TACKLING THE THICKET: A COMPARATIVE ANALYSIS OF BIOLOGIC DRUGS AND BIOSIMILARS IN THE UNITED STATES AND ABROAD

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I. AN INTRODUCTION TO BIOLOGIC DRUGS

Biologic drugs are not new.[1] Examples of long-existing biologics include human growth hormone, certain types of insulin, vaccines, and stem cell therapies. Some of these biologics—vaccines in particular—date back to the nineteenth century.[2] As knowledge of genetics and cell processes has increased, pharmaceutical companies and medical researchers have been able to significantly expand the range of biologics available to treat both common and rare medical conditions, ranging from anemia and diabetes to certain cancers and autoimmune diseases.[3]

Despite their long history, defining biologic drugs remains difficult. Biologics are also known as "biopharmaceuticals, recombinant DNA expressed products, bioengineered, or genetically engineered drugs."[4] They are developed using living organisms with the help of biotechnology or genetic engineering, and may be composed of sugars, proteins, or nucleic acids.[5] They may take the form of "virus[es], therapeutic serum[s], toxin[s], antitoxin[s], vaccine[s], blood, blood component[s] or derivative[s], allergenic product[s], or analogous product[s]" which are "applicable to the prevention, treatment, or cure of a disease or condition."[6] They are distinct from chemically derived drugs (also known as small molecule drugs) in both their structure and manufacturing process; "[they] are relatively large molecules with an inherently heterogeneous structure that can contain hundreds of amino acids" and they can only be produced by living systems.[7] More expansive definitions might include any substances composed of organic

1 Thomas Morrow & Linda Hull Felcone, *Defining the Difference: What Makes Biologics Unique*, 1 BIOTECHNOLOGY HEALTHCARE 24, 24 (2004).

2 *Id.*; *Biologicals*, WORLD HEALTH ORG., https://www.who.int/health-topics/biologicals [https://perma.cc/T79Y-8DZQ] (last visited Oct. 24, 2022); *Biologics vs. Biosimilars: Understanding the Difference*, PFIZER (Sept. 22, 2022), https://www.pfizer.com/news/articles/biologics_vs_biosimilars_key_differences_explained [https://perma.cc/987N-NFUE].

3 Morrow & Felcone, *supra* note 1, at 24.

4 Kamal Kishore & Pawan Krishan, *Pharmacology of Recombinant or Genetically Engineered Drugs*, 1 J. YOUNG PHARMACISTS 141, 141 (2009).

5 *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-answers [https://perma.cc/KJ9S-ACZX].

6 JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW, ch. 19 § I (2020) (ebook).

7 Morrow & Felcone, *supra* note 1, at 25; *see also* Katherine Macfarlane, *Camouflaging State Biosimilar Laws as Pro-Patent Legislation*, 26 ANNALS HEALTH L. 52, 54 (2017).

molecules regardless of size, any complex molecules despite their method of manufacturing, or any substances created in other organisms despite their complexity.[8] The search for a uniform definition is further complicated by the fact that biologics are a fast-growing class of drugs, so definitions need to adapt to the development of new products and changing market conditions.

Biologics are also harder to manufacture than purer, more stable chemical drugs, which may be produced in larger uniform quantities.[9] Biologics are often sensitive to heat and susceptible to microbial contamination, requiring greater care during manufacture and transport.[10] They are also generally manufactured in small quantities due to their complex production process, making it difficult to "scale up . . . from laboratory quantities used for early analysis and preclinical testing to larger-scale batches and maintain product purity and batch-to-batch equivalence."[11] For reference, the "typical manufacturing process for a chemical drug might contain 40 to 50 critical tests . . . [whereas] [t]he process for a biologic might contain 250 or more."[12]

As can be expected, the stringent manufacturing and storage requirements that biologics demand come at a high cost.[13] On average, biologics cost $10,000 to $30,000 per year, though some may exceed $500,000.[14] By another metric, the average daily cost of a biologic in the United States is $45, which may be put into perspective by comparison to the daily cost of small-molecule (chemical) drugs, which is $2.[15] In 2017, biologics were responsible for 37% of net drug spending, totaling $120 billion, despite only accounting for 2% of all

8 Morrow & Felcone, *supra* note 1, at 25.

9 *Id.* at 26.

10 U.S. FOOD & DRUG ADMIN., *supra* note 5.

11 Morrow & Felcone, *supra* note 1, at 26.

12 *Id.* at 28.

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

14 *Id.*

15 Erwin A. Blackstone & P. Fuhr Joseph, Jr., *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS 469, 469 (2013).

prescriptions written in the United States.[16] Additionally, biologics account for 93% of the overall growth in net drug spending since 2014.[17]

In October 1982, the U.S. Food and Drug Administration ("FDA") approved the first recombinant DNA product, Humulin, a form of human insulin developed by Genentech and Eli Lilly, for use in the United States.[18] Research on recombinant DNA technology began at Stanford University in the early 1970s, and this research proved that "genes from one organism could be isolated and cloned into vectors for expression in unrelated organisms."[19] This research, however, was complicated by the initial worry that experimentation with certain DNA components, particularly those that were tumor-derived, would transmit cancer to people working with them.[20] In response to this worry, recombinant DNA research was temporarily paused and a conference on recombinant DNA in 1975 provided guidelines for future work with such components.[21] The process by which recombinant products are created involves "inserting a DNA fragment into a small DNA molecule [a DNA vector] and then allowing this molecule to replicate inside a simple living cell such as a bacterium."[22] The small replicating molecules are most often plasmids, "circular DNA

16 Avik Roy, *Biologic Medicines: The Biggest Driver of Rising Drug Prices*, FORBES (Mar. 8, 2019, 8:20 PM), https://www.forbes.com/sites/theapothecary/2019/03/08/biologic-medicines-the-biggest-driver-of-rising-drug-prices/ [https://perma.cc/R9YG-PQZE]; Joel Lexchin, *Affordable Biologics for All*, 3 JAMA NETWORK OPEN, Apr. 27, 2020, at 1; *see also* IQVIA INST., MEDICINE USE AND SPENDING IN THE U.S.: A REVIEW OF 2017 AND OUTLOOK TO 2022 (2018), https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022 [https://perma.cc/RV9V-Y75V].

17 Roy, *supra* note 16.

18 Recombinant drugs are made by "inserting genes from one species into a host species . . . where they do not naturally occur," permitting the growth of genetically modified host organisms. *Humulin N, NPH, Human Insulin (Recombinant DNA Origin) Isophane Suspension*, NAT'L MUSEUM OF AM. HIST., https://americanhistory.si.edu/collections/search/object/nmah_1000967 [https://perma.cc/HN7F-65S7] (last visited Nov. 20, 2022). In the case of Humulin, genes coding for human insulin are inserted into bacteria, which then product the insulin harvested and used in Humulin. *Id.*; Michael S. Kinch, *An Overview of FDA-Approved Biologic Medicines*, 20 DRUG DISCOVERY TODAY 393, 393 (2015).

19 Kinch, *supra* note 18, at 393.

20 *Id.*

21 *Id.* The conference in question was the Asilomar Conference on Recombinant DNA.

22 Anthony J.F. Griffiths, *Recombinant DNA: Genetic Engineering*, BRITANNICA, https://www.britannica.com/science/recombinant-DNA-technology [https://perma.cc/FTF3-HHR4] (Mar. 28, 2024).

molecules that originated from bacteria," viruses, and yeast cells.[23] Plasmids in particular are "small enough to be conveniently manipulated experimentally" and, significantly, "they will carry extra DNA that is spliced into them."[24]

Before being inserted into the vector, the DNA fragment must be extracted. This is most often accomplished by cleaving, or cutting into small fragments suitable for cloning, with a restriction endonuclease, a type of enzyme.[25] These restriction enzymes "can be thought of as "molecular scissors," cutting the DNA at specific target sequences."[26] The DNA vector is also cut using the same restriction enzyme, which creates "a strong possibility that the donor [DNA] fragment[] and the cut vector will splice together."[27] The resulting molecule is recombinant DNA "in the sense that it is composed of DNA from two different sources," the extracted DNA fragment and the DNA vector.[28] The resulting recombinant molecule is then inserted into a host cell or expression system, often *E. coli* or Yeast, after which the recombinant molecule multiplies, forming clones.[29] The clones are then harvested or fermented to produce recombinant drugs, undergoing purification, preformulation, and animal and human testing.[30]

II. AN INTRODUCTION TO BIOSIMILARS IN THE UNITED STATES AND EUROPE

In any discussion surrounding the exorbitant price of biologics, biosimilars are a necessary part of the conversation. Biosimilars are "highly similar but not structurally identical" drugs that mimic the effects of specific brand-name biologics, also known as reference products.[31] They are comparable to generics in the chemical drug market, but while generics are exact copies of brand-name drugs, biosimilars are "highly similar."[32] They cannot be identical to the brand-name

23 *Id.*

24 *Id.*

25 Kishore & Krishan, *supra* note 4, at 142; Griffiths, *supra* note 22.

26 Griffiths, *supra* note 22.

27 *Id.*

28 *Id.*

29 Kishore & Krishan, *supra* note 4, at 142.

30 *Id.*

31 CONG. RSCH. SERV., R44620, BIOLOGICS AND BIOSIMILARS: BACKGROUND AND KEY ISSUES 1 (2019), https://crsreports.congress.gov/product/pdf/R/R44620 [https://perma.cc/BK5H-PWXY].

