signed into law the Biosimilars Act, which was intended to facilitate the efficient entry of competition into the market for biologic medicine.[288] The case of insulin provides a natural experiment for examining the effectiveness of part of this pathway, the FDA's public-facing Purple Book, which contains information on all biologic drugs licensed for sale in the United States.[289] In particular, insulin products moved from the FDA's Orange Book to the Purple Book in March of 2020—a move that inherently facilitates comparison of the universe of patent information that might be disclosed in the Purple Book to the information that is actually disclosed.[290]

In initiating the project, we hypothesized that the Purple Book would provide less than complete information on patent rights. The results are even more dismal. The Purple Book provides no information at all about any patents or exclusivities in relation to any of the thirty insulin products licensed for sale.[291]

285. Such a proposal offers a variant of a one-and-done approach. *See* Feldman, *supra* note 62, at 640–43.

286. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA 11–16 (Apr. 2004).

287. Per a prevailing practice in United States patent law, if a party applies for a patent that is obviously a variation of a preexisting patent it holds, then that new patent can be approved, but it will be issued with a terminal disclaimer. In other words, a terminal disclaimer indicates that two inventions are patentably indistinct. In contrast, such a patent application in the EU would be rejected for duplicating another patent. *See* Rachel Goode & Bernard Chao, *Biological Patent Thickets and Delayed Access to Biosimilars, An American Problem*, 9 J.L. & BIOSCIENCES 1, 2 (2022).

288. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, 124 Stat. 804 (Mar. 23, 2010).

289. Karst, *supra* note 234.

290. *See supra* note 24 and accompanying text.

291. *See supra* notes 29–30 and accompanying text.

This is true despite the existence of patents that were listed in the old Orange Book entries and are still in force, the passage of several years, and the fact that two insulin biosimilars have gone through the patent dance. Insulin is no outlier in this regard. With 563 prescription biologics licensed (not including biosimilars and interchangeables), the Purple Book contains no patent information for 98% of them.[292] The Purple Book simply fails to provide an effective method of publicly conveying the type of intellectual property information that has helped facilitate entry of generics. Without this information, biosimilar competitors are forced to dance in the dark, guessing about the various rights that might be asserted against a biosimilar version of the drug and the strength of those rights.

To better encourage competition in the biologics market at the appropriate time, biologic companies should be asked at the time of FDA licensing of the drug to list all patents and exclusivities that could be asserted against an alleged infringer. Following the model of the Hatch-Waxman and Biosimilars Acts, Congress could grant additional assurance of no biosimilar entry until a certain, critical point in the patent dance, perhaps a period paralleling the thirty-month stay of litigation in the Hatch-Waxman Act. This type of revision has the potential to streamline competitive entry in the biologics market at the appropriate time, encouraging the price-disciplining effects of competition and increasing access to life-saving medicines.

292. *See supra* note 31 and accompanying text.