32 *Id.*

drugs whose effects they mimic due to the "inherent variability in biological products from natural sources,"[33] but they compete with brand name biologics regardless, and may lead to lowered drug costs as a result.[34]

Biologic drugs are often more expensive in the United States than in Europe, where the introduction of biosimilars has reduced the prices for biologics.[35] Since 2006, when the European Union approved the first biosimilar (Omnitrope, a human growth hormone), the European Union has approved "the highest number of biosimilars worldwide."[36] The European biologic regulatory framework is governed by the Committee for Medicinal Products for Human Use ("CHMP") under the European Medicines Agency ("EMA").[37] In 2005 and 2006, the EMA issued an "overarching biosimilars guideline," as well as two more specific guidelines regarding "quality, clinical, and nonclinical issues relating to the development of biosimilars."[38]

A comparative price analysis on biologics used to treat rheumatoid arthritis among eighteen European countries revealed that manufacturer prices for two specific biosimilars, etanercept and rituximab, were, respectively, 36% and 39% lower than the prices for the corresponding reference biologics.[39] Retail prices for these biosimilars were also, respectively, 11% and 86% lower than the prices for the

33 *Id.* at 8.

34 David L. Carl, Yannic Laube, Miquel Serra-Burriel, Huseyin Naci, Wolf-Dieter Ludwig & Kerstin N. Vokinger, *Comparison of Uptake and Prices of Biosimilars in the US, Germany, and Switzerland*, 5 JAMA NETWORK OPEN, Dec. 2, 2022, at 1-2, 7-8.

35 *See generally id.*

36 EUR. MEDS. AGENCY, EUR. COMM'N, BIOSIMILARS IN THE EU: INFORMATION GUIDE FOR HEALTHCARE PROFESSIONALS 3 (2019), https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf [https://perma.cc/YK3H-D55J].

37 *Id.* at 12; Aydin Harston, *How the U.S. Compares to Europe on Biosimilar Approvals and Products in the Pipeline (Updated)*, JD SUPRA (Nov. 16, 2021), https://www.jdsupra.com/legalnews/how-the-u-s-compares-to-europe-on-6251301/ [https://perma.cc/SUQ9-QYFU].

38 Martin Schiestl, Markus Zabransky & Fritz Sörgel, *Ten Years of Biosimilars in Europe: Development and Evolution of the Regulatory Pathways*, 11 DRUG DESIGN, DEV. & THERAPY 1509, 1510 (2017).

39 *See* Jeffrey Wu & Claire Wan-Chiung Cheng, *Into the Woods: A Biologic Patent Thicket Analysis*, 19 CHI.-KENT J. INTELL. PROP. 93, 152 (2020) (citing Manoela Manova, Alexandra Savova, Maria Vasileva, Silvia Terezova, Maria Kamusheva, Daniela Grekova, Valentina Petkova & Guenka Petrova, *Comparative Price Analysis of Biological Products for Treatment of Rheumatoid Arthritis*, 9 FRONTIERS PHARMACOLOGY, Sept. 20, 2018, at 5).

corresponding reference biologics.[40] It is clear that increased competition can lower the price of name-brand biologics and increase the number of offerings available on the market. In Europe, where biosimilars for AbbVie Inc.'s ("AbbVie") brand-name biologic, Humira, are available, AbbVie has offered "an 80% discount . . . in the European tender markets."[41]

In the United States, where nine biosimilars for Humira entered the market in 2023,[42] Humira's list price has continued to increase.[43] More specifically, Humira's list price has risen 60% since 2016, with its annual cost now totaling more than $80,000 per year.[44] Additionally, AbbVie and its former parent company increased the price of Humira approximately thirty times over the past twenty years, during which it enjoyed exclusive patent protection.[45]

The market debut of these nine biosimilars had a major financial impact on AbbVie.[46] In February 2023, a month after Amjevita, the first-launched biosimilar, entered the market, AbbVie stated that it "expects sales of its flagship rheumatoid arthritis drug Humira to decline 37% this year due to competition from cheaper biosimilars in the

40 *Id.*

41 *Id.*

42 *Amjevita™ (Adalimumab-Atto), First Biosimilar to Humira®, Now Available in the United States*, AMGEN (Jan. 31, 2023), https://www.amgen.com/newsroom/press-releases/2023/01/amjevita-adalimumabatto-first-biosimilar-to-humira-now-available-in-the-united-states [https://perma.cc/UAB8-WLZB]. Also note that though Amjevita entered the market in 2023, it and eight other biosimilars were approved by the FDA starting in September 2016, when Amjevita became the first FDA-approved Humira biosimilar. *Biosimilar Product Information*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-product-information [https://perma.cc/TNZ9-HWQT] (Nov. 1, 2023); Drew Goodrich, *A Review of Newly Available Biosimilars for Pharmacists*, PHARMACY PRAC. NEWS (Nov. 22, 2023), https://www.pharmacypracticenews.com/Review-Articles/Article/12-23/A-Review-of-Newly-Available-Humira-Biosimilars-for-Pharmacists/72110 [https://perma.cc/4VMM-HRHK].

43 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/TT5F-4BXC].

44 *Id.*

45 *Id.*

46 Goodrich, *supra* note 42; Leroy Leo & Mariam E. Sunny, *AbbVie Sees 37% Drop in Humira Sales This Year as Biosimilars Hit U.S. Market*, REUTERS (Feb. 9, 2023, 6:40 PM), https://www.reuters.com/business/healthcare-pharmaceuticals/abbvies-2023-profit-forecast-misses-humira-faces-heat-rivals-2023-02-09/ [https://perma.cc/9XCY-YAF5].

United States, [though it] sees that stabilizing by the end of 2024."[47] Though this drop seems precipitous, it is "at the lower end of a 35-55% fall the company had previously estimated."[48] Despite this relatively sunny forecast for AbbVie, the introduction of biosimilars still seems to clearly affect pharmaceutical companies' profits. AbbVie's revenue from Humira sales in the U.S. increased from $13.69 billion in 2018 to $18.62 billion in 2022, while internationally, Humira sales declined from $6.25 billion in 2018 to $2.62 billion in 2022.[49]

In July 2023, after eight additional biosimilars entered the market, AbbVie "trimmed its 2023 view for declining sales of its flagship arthritis drug Humira despite new competition, as favorable positions on insurance drug coverage lists helped it continue to reach U.S. patients."[50] AbbVie stated that it "now expects Humira sales to fall by 35% instead of 37%," a somewhat positive update for the company.[51] At this announcement, AbbVie shares "surged 5.3% to $149.41."[52] This improved forecast for the company can be attributed, at least in part, to a multitude of factors, including (1) the fact that AbbVie has two-year deals with pharmacy benefit managers ("PBMs")[53] that put Humira on their reimbursement lists; and (2) the success of other, newer AbbVie biologics, Skyrizi and Rinvoq.[54] These two newer biologics both exceeded sales expectations, with Skyrizi recording $1.88 billion in global sales after estimates of $1.82 billion and Rinvoq recording $918 million in global sales after estimates of $897 million.[55] These drugs are quickly gaining in terms of popularity and revenue-

47 Leo & Sunny, *supra* note 46.

48 *Id.*

49 *Id.* (illustrated in a helpful diagram titled "Sales of Abbvie's Humira").

50 Leroy Leo & Patrick Wingrove, *AbbVie Trims Forecast for Humira Sales Drop on Favorable Coverage*, REUTERS (July 27, 2023, 1:55 PM), https://www.reuters.com/business/healthcare-pharmaceuticals/abbvie-raises-annual-profit-forecast-humira-stays-strong-new-drugs-impress-2023-07-27/ [https://perma.cc/9DA6-KF3E].

51 *Id.*

52 *Id.*

53 PBMs (examples include CVS Health's Caremark, Cigna's Express Scripts, and United Health's Optum Rx) function as intermediaries between insurance companies and pharmaceutical manufacturers, recommending coverage for drugs via the creation of formularies and negotiating prices and rebates, among other things. PBMs generate a profit by taking a cut of the savings they negotiate. Center for Insurance Policy & Research, *Pharmacy Benefit Managers*, NAT'L ASS'N OF INS. COMM'RS, https://content.naic.org/cipr-topics/pharmacy-benefit-managers [https://perma.cc/LLG2-FX6Z] (June 1, 2023); Leo & Wingrove, *supra* note 50.

54 Leo & Wingrove, *supra* note 50.

55 *Id.*

generating ability for Abbvie. On a recent investor call in July 2023, AbbVie bumped its 2023 global sales forecast for Skyrizi to a whopping $7.6 billion.[56]

The graphic below illustrates AbbVie's expectations for Skyrizi and Rinvoq amidst declining Humira sales due to the introduction of biosimilars into the U.S. market. Though data on declining Humira sales are still emerging, it is clear that AbbVie has other tools in its arsenal—in other words, new drugs—to combat competition from biosimilar manufacturers. More specifically, AbbVie is "banking on the robust sales growth of its newer immunology drugs Skyrizi and Rinvoq to offset a decline in sales of Humira as biosimilars for the blockbuster arthritis drug enter the U.S. market."[57]

Despite their similarities to their respective reference products, biosimilars must be labeled *interchangeable* by the FDA during its approval process in order to be substituted for their reference product at the pharmacy without physician intervention.[58] As Thomas Seck, Senior Vice President of Medicine and Regulatory Affairs at Boehringer Ingelheim, explained to The Center for Biosimilars:

> In addition to meeting the requirements of biosimilarity, an interchangeable biosimilar must first have a highly similar profile and the same clinical result as the reference product in any given patient. Then it must *additionally* demonstrate that the risk in terms of safety or diminished efficacy of switching with the reference product is not greater than staying on the reference product.[59]

This demonstration may be done via an interchangeability study in which patients are switched between the reference product and the biosimilar so that outcomes can be studied and physicians can be sure that the switch does not compromise immunogenicity, safety, and efficacy.[60] Though interchangeability may save patients money by

56 *Id.*

57 *Id.*

58 *Biosimilar and Interchangeable Biologics: More Treatment Choices*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices [https://perma.cc/T3MJ-R2N8] (Aug. 17, 2023).

59 Tony Hagen, *The Difference Between an Interchangeable Biosimilar and One that Isn't*, THE 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/WYS4-962N] (emphasis added).

60 *Id.*

allowing for automatic substitution of a highly similar drug without obtaining the prescribing provider's approval, obtaining interchangeable status is a separate, time-consuming process on top of the standard FDA requirements for biosimilar manufacturers seeking regulatory approval.[61]

An interchangeability study might begin with a fourteen-week run-in period, during which all patients receive the reference product.[62] Subsequently, patients are randomly placed in either treatment or control groups.[63] The double-bind period then begins, during which (1) the treatment group receives the interchangeable biosimilar candidate; (2) the treatment group switches to the reference product; and (3) the treatment group again switches back to the interchangeable biosimilar candidate.[64] The first two of these three steps each take four weeks, with the third step taking eight weeks.[65] During the entire double-blind period, the control group remains on the reference product. In total, this process takes at least 30 weeks.[66]

As of April 2024, Humira had ten biosimilars on the market but only four that were interchangeable: Cyltezo, Abrilada, Hyrimoz, and Simlandi.[67] More generally, as of March 2023, "only 4 of the 40 biosimilars licensed for use in the [United States] [were] designated as interchangeable."[68] The three aforementioned drugs are part of a small handful of interchangeable biosimilars on the market despite the growing pool of available biosimilars, illustrating the dearth of interchangeable drugs and suggesting that "[i]nterchangeability remains the exception, not the rule, when it comes to biosimilars."[69]

Given this dearth of interchangeable drugs, pharmacy substitution must be allowed in order for biosimilars to significantly reduce

61 *Id.*

62 *Id.* See "Chart: A Sample Outline for an Interchangeability Study," for a visual representation of this process.

63 *Id.*

64 *Id.*

65 Hagen, *supra* note 59.

66 *Id.*

67 *Purple Book Database of Licensed Biological Products: Simple Search Results for:* Humira, U.S. FOOD & DRUG ADMIN., https://purplebooksearch.fda.gov/results?query=adalimumab&title=Humira [https://perma.cc/8SCS-YQLA] (last visited Apr. 27, 2024).

68 Maria Sheridan, Matthew Massich, & Nazanin Ashourian, *Biosimilars: From Production to Patient*, 47 J. INFUSION NURSING 19, 24 (2024).

69 *5 Things Worth Knowing About Biosimilars and Interchangeability*, PFIZER (Oct. 12, 2022), https://www.pfizer.com/news/articles/5_things_worth_knowing_about_biosimilars_and_interchangeability [https://perma.cc/7EQ8-XAQ7].

drug prices.[70] Pharmacy substitution policies permit pharmacists to switch patients from brand-name drugs to their generic or biosimilar counterparts without permission from the prescribing doctor.[71] These policies exist in many states in the United States and in most countries, but they generally pertain to small-molecule chemical drugs only.[72] While the EMA handles all product authorization decisions for biologics and biosimilars alike in the European Union, policies concerning prices and procurement (such as substitution policies) are left up to individual countries, resulting in variation in product entry and uptake.[73] Many countries in Europe have opposed pharmacy substitution.[74] Spain is a prime example; the country has a no-substitution policy for biologics even if the two products have the same generic name, effectively prohibiting substitution of anything other than the drug specified by the prescribing physician and placing the burden of substitution on the physician.[75]

Despite the time advantage the European Union has on the United States in terms of biosimilar introduction, major pharmaceutical companies still produce a majority of biosimilars in Europe.[76] For example, Sandoz, the generic drug unit of Novartis, manufactures and markets three biosimilars in the European Union, which make up 50% of its total biosimilar market.[77] Sandoz generated $9.7 billion in sales in 2021, which comprised only 20% of Novartis's total annual revenue.[78]

70 Anita Afzali, Daniel Furtner, Richard Melsheimer & Philip J. Molloy, *The Automatic Substitution of Biosimilars: Definitions of Interchangeability Are Not Interchangeable*, 38 ADVANCES THERAPY 2077, 2078 (2021).

71 Fiona M. Scott Morton, Ariel Dora Stern & Scott Stern, *The Impact of the Entry of Biosimilars: Evidence from Europe*, 53 REV. INDUS. ORG. 173, 182 (2018).

72 *Id.*

73 *Id.*

74 Louise C. Druedahl, Sofia K. . .lvemark Sporrong, Timo Minssen, Hans Hoogland, Marie Louise De Bruin, Marco van de Weert & Anna Birna Almarsdóttir, *Interchangeability of Biosimilars: A Study of Expert Views and Visions Regarding the Science and Substitution*, 17 PLOS ONE, Jan. 11, 2022, at 11, 13.

75 Morton et al., *supra* note 71.

76 IQVIA INST., *supra* note 16, at 9.

77 Blackstone & Joseph, *supra* note 15, at 471.

78 Ludwig Burger, *Novartis May Divest Generic Unit Sandoz as Price Pressures Mount*, REUTERS (Oct. 26, 2021, 6:24 AM), https://www.reuters.com/business/novartis-more-bullish-cosentyx-entresto-sales-q3-profit-rises-2021-10-26/ [https://perma.cc/6K84-CY3R]; *Novartis Announces Intention to Separate Sandoz Business to Create a Standalone Company by Way of a 100% Spin-off*, NOVARTIS (Aug. 25, 2022), https://www.novartis.com/news/media-releases/novartis-announces-intention-separate-sandoz-business-create-standalone-company-way-100-spin [https://perma.cc/847C-SKKS].

This illustrates the importance of prioritizing innovation for smaller pharmaceutical companies; otherwise, major pharmaceutical companies will likely dominate the manufacturing of biosimilars, allowing them to maintain monopolistic market shares despite the appearance of competition.

III. PATENT PROTECTIONS AND LITIGATION REGARDING BIOSIMILARS IN THE UNITED STATES

Pharmaceutical companies in the United States protect their brand-name biologics through the use of patent "thickets," which have been described as "a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology."[79] This type of protection was initially made possible by the U.S. Supreme Court in *Diamond v. Chakrabarty*, in which it held that live, human-made genetically engineered microorganisms could be patented under 35 U.S.C. § 101.[80] Though the Supreme Court may not have known that patent protections for such products would be manipulated in such a way as to discourage cheaper alternatives from reaching the market, *Diamond v. Chakrabarty* paved the way for "evergreening" and other exclusionary practices.[81]

A. Evergreening and Its Protective Effects for Brand-Name Biologic Manufacturers

Discussion of biologic patent thickets also relates to the concept of "evergreening," which occurs when drug companies "extend the market exclusivity of a drug beyond the life of its original patent by obtaining multiple patents that cover different aspects of that drug, including the active ingredient, formulations, methods of

79 Stefan Wagner, *Are 'Patent Thickets' Smothering Innovation?*, YALE INSIGHTS (Apr. 22, 2015), https://insights.som.yale.edu/insights/are-patent-thickets-smothering-innovation [https://perma.cc/TR5E-XJQZ].

80 *See* Suzanne White Junod, *Celebrating a Milestone: FDA's Approval of First Genetically-Engineered Product*, U.S. FOOD & DRUG ADMIN., https://fda.report/media/110447/Celebrating-a-Milestone—FDA%27s-Approval-of-the-First-Genetircally-Engineered-Product.pdf [https://perma.cc/W832-CKWZ] (last visited Nov. 20, 2022) (discussing *Diamond v. Chakrabarty*, 447 U.S. 303 (1980)). 35 U.S.C. § 101 permits the issuance of patents to individuals who invent or discover "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."

81 *Id.*

manufacturing, chemical intermediates, mechanisms of actions, packaging, screening methods, and biological targets."[82] Patent thickets may be distinguished from evergreening in that the "concern of the former is the number of patents while that of the latter is the increased year span of the collective patent term."[83] Evergreening, however, is a common practice even among companies manufacturing small-molecule drugs.[84]

Various patents that AbbVie secured on Humira exemplify evergreening in action. An earlier patent on the drug, which expired in 2016, covered its use in treating ankylosing spondylitis,[85] a type of inflammatory arthritis causing chronic inflammation of the spine.[86] In 2014, two years prior to the earlier patent's expiration, AbbVie "applied for another patent for a method of treating ankylosing spondylitis with a specific dosing of 40 milligrams of Humira."[87] This application was eventually approved, granting AbbVie an additional eleven years of patent protection from 2016 onward.[88]

AbbVie's own description of its strategy in a 2015 presentation is a prime example of pharmaceutical companies' manipulation of patents to protect their biologics. In the presentation, AbbVie "proudly" described its "patent estate," comprised of seventy-five patents that covered "formulations, treatment uses and manufacturing processes" for Humira.[89] This "estate" has only grown larger in the following years.[90] In 2023, the Initiative for Medicines, Access, and Knowledge, which collects information on drug patents, found that "AbbVie and its affiliates have applied for 311 patents, of which 165 have been granted."[91]

In 2014, Bill Chase, an AbbVie executive, disclosed at a conference that the company's patent strategy was explicitly designed to

82 Joanna T. Brougher, *Evergreening Patents: The Indian Supreme Court Rejects Patenting of Incremental Improvements*, 19. J. COM. BIOTECHNOLOGY 54, 55 (2013).

83 Wu & Cheng, *supra* note 91, at 110.

84 *Id.*

85 Robbins, *supra* note 43.

86 *Ankylosing Spondylitis (AS)*, CLEVELAND CLINIC (July 21, 2020), https://my.clevelandclinic.org/health/diseases/16595-ankylosing-spondylitis-as [https://perma.cc/AFG2-NGGN].

87 Robbins, *supra* note 43.

88 *Id.*

89 Wu & Cheng, *supra* note 39, at 111.

90 Robbins, *supra* note 43.

91 *Id.*

"make it more difficult for a biosimilar to follow behind."[92] In 2019, AbbVie's CEO, Richard Gonzalez, noted that the company was successful in securing 136 patents on Humira.[93] These patents have at least in part contributed to Humira's exorbitant sales, which totaled almost $193 billion from its introduction in 2003 through the end of 2021.[94]

On January 28, 2023, the New York Times published an article detailing AbbVie's "savvy but legal exploitation of the U.S. patent system," making Humira the "most lucrative franchise in pharmaceutical history."[95] It noted that, though "AbbVie did not invent the[] patent-prolonging strategies [employed]," its "success with Humira stands out even in an industry adept at manipulating the U.S. intellectual-property regime."[96]

Patent thickets may be manipulated by pharmaceutical companies to force biosimilar manufacturers into settlements.[97] Multiple patents are granted for "minor variations on a single invention,"[98] making it more difficult for biosimilar manufacturers to sell their products without being sued for patent infringement. As of May 2019, eight Humira biosimilars existed, but all entered into settlements with AbbVie, the manufacturer of Humira.[99] A pharmaceutical company with a greater number of patents on a biologic stands a greater chance of winning in litigation against a biosimilar manufacturer.[100] Even if a biosimilar manufacturer succeeds, litigation in general—let alone against a major pharmaceutical company—is incredibly expensive and time-consuming.[101] These patent thickets also provide the pharmaceutical companies making reference products with leverage in

92 *Id.*

93 Wu & Cheng, *supra* note 39, at 111.

94 Angel Adegbesan, *Top-Seller Humira Set for U.S. Rival After $193 Billion in Sales*, BLOOMBERG L. (Apr. 1, 2022, 10:00 AM), https://www.bloomberglaw.com/bloomberglawnews/health-law-and-business/X52J7GSC000000 [https://perma.cc/9SHJ-9JQC].

95 Robbins, *supra* note 43.

96 *Id.*

97 Wu & Cheng, *supra* note 39, at 148.

98 Blake Brittain, *U.S. Senators Ask Regulators to Clear Drug Patent 'Thickets'*, REUTERS (June 8, 2022, 8:43 PM), https://www.reuters.com/legal/litigation/us-senators-ask-regulators-clear-drug-patent-thickets-2022-06-08/ [https://perma.cc/SHP4-BAQT].

99 Wu & Cheng, *supra* note 39, at 148.

100 *Id.*

101 *Id.*

negotiating settlements with biosimilar manufacturers, allowing them to reach more favorable deals.[102]

B. Recent U.S. Supreme Court Jurisprudence Regarding Competition Between Biologic and Biosimilar Manufacturers

Two U.S. Supreme Court cases, *Sandoz Inc. v. Amgen Inc.*[103] and *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*,[104] have recently colored the biologic-biosimilar competitive landscape. *Sandoz v. Amgen* involved the Biologics Price Competition and Innovation Act ("BPCIA"), which, in pertinent part, requires that "an applicant that seeks FDA approval of a biosimilar must provide its application materials and manufacturing information to the manufacturer of the corresponding biologic within 20 days of the date the FDA notifies the applicant that it has accepted the application for review."[105] An applicant is then required to "give notice to the manufacturer at least 180 days before marketing the biosimilar commercially."[106]

> The Act functions in the following way:
> The BPCIA facilitates litigation during the period preceding FDA approval so that the parties do not have to wait until commercial marketing to resolve their patent disputes. It enables the parties to bring infringement actions at certain points in the application process, even if the applicant has not yet committed an act that would traditionally constitute patent infringement. . . . . Specifically, it provides that the mere submission of a biosimilar application constitutes an act of infringement.[107]

The Court refers to "this kind of preapproval infringement as 'artificial' infringement."[108] This process—also referred to as the "patent dance"—is ultimately designed to complete patent litigation early so that biosimilar manufacturers can market their products without the threat of such litigation hanging over their heads.[109] The Supreme

102 *Id.*
103 Sandoz Inc. v. Amgen Inc., 582 U.S. 1 (2017).
104 Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC, 584 U.S. 325 (2018).
105 *Sandoz*, 582 U.S. at 5.
106 *Id.* at 6.
107 *Id.* at 7-8.
108 *Id.* at 8.
109 Chen et al., *supra* note 13, at 1778.

Court, however, held that the "patent dance" is optional.[110] This meant that, on the one hand, biosimilar manufacturers would not need to engage in a process that required them to openly exchange information and potentially expose trade secrets, which are "protected by law against infringement" and do not have expiration dates.[111] On the other hand, however, because fewer potential disputes may be resolved before FDA approval of biosimilars, biosimilar manufacturers face increased risks once they have brought their products to market and invested significant time and money.[112]

Oil States v. Greene's Energy Group, however, did not involve biologics or drugs of any kind but rather the process of inter partes review ("IPR") established by the Leahy-Smith America Invents Act (35 U.S.C. § 100 et seq.).[113] This process allows the U.S. Patent and Trademark Office ("USPTO") to reconsider and cancel previously issued patents in certain situations at any point in time.[114] Plaintiffs in this case argued that their property rights, which included patents, could not be taken away without a jury trial, and that the IPR process therefore violated Article III and the Seventh Amendment of the Constitution.[115] Here, the Court held that IPR did not violate either Constitutional provision and found government-granted patents to be "public franchise[s]" rather than private property, allowing for validity determinations by the USPTO without jury trials.[116] The outcome in this case ultimately allowed biosimilar manufacturers to continue bringing IPR challenges to brand-name biologic manufacturers at any point, instead of requiring them to wait for FDA approval.[117]

Biosimilar manufacturers have used the IPR process fairly readily. Since 2012, biosimilar manufacturers have instituted "over 100 IPR challenges against key patents held by reference biologic makers."[118] However, neither the availability of the IPR process nor the victories for biosimilar manufacturers in *Sandoz* and *Oil States* have resulted in greater ubiquity of biosimilars in the United States.[119]

110 *Id.*
111 *Id.*
112 *Id.*
113 *Oil States*, 584 U.S. at 328.
114 *Id.*; Chen et al., *supra* note 13, at 1779.
115 *Oil States*, 584 U.S. at 344-45; *see also* Chen et al., *supra* note 13, at 1778-79.
116 Chen et al., *supra* note 13, at 1779.
117 *Id.*
118 *Id.*
119 *Id.*

IV. PATENT PROTECTIONS AND LITIGATION REGARDING BIOSIMILARS IN EUROPE

Though pharmaceutical companies producing brand-name biologics in European markets can challenge the entry of biosimilars in some ways, European markets have greater competition overall than the United States.[120] In Europe, patents may be obtained on a country-by-country level or via the European Patent Office ("EPO"). Patents obtained from the EPO are valid in all countries that are signatories to the European Patent Convention ("EPC") and are granted the same rights in all signatory countries as "would be conferred by a national patent granted in that state [which originally granted such patent]."[121] The EPC, which provides "a single application and created a uniform body of substantive patent law," was designed to "provide easier, cheaper and stronger protection for inventions in the contracting states."[122]

Inversely, if biosimilar manufacturers want to challenge the patents held by companies making brand-name biologics, they may do so in the EPO—a single, unified forum.[123] Additionally, Europe's biosimilars market is more advanced because the exclusivity period for brand-name biologics is shorter than the United States'. In Europe, the European Medicines Agency permits biosimilars to come to market after ten years, compared to twelve years in the United States.[124]

120 *See* Evelien Moorkens, Arnold G. Vulto & Isabelle Huys, *An Overview of Patents on Therapeutic Monoclonal Antibodies in Europe: Are They a Hurdle to Biosimilar Market Entry?*, 12 MABS 1, 2, 11 (2020).

121 *Id.*; EUROPEAN PATENT OFFICE, EUROPEAN PATENT GUIDE 10 (2023), https://link.epo.org/web/legal/guide-epc/en-how-to-get-a-european-patent-2023.pdf [https://perma.cc/97BB-TX9B] (chapter 2.2.001) (the signatory states to the EPC are Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Türkiye, and the United Kingdom); *see also* EUROPEAN PATENT OFFICE, EUROPEAN PATENT CONVENTION 44 (2020), https://link.epo.org/web/EPC_17th_edition_2020_en.pdf [https://perma.cc/EL6M-ZKCG] (art. 2(2)).

122 EUROPEAN PATENT GUIDE, *supra* note 121, at 10 (chapter 2.2.001).

123 Brian J. Malkin, *Biosimilars Patent Litigation in the EU and the U.S.: A Comparative Strategic Overview*, 4 GENERICS & BIOSIMILARS INITIATIVE J. 113, 114 (2015).

124 Bruce Love, *US Plays Catch-Up with Europe over Biosimilar Patents*, FIN. TIMES (June 16, 2021), https://www.ft.com/content/3f7ca3f4-8256-4570-a6a3-b255e185f162 [https://perma.cc/W6D5-Q8LT].

A study conducted by Rachel Goode and Bernard Chao and published in 2022 found that "on average[,] 12 times more patents are asserted [in patent litigations taking place in the U.S.] when compared to the UK."[125] The study also observed that biosimilars entered the United Kingdom's market more quickly than they did in the United States.[126] Comparing AbbVie's patent portfolio for Humira in both the United States and the European Union, Goode and Chao found that Humira's core patent portfolio in the United States contained approximately seventy-three patents, "80% of which are non-patentably distinct from one another[, which] is permitted under USPTO obvious-type double patenting rules through the use of terminal disclaimers."[127] In the European Union, AbbVie's patent portfolio for Humira was "comprised of only eight non-duplicative patents," a marked difference.[128]

V. ANTITRUST IMPLICATIONS AND THE CHILLING EFFECT OF PATENT THICKETS

One of the most recent cases involving alleged antitrust violations and the use of patent thickets is *Mayor of Baltimore v. AbbVie Inc.*,[129] in which the Seventh Circuit affirmed the district court's decision granting the defendant's motion to dismiss and finding that the plaintiffs failed to state a claim.[130] The plaintiffs, including the City of Baltimore and employee welfare benefit plans, indirectly purchased Humira on behalf of their beneficiaries.[131] They sued AbbVie and other pharmaceutical companies in district court, alleging that AbbVie's use of its additional 132 patents obtained around the 2016 expiration of the basic patent for Humira, the last of which expires in 2034, violated sections 1 and 2 of the Sherman Antitrust Act by pressuring the plaintiffs into accepting settlements resulting in the delay of

125 Rachel Goode & Bernard Chao, *Biological Patent Thickets and Delayed Access to Biosimilars, an American Problem*, 9 J. LAW & BIOSCIENCES 1, 3 (2022).

126 *Id.*

127 *Id.* at 4.

128 *Id.*

129 *In re* Humira (Adalimumab) Antitrust Litig., 465 F. Supp. 3d. 811 (N.D. Ill. 2020), *aff'd sub nom.* Mayor of Baltimore v. Abbvie Inc., 42 F.4th 709, 712 (7th Cir. 2022).

130 *Mayor of Baltimore*, 42 F.4th at 715.

131 *Id.* at 711.

their products' entry into the market to avoid patent infringement lawsuits.[132]

The plaintiffs brought class action claims on behalf of two classes.[133] On behalf of the first class, which consisted of "[a]ll entities in the United States, the District of Columbia, and Puerto Rico who indirectly purchased, paid and/or provided reimbursement for some or all of the purchase price of Humira, other than for resale, from December 31, 2016, through [the time of filing]," the plaintiffs sought injunctive relief.[134] On behalf of the second class, which encompassed "'[a]ll entities who indirectly purchased, paid and/or provided reimbursement for some or all of the purchase price for Humira, other than for resale,' in thirty-one states and the District of Columbia, 'from December 31, 2016, through [the time of filing],'" the plaintiffs sought damages.[135]

The defendants moved to dismiss the complaint, addressing the alleged violations of sections 1 and 2 of the Sherman Act separately and jointly. Section 1 of the Sherman Act prohibits "'[e]very contract, combination in the form of trust or other-wise, or conspiracy, in restraint of trade or commerce'"[136] and requires that a plaintiff plead "'(1) a contract, combination, or conspiracy; (2) a resultant unreasonable restraint of trade in [a] relevant market; and (3) an accompanying injury.'"[137] Section 2 of the Act prohibits the "wrongful monopolization of interstate trade or commerce" and requires a plaintiff to show "'(1) the possession of monopoly power in the relevant market and (2) the willful acquisition or maintenance of that power as distinguished from growth or development as a consequence of a superior product, business acumen, or historic accident.'"[138]

The plaintiffs asserted that Defendants AbbVie, Amgen, Samsung Bioepis, and Sandoz violated section 1 when they entered into settlement agreements requiring Amgen, Samsung, and Sandoz to hold off on launching their biosimilars in the United States in exchange for permission to launch them in Europe.[139] Defendants argued

132 *In re Humira*, 465 F. Supp. 3d. at 819.

133 *Id.* at 811.

134 Class Action Complaint at 42-43, In re Humira (Adalimumab) Antitrust Litigation, 465 F. Supp. 3d. 811 (N.D. Ill. 2020) (No. 1:19-CV-01873).

135 *Id.*

136 Sherman Antitrust Act, 15 U.S.C. § 1 (1890).

137 *In re Humira*, 465 F. Supp. 3d. at 835.

138 *Id.* at 827 (interpreting the Sherman Antitrust Act § 2).

139 *Id.* at 836.

in response that the settlements do not violate antitrust law because they "allow AbbVie's competitors to enter the market before the expiration of AbbVie's patents, do not involve any reverse payments from AbbVie (the patentee) to Amgen, Samsung Bioepis, and Sandoz (the alleged infringers), and only divvy up the market in ways consistent with AbbVie's patent rights."[140] The district court found that the agreements ultimately benefited consumers by allowing Amgen, Samsung Bioepis, and Sandoz to enter the European and U.S. markets earlier than they might otherwise have been able to, ultimately making the market more competitive.[141]

The plaintiffs alleged that the defendants violated section 2 via a "new theory" of antitrust liability. The plaintiffs did not claim that AbbVie "obtained its patents by knowing and willful fraud," nor did they claim that their accumulation of patents surrounding Humira was anticompetitive.[142] Instead, the plaintiffs argued that AbbVie "abused its monopoly over the U.S. market for adalimumab (which includes Humira and its biosimilars) when it gummed up progress toward lower prices by obtaining and asserting 'swaths of invalid, unenforceable, or noninfringed patents without regard to the patents' merits,'" and that this delay in progress allowed them to "reap a few more years' worth of monopoly profit on its lucrative, patent-protected product.'"[143] In response, the defendants argued that amassing a large portfolio of legitimate patents, even if a few "were issued erroneously," did not expose them to liability.[144] The district court dismissed the section 2 claims, finding that AbbVie's conduct did not plausibly "intimidate[] the other defendants into delaying the launch of their biosimilars (or otherwise caused any antitrust injury)."[145]

On appeal, the Seventh Circuit affirmed the district court's order, holding that the sheer number of patents in AbbVie's portfolio was not a significant detail in the antitrust analysis.[146] The Seventh Circuit found that "[b]oth the U.S. settlement and the E.U. settlement are traditional resolutions of patent litigation," which should not be construed as a sort of "reverse payment," and that the plaintiffs had failed

140 *Id.* at 826.
141 *Id.* at 841.
142 *Id.* at 827.
143 *In re Humira*, 465 F. Supp. 3d at 827.
144 *Id.* at 826.
145 *Id.* at 835.
146 Mayor of Baltimore v. Abbvie Inc., 42 F.4th 709, 712-13 (7th Cir. 2022).

to state a claim under sections 1 and 2 of the Sherman Act, ending the litigation.[147]

VI. BIOLOGICS' REGULATION: THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT, THE INFLATION REDUCTION ACT, AND A POTENTIAL WAY FORWARD FOR THE U.S. BIOSIMILAR MARKET

Due to their unique manufacture, biologic drugs are regulated differently than small molecule chemical drugs.[148] Since 1972, the FDA has regulated biologics pursuant to its authority under the Public Health Service Act ("PHSA"),[149] though certain biologics are regulated as drugs under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), which is also responsible for regulating small molecule drugs.[150] Both the Center for Biologics Evaluation and Research ("CBER") and the Center for Drug Evaluation and Research ("CDER") share the responsibility of regulating biologics under the FDA's authority.[151] CBER regulates "traditional" biologics like vaccines, blood/blood products, and cellular therapy products, while CDER regulates most therapeutic biologics, which include monoclonal antibodies and immunomodulators.[152]

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act, to facilitate the entry of generic chemical drugs into the pharmaceutical market and lower drug costs for consumers.[153] While the Hatch-Waxman Act provided "a mechanism for the approval of generic drugs and certain [biosimilars] under the FFDCA," it did not provide an avenue for the same for biologics and biosimilars under the PHSA.[154] Because the bulk of therapeutic biologics and biosimilars fall under the PHSA, pharmaceutical companies were effectively prevented from seeking approval for a huge portion of this class of drugs.[155]

In 2010, the Biologics Price Competition and Innovation Act ("BPCIA"), Title VII of the Patient Protection and Affordable Care Act, solved this problem, providing the FDA with the authority to

147 *Id.* at 716.
148 Roy, *supra* note 16.
149 *Id.* The Act is codified at 42 U.S.C. § 201 *et seq.*
150 CONG. RSCH. SERV., *supra* note 31, at 1, 5.
151 *Id.* at 3.
152 *Id.*
153 *Id.* at 5.
154 *Id.* at 6.
155 *Id.*

create an "abbreviated licensure pathway . . . for biological products [under the PHSA] that are demonstrated to be 'highly similar' (biosimilar) to or 'interchangeable' with an FDA-licensed biological product."[156] The BPCIA's scheme allowed "branded pharmaceutical companies to identify relevant patents and for potential competitors to challenge those patents."[157] If those challenges were successful and the patents protecting the brand-name products were found invalid, biosimilars could enter the market earlier than they would have been able to had they been forced to wait for the patents to expire.[158]

Under the BPCIA, companies interested in marketing biosimilars must submit applications to the FDA showing "biosimilarity based on data from analytical studies (structural and functional tests), animal studies (toxicity tests), and a clinical study or studies (tests in human patients)."[159] Interchangeability could be demonstrated by showing both that the biologic was biosimilar to the brand-name/reference product it was based on and that it was expected to produce the same clinical results as the brand-name biologic in patients.[160] Final guidance on the implementation of this pathway, however, was not issued until 2015.[161]

The BCPIA's framework is only relevant once the reference product's patent protection expires.[162] Patent protection for biologics extends for twenty years from the date the patent application in question is filed, and the BCPIA provides twelve-year market exclusivity and four-year data exclusivity, which begin once the biologic manufacturer receives FDA approval.[163] This means that biosimilar manufacturers cannot seek approval for their products until four years after the reference product was first introduced, and these biosimilars cannot be marketed until twelve years after the reference product was approved for use.[164] The four-year regulatory exclusivity protection is often characterized as "data protection" by certain authorities while the twelve-year protection is seen as a "marketing exclusivity."[165]

156 CONG. RSCH. SERV., *supra* note 31, at 8.
157 Goode & Chao, *supra* note 125, at 2.
158 *Id.* at 3.
159 CONG. RSCH. SERV., *supra* note 31, at 8.
160 *Id.*
161 Schiestl et al., *supra* note 38, at 1513.
162 Blackstone & Joseph, *supra* note 15, at 470.
163 *Id.*
164 *Id.*
165 THOMAS, *supra* note 6, ch. 19, § III.A.

There is only one exception to these timelines, which is invoked when a biologic qualifies as an "orphan drug."[166] "Orphan drug" is a designation granted by the FDA pursuant to the Orphan Drug Act of 1983,[167] which was passed to provide regulatory protections and financial incentives as a means of encouraging pharmaceutical companies to develop drugs to treat rare diseases like Huntington's disease, ALS (Lou Gehrig's disease), and muscular dystrophy.[168] Once a product has been deemed an "orphan drug," it receives "a seven-year period of regulatory exclusivity commencing from the date the FDA allowed the orphan drug to be marketed."[169] These protections extend to "drugs that treat a rare disease or condition (1) affecting less than 200,000 people in the United States, or (2) affecting more than 200,000 people in the United States but for which there is no reasonable expectation that sales of the drug would recover the costs [of development]."[170]

Though the patents surrounding biologics may be challenged in court, the twelve- and four-year exclusivity protections cannot.[171] These protections are designed to reward pharmaceutical companies for their drug research and development, but the data exclusivity period's markedly shorter length than the marketing period is intended to allow biosimilar manufacturers to begin working on drug development so that they may have a product ready for rapid market entry upon expiration of the longer market exclusivity period.[172] Twelve years after the BPCIA's passage, however, few biosimilars have entered the U.S. market and the BPCIA has done little to combat the exorbitant prices of biologics and their effect on patients in need.[173]

The Inflation Reduction Act ("IRA"), signed into law by President Biden on August 16, 2022,[174] is the most recent piece of

166 *Id.*

167 *Id.*; *FDA Doubles Down on Its Pre-Catalyst Stance on Orphan Drug Exclusivity*, COOLEY (Jan. 27, 2023), https://www.cooley.com/news/insight/2023/01-27-23-fda-doubles-down-on-its-pre-catalyst-stance-on-orphan-drug-exclusivity [https://perma.cc/2QDX-55WX].

168 Alexis-Danielle Roberts & Roopma Wadhwa, *Orphan Drug Approval Laws*, NIH NAT'L LIBR. OF MED. https://www.ncbi.nlm.nih.gov/books/NBK572052/ [https://perma.cc/MJ22-J6KT] (June 5, 2023).

169 THOMAS, *supra* note 6, ch. 19, § III.A.

170 *Id.*

171 Blackstone & Joseph, *supra* note 15, at 470.

172 *Id.*

173 Goode & Chao, *supra* note 125.

174 Inflation Reduction Act of 2022, H.R. 5376, 117th Cong. (2022).

legislation at least partially directed at addressing prescription drug costs.[175] The IRA permits the government to negotiate drug prices "for a small number of single-source brand-name drugs or biologics without generic or biosimilar competitors that are covered under Medicare Part D (starting in 2026) and Part B (starting in 2028)."[176]

The broad timeline set forth in the text of the IRA regarding drug pricing began in 2023 with the requirement that pharmaceutical companies pay rebates if prices for their drugs rise faster than inflation.[177] In 2024, the 5% coinsurance for Medicare catastrophic drug coverage was eliminated.[178] In 2025, a $2000 out-of-pocket cap will be imposed on seniors enrolled in Medicare, and from 2026 to 2029, the government will be required to negotiate prices for up to 20 eligible high-cost drugs.[179]

Concerning the fourth step, on August 29, 2023, the Centers for Medicare & Medicaid Services ("CMS"), part of the Department of Health and Human Services ("HHS") "announced the 10 drugs covered under Medicare Part D selected for the first cycle of negotiations."[180] The ten drugs (and their manufacturers) are Eliquis (Bristol Myers Squibb), Enbrel (Amgen), Farxiga (AstraZeneca), Fiasp/NovoLog (Novo Nordisk), Entresto (Novartis), Imbruvica (Pharmacyclics (AbbVie) and Janssen (Johnson & Johnson)), Januvia (Merck),

175 Juliette Cubanski, Tricia Neuman & Meredith Freed, *Explaining the Prescription Drug Provisions in the Inflation Reduction Act*, KAISER FAM. FOUND. (Jan. 24, 2023), https://www.kff.org/medicare/issue-brief/explaining-the-prescription-drug-provisions-in-the-inflation-reduction-act/ [https://perma.cc/CQG3-G24P].

176 *Id.*

177 Celine Castronuovo, *Drug Pricing Oversight to Get Prime Focus Under New Congress*, BLOOMBERG L. (Jan. 3, 2023, 5:32 AM), https://www.bloomberglaw.com/bloomberglawnews/health-law-and-business/XBJL8OA4000000 [https://perma.cc/JXS4-E5XG]. In the last quarter of 2023 alone, "48 Medicare Part B drugs raised their prices faster than inflation, and some drug companies raised the prices of certain medications faster than inflation for every quarter over the last year." Press Release, The White House, FACT SHEET: Biden-Harris Administration Announces Dozens of Pharma Companies Raised Prices Faster than Inflation, Triggering Medicare Rebates (Dec. 14, 2023), https://www.whitehouse.gov/briefing-room/statements-releases/2023/12/14/fact-sheet-biden-harris-administration-announces-dozens-of-pharma-companies-raised-prices-faster-than-inflation-triggering-medicare-rebates/ [https://perma.cc/CW5B-VLM2].

178 Castronuovo, *supra* note 177.

179 *Id.*

180 CTRS. FOR MEDICARE & MEDICAID SERVS., MEDICARE DRUG PRICE NEGOTIATION PROGRAM: MANUFACTURER AGREEMENTS FOR SELECTED DRUGS FOR INITIAL PRICE APPLICABILITY YEAR 2026 (2023), https://www.cms.gov/files/document/fact-sheet-manufacturer-agreements-selected-drugs-ipay-2026.pdf [https://perma.cc/E9QE-E2JS].

Jardiance (Boehringer Ingelheim and Eli Lilly), Stelara (Janssen (Johnson & Johnson)), and Xarelto (Janssen (Johnson & Johnson)).[181] These drugs are used to treat diabetes, heart failure, leukemia, and Crohn's disease, among other conditions.[182]

These 10 drugs were selected after consideration of various criteria, including Medicare "spending data for the 12-month period from June 1, 2022 to May 31, 2023."[183] The total Medicare spending for each drug during the aforementioned period ranged from $2,638,929,000 (Stelara) to $16,482,621,000 (Eliquis), and the spending for all ten drugs during said period totaled $50,482,188,000.[184]

Certain categories of drugs excluded from the negotiation process include drugs with a generic or biosimilar available and biologic drugs that are less than thirteen years from their FDA approval or licensure date.[185] Biologic drugs may also be exempt from negotiation for up to two years if a biosimilar product is "likely to enter the market in that time."[186] The IRA establishes an upper limit, or a "maximum fair price," for all drugs subject to negotiation.[187] Significantly, the IRA also bars "'administrative or judicial review' of [Medicare's determination of negotiation-eligible] drugs or the final determination of the 'maximum fair price.'"[188]

On February 1, 2024, the U.S. Department of Health and Human Services ("HHS"), through CMS, sent "initial [non-public] offers to the participating drug companies of the first 10 prescription drugs

181 Juliette Cubanski, *FAQs About the Inflation Reduction Act's Medicare Drug Price Negotiation Program*, KAISER FAM. FOUND. (Jan. 31, 2024), https://www.kff.org/medicare/issue-brief/faqs-about-the-inflation-reduction-acts-medicare-drug-price-negotiation-program/#Key_activities_timeline [https://perma.cc/KMY6-BPP9].

182 *Id.*

183 *Id.*

184 *Id.*

185 Jeannie Baumann, *Drug Negotiations Will Drive Biosimilars as Patent Tactics Shift*, BLOOMBERG L. (Aug. 25, 2022, 5:35 AM), https://news.bloomberglaw.com/health-law-and-business/drug-negotiations-will-drive-biosimilars-as-patent-tactics-shift [https://perma.cc/Z4XX-SNX8]; Cubanski, Neuman & Freed, *supra* note 175.

186 Cubanski et al., *supra* note 175.

187 *Id.*

188 Alexandra Lu & Matt Wetzel, *First Drugs Selected for Price Negotiations Under the Inflation Reduction Act to Be Announced Next Week: A Recap of What that Means – The Drug Price Negotiation Program and Pending Legal Challenges*, GOODWIN (Aug. 25, 2023), https://www.goodwinlaw.com/en/insights/blogs/2023/08/first-drugs-selected-for-price-negotiations-under-the-inflation-reduction-act-to-be-announced-next-w [https://perma.cc/L277-C77F].

selected for negotiation in the first cycle of the Medicare Drug Price Negotiation Program."[189] These offers contained maximum fair prices ("MFPs") for each drug, which were based on the lower of two measures outlined in the IRA.[190] The first measure "would initially set the MFP ceiling at 40 percent of the 'non-Federal average manufacturers price' (non-FAMP) for any drug with at least 16 years of market exclusivity, but at 75 percent of non-FAMP for any other selected drug."[191] A non-Federal average manufacturers price (non-FAMP) is "a confidential price reported to the Department of Veterans Administration (VA) by manufacturers," which "reflects the average price wholesalers pay manufacturers for a brand drug distributed to nonfederal purchasers."[192] Significantly, "non-FAMP does not reflect the rebates a manufacturer pays to health plans and pharmacy benefit managers."[193]

The second measure for determining each drug's MFP sets the ceiling at "100% percent of the average net Medicare Part D price."[194] This net price "reflects the enrollment-weighted average price for all national drug codes (NDCs) of a selected drug for all Part D plans."[195] The manufacturers of the 10 drugs selected for negotiation have 269 different NDCs, each reflecting different dosages, administration routes, and package sizing.[196] The net price also "includes rebates, [which are] non-public information that [healthcare] plans report to CMS as 'direct and indirect renumeration.'"[197]

By March 2, 2024, all involved drug manufacturers responded to CMS's initial offers, either accepting them and ending the negotiation

189 Press Release, U.S. Dep't Health & Hum. Servs., Biden-Harris Administration to Make First Offer for Drug Price Negotiation Program, Launches New Resource Hub to Help People Access Lower-Cost Drugs (Feb. 1, 2024), https://www.hhs.gov/about/news/2024/02/01/biden-harris-administration-make-first-offer-drug-price-negotiation-program-launches-new-resource-hub-help-people-access-lower-cost-drugs.html [https://perma.cc/ZT77-XHJX].

190 Steve M. Lieberman & Paul B. Ginsberg, *Knowing Actual Prices Will Help HHS Set the Maximum Fair Price Under the Inflation Reduction Act*, HEALTH AFFS. (Feb. 16, 2024), https://www.healthaffairs.org/content/forefront/knowing-actual-prices-help-hhs-set-maximum-fair-price-under-inflation-reduction-act.

191 *Id.*

192 *Id.*

193 *Id.*

194 *Id.*

195 *Id.*

196 Lieberman & Ginsberg, *supra* note 190.

197 *Id.*

process or rejecting them and submitting counteroffers.[198] By April 1, 2024, CMS responded to any manufacturers' counteroffers, either accepting them and ending negotiations or rejecting them. If CMS rejected any counteroffers, up to 3 meetings between CMS and the manufacturer in question may occur to discuss offers and counteroffers.[199] By June 28, 2024, such meetings must be completed, and by July 15, 2024, CMS must make its final written MFP offers to the manufacturers of the 10 selected drugs.[200]

By July 31, 2024, the manufacturers of the 10 selected drugs must accept or reject CMS's final written MFP offer.[201] If drug manufacturers choose not to comply with the negotiation process or reject CMS's final written MFP offer, an excise tax will be levied on them.[202] The tax "starts at 65% of a product's sales in the U.S. and increases by 10% every quarter to a maximum of 95%."[203] If drug companies wish to avoid paying they tax, they can also opt to withdraw all of their drugs from coverage under Medicare and Medicaid.[204] Additionally, manufacturers that do not offer pre-negotiated prices selected drugs to "maximum fair price eligible individuals" or providers that service those individuals "pay a civil monetary penalty equal to 10 times the difference between the price charged and the maximum fair price."[205]

August 1, 2024 marks the deadline for the completion of the price negotiation process between CMS and the drug manufacturers.[206] By September 1, 2024, CMS must publish the negotiated MFPs for the 10 selected drugs, and CMS must also publish public explanations for the negotiated MFPs by March 1, 2025.[207] Finally, on January 1, 2026, the MFPs for the 10 selected drugs become effective, and the drugs will become available at their respective MFPs for all individuals enrolled in Medicare Part D plans.[208]

198 Cubanski, *supra* note 181.
199 *Id.*
200 *Id.*
201 *Id.*
202 Cubanski et al., *supra* note 175.
203 *Id.*
204 *Id.*
205 *Id.*
206 Cubanski, *supra* note 181.
207 *Id.*
208 *Id.*

In 2027, another fifteen Part D drugs will be selected for price negotiation.[209] In 2028, another fifteen Part D and Part B drugs will be selected, and in 2029 and onward, twenty Part D and Part B drugs will be selected for negotiation each year so that the "number of drugs with negotiated prices available will accumulate over time."[210] These drugs will all be selected from the fifty drugs with the highest total Medicare Part D spending and the fifty drugs with the highest total Medicare Part B spending.[211]

The IRA also "requires drug manufacturers to pay a rebate to the federal government if prices for single-source drugs and biologicals covered under Medicare Part B and nearly all covered drugs under Part D increase faster than the rate of inflation."[212] More specifically, the law "sets a $2,000 annual cap on Medicare beneficiaries' out-of-pocket pharmacy costs starting in 2025, and as of Jan. 1, Americans enrolled in Medicare won't need to pay more than $35 per month on insulin."[213]

A. Pharmaceutical Companies' Responses to the IRA

Pharmaceutical companies have already expressed their displeasure with the IRA.[214] Victor Bulto, President of Novartis's Innovative Medicines for the U.S. market, disclosed to Reuters early this year that the "most concerning piece in that legislation for us is the price setting after nine years for small molecules and 13 years for biologics," arguing that "some of the most promising new treatment approaches belong to the [small molecule] group" and the IRA would have the "'unintended' effect of discouraging work on [said drugs]."[215]

This discontent may come with consequences that are even more concrete and damaging than displeased expressions in an interview. The Centers for Medicare & Medicaid Services ("CMS"), part of the

209 Cubanski et al., *supra* note 175.

210 *Id.*

211 *Id.*

212 *Id.*

213 Castronuovo, *supra* note 177.

214 Ludwig Burger, *Novartis Warns U.S. Plan to Curb Drug Prices Could Hit Key Research*, REUTERS (Jan. 20, 2023, 4:42 PM), https://www.reuters.com/business/healthcare-pharmaceuticals/novartis-warns-us-plan-curb-drug-prices-could-hit-key-research-2023-01-20/ [https://perma.cc/85VE-MU6J].

215 *Id.*

Department of Health and Human Services ("HHS"),[216] has been tasked with implementing the IRA's drug price negotiation provisions via "Program Instructions" for the first three years of the program.[217] This "process through which stakeholders will be able to engage and provide weigh-in appears to be different from the formal process that [is] normally [expected] under the Administrative Procedure Act in notice and comment rulemaking."[218]

Though the CMS has committed to "issuing 'voluntary' requests for comments from the public on a limited set of topics" in the Federal Register, legal observers have opined that "it's all but certain the CMS will see a legal challenge at some point" due to the use of guidance rather than formal notice-and-comment rulemaking.[219] These legal challenges stemming from confusion over guidance could come from the pharmaceutical industry which could seek to "hold the agency accountable during implementation" and "demand answers from the CMS . . . including the agency's processes for determining which drugs qualify for the law's negotiation exemptions."[220]

Challenges regarding the actual determination of drugs eligible for negotiation are complicated by language in the IRA barring administrative or judicial review of such determinations.[221] Pharmaceutical companies may need to be creative in crafting legal theories to support these types of challenges. Legal experts predict that "[p]otential

216 *About Us*, CMS.GOV, https://www.cms.gov/marketplace/resources/about-us [https://perma.cc/6NAT-ULQG] (last visited Apr. 12, 2024).

217 Matt Wetzel & Heath R. Ingram, *CMS Issues First Request for Public Comments on the Medicare Drug Price Negotiation Program "Small Biotech" Exception – Due March 27, 2023*, GOODWIN (Jan. 26, 2023), https://www.goodwinlaw.com/en/insights/publications/2023/01/01_26-cms-issues-first-request-for-public-comments [https://perma.cc/3NY7-HTVC]. The first three years of the program are 2026, 2027, and 2028. *Id.*

218 Celine Castronuovo, *Drug Price Negotiation Deadlines Expose Medicare to Litigation*, BLOOMBERG L. (Feb. 22, 2023), https://news.bloomberglaw.com/health-law-and-business/drug-price-negotiation-deadlines-expose-medicare-to-litigation [https://perma.cc/56EY-BH3Z] (quoting Margaux Hall, a partner in the health care practice at Ropes & Gray LLP and a member of the American Health Lawyers Association).

219 Wetzel & Ingram, *supra* note 217; Castronuovo, *supra* note 218. An example of one of CMS's publications in the Federal Register regarding the IRA can be found at 88 Fed. Reg. 4184 (Jan. 24, 2023).

220 Castronuovo, *supra* note 218.

221 Kaustuv Basu, *Drug Price Law to Spur Creative Claims as Industry Readies Fight*, BLOOMBERG L. (Sept. 29, 2022), https://news.bloomberglaw.com/health-law-and-business/drug-price-law-to-spur-creative-claims-as-industry-readies-fight [https://perma.cc/79JV-TDBZ].

avenues for lawsuits [might] include invoking the US Constitution, particularly the Due Process and Takings clause."[222] Despite the varied bases for legal challenges, such challenges would "delay implementation of the negotiations" and other IRA provisions "while increasing leverage through political bargaining," forestalling the introduction of price-curbing policies and harming consumers.[223]

Though CMS's initial offers to the manufacturers of the ten drugs selected for negotiation are not public, pharmaceutical executives received optimistic reactions to initial offers from Medicare during drug price negotiations.[224] AstraZeneca's CEO told reporters in February that "we've seen . . . [a] relatively encouraging comeback from CMS."[225] Relatedly, Pfizer's CFO told investors in March that the company has "products that are nearing the end of their life cycle, and therefore, the impact of the IRA over time would be modest."[226]

Despite these relatively upbeat responses, drug manufacturers and others have nevertheless filed various lawsuits alleging they were harmed by the IRA's drug negotiation program.[227] The Georgetown University Law Center O'Neill Institute for National and Global Health Law's IRA litigation tracker is monitoring eleven cases in federal district and appellate courts involving IRA legislation.[228] In two of those eleven cases, dispositive decisions have issued; one case was brought by AstraZeneca and the other by the National Infusion Center Association.[229] In the case filed by AstraZeneca, the U.S. District Court for the District of Delawaredenied AstraZeneca's motion for summary judgment and granted the Government's.[230] While the Court acknowledged that "[u]nderstandably, drug manufacturers like AstraZeneca don't like the IRA [because] lower prices mean lower profits,"

222 *Id.*

223 *Id.*

224 Joseph Choi, *Drugmakers Give Surprising Response to Medicare Drug Price Offers*, THE HILL (Mar. 20, 2024, 6:00 AM), https://thehill.com/policy/healthcare/4535500-drug-makers-surprising-response-medicare-drug-price/ [https://perma.cc/99NA-2QD5].

225 *Id.*

226 *Id.*

227 *Inflation Reduction Act*, O'NEILL INST.: HEALTH CARE LITIG. TRACKER, https://litigationtracker.law.georgetown.edu/issues/inflation-reduction-act/ [https://perma.cc/22FH-ETSP] (last visited Apr. 26, 2024).

228 *Id.*

229 *Id*. The two cases are *AstraZeneca Pharmaceuticals LP v. Becerra*, 1:23-cv-00931, 2024 WL 895036 (D. Del. Mar. 1, 2024) and *National Infusion Center Association v. Becerra*, 1:23-cv-00707, 2024 WL 561860 (W.D. Tex. Feb. 12, 2024).

230 *AstraZeneca Pharms.*, 2024 WL 895036, at *16.

it ultimately found that "AstraZeneca's 'desire' or even 'expectation' to sell its drugs to the Government at the higher prices it once enjoyed does not create a protected property interest."[231] In the National Infusion Center Association's case, the U.S. District Court for the Western District of Texas granted the government's motion to dismiss the case for lack of venue under Federal Rule of Civil Procedure 12(b)(3).[232]

Apart from legal challenges to the IRA, biologic manufacturers may find other ways to work the system in their favor.[233] They may attempt to "forestall [Medicare] negotiations" by developing and introducing their own biosimilars or by reaching deals with biosimilar manufacturers that result in biosimilars' delayed market entry (like conduct at issue in the *Abbvie* case).[234] Therefore, it will be important for reporters, researchers, and the CMS (if not already overburdened by compliance with the deadlines set forth in the IRA) to keep an eye out for attempts by pharmaceutical companies to skirt regulation.[235]

VII. THE IMPACT OF BIOSIMILARS' ENTRY INTO THE PHARMACEUTICAL MARKET ON STEP THERAPY LEGISLATION

Because the IRA is new, and it is unclear whether it will facilitate lower drug prices, step therapy reform may provide an alternative method of curbing excessive price increases and encouraging competition. Step therapy policies, also known as "fail-first" policies, are implemented by insurance companies to encourage doctors to prescribe lower-cost treatments to their patients before turning to more expensive therapies.[236] These policies force doctors to make decisions about medications *not* based on "evidence-based best-practice clinical guidelines, but rather [on] the insurance policy algorithm."[237]

The treatment of inflammatory bowel disease ("IBD") (an umbrella diagnosis encompassing Crohn's disease and ulcerative

231 *Id.* at *15.

232 *Nat'l Infusion Ctr. Ass'n*, 2024 WL 561860, at *5.

233 Baumann, *supra* note 185.

234 *Id.* (quoting Amitabh Chandra, director of health policy research at the John F. Kennedy School of Government at Harvard University).

235 *Id.*

236 Louis Tharp & Zoe Rothblatt, *Do Patients Benefit from Legislation Regulating Step Therapy?*, 17 HEALTH ECON., POL'Y & L. 282, 282 (2022).

237 *Id.*

colitis[238]) for example, often involves biologics, and "[a] review of 50 insurance policies regarding reimbursement of [IBD] treatments showed that 98% of policies were inconsistent with the American Gastroenterological Association ("AGA") evidence-based guidelines for ulcerative colitis, and 90% did not follow the AGA guidelines for Crohn's disease."[239] This review noted that step therapy protocols generally required IBD patients to fail corticosteroid treatment before biologics would be approved "despite evidence and guidelines supporting biologics as first-line treatments and recommending avoidance of long-term corticosteroid therapies."[240] These policies often interfere with patient care and may ultimately make treatment more expensive by ensuring that potentially more suitable drugs are unavailable until their diseases have progressed.[241] These policies also significantly burden doctors and their practices by requiring them to complete paperwork justifying their medication choices; the AMA estimated physicians spent 14.6 hours per week completing this paperwork.[242]

Research has also shown that there is "wide variation in the frequency with which health plans apply step therapy protocols in their specialty drug coverage decisions."[243] The Tufts Medical Center Specialty Drug Evidence and Coverage Database found that among seventeen health plans, the frequency at which the plans applied step therapy protocols ranged from almost 50% to close to 0%.[244]

Laws to limit step therapy, specifically by requiring insurance companies to accept certain exemptions to step therapy protocols, have been passed in twenty-nine states.[245] Federal efforts have also attempted to combat step therapy policies. In particular, the Safe Step Act, first introduced in 2019 and most recently introduced in 2023,

238 *Inflammatory Bowel Disease (IBD)*, CTRS. FOR DISEASE CTRL. & PREVENTION, https://www.cdc.gov/ibd/index.htm#:~:text=Inflammatory%20Bowel%20Disease%20(IBD)%20is,Crohn's%20disease%20and%20ulcerative%20colitis [https://perma.cc/F2WL-SL4B] (Apr. 17, 2023).

239 Tharp & Rothblatt, *supra* note 236, at 282.

240 *Id.* at 282-83.

241 *Id.* at 283.

242 *Id.*

243 James D. Chambers, Ari D. Panzer & Peter J. Neumann, *Variation in the Use of Step Therapy Protocols Across US Health Plans*, HEALTH AFFS. (Sept. 14, 2018), https://www.healthaffairs.org/do/10.1377/forefront.20180912.391231/ [https://perma.cc/4XGP-CZH2].

244 *Id.* For further detail see "Exhibit 1: Frequency That Health Plans Apply Step Therapy Protocols In Their Specialty Drug Coverage Decisions" within the article.

245 Tharp & Rothblatt, *supra* note 236, at 282.

proposed requiring group health plans to provide exception processes for step therapy protocols under a number of circumstances, including when a plan's required treatment has been ineffective or when the required treatment "is expected to be ineffective and delay effective treatment leading to irreversible consequences."[246] Step therapy policies may be made unnecessary, however, if biosimilars and other cheaper alternatives to brand-name biologics are made more widely available.

VIII. CONCLUSION

The discussion surrounding biologics, drug pricing, and legal implications is complicated, full of figures, mathematical models, and high-level science. Among this complexity, it is easy to forget how much is at stake for individual people. Patients may be forced to stop taking biologic drugs if they cannot afford them, and even if they are later able to use such drugs, anti-drug antibodies may have already formed, rendering the drugs useless.[247] Forcing people to suffer while drug companies and the U.S. government battle over regulatory details is cruel, but that is exactly what has happened and will likely continue to happen. In the meantime, every discussion on drug pricing and legislation is, at its core, a discussion about people in need of care. Though it will take years to determine the full effects of the IRA and other policies on the biologic landscape, we must remember to center these people as we continuously work toward a future in which pharmacological medicine is more effective, available, and affordable to all.

246 Andis Robeznieks, *Bipartisan Bill Aims to Reform Step Therapy, Ensure Timely Care*, AM. MED. ASS'N (Aug. 2, 2021), https://www.ama-assn.org/practice-management/prior-authorization/bipartisan-bill-aims-reform-step-therapy-ensure-timely-care [https://perma.cc/FL2L-C2FG].

247 J.M. Carrascosa, *Immunogenicity in Biologic Therapy: Implications for Dermatology* 104 ACTAS DERMO-SIFILIOGRÁFICAS 471, 475 (2013) (citing J. Barker, M. Hoffmann, G. Wozel, J.-P. Ortonne, H. Zheng, H. van Hoogsraten & K. Reich, *Efficacy and Safety of Infliximab vs. Methotrexate in Patients with Moderate-to-Severe Plaque Psoriasis: Results of an Open-Label, Active-Controlled, Randomized Trial (RESTORE1)*, 165 BRIT. J. DERMATOLOGY 1109 (2011)).