Journal of Law and the Biosciences, 1–34
https://doi.org/10.1093/jlb/lsad033
Original Article

OXFORD

# Leading with the trailing edge: facilitating patient choice for insulin products

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## ABSTRACT

Insulin prices have risen sharply, despite a century since its introduction. Against this backdrop, companies have discontinued dozens of insulin products. Discontinuation could relate to safety or effectiveness, or to the overwhelming benefits of newer products. On the other hand, discontinuation could suggest strategic behavior hampering competition and supporting prices. To test these theories, this project examined every insulin discontinuation, analyzing the role discontinuations play in insulin affordability. No evidence emerged of any discontinuation for safety or effectiveness. Rather, dozens of viable products were removed from the market, followed by more expensive versions, often with little or no clinical improvement. Insulin pens with a phone app may provide advantages, for example. However, for older patients, who may find the technology confusing, or for patients with budget constraints, the value proposition falters. Moreover, discontinuation blocks biosimilars from market entry because they cannot demonstrate biosimilarity without the drug. The problem exists for all biosimilars. If there are willing buyers and willing sellers of clinically effective products that are off-patent, entry should be facilitated. This article suggests a requirement that companies deposit samples at the time of FDA approval, laying the groundwork for later entry of trailing-edge products with clinically viable outcomes.

**KEYWORDS**: insulin, prices, patents, biosimilars, FDA, biologics

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## I. INTRODUCTION

As with many industries, leading-edge technologies are widely heralded in the insulin market. The leading edge is highlighted as a marker of scientific advancement and as offering patients the newest and most advanced treatments available, an attractive prospect for many. The leading edge, however, is not the only corner of a market. *Trailing-edge* technologies—that is, older treatments that remain effective—are often cheaper than their newer counterparts and can be clinically comparable for many patients. In the insulin market, which has become a poster child for burdensome prescription drug costs, trailing-edge technologies could offer more affordable options allowing patients with budget constraints to access consistent treatment.

Unfortunately, these trailing-edge products frequently are discontinued from the market, pushing patients toward newer and more expensive products without the option of the older and cheaper alternatives. Such discontinuations have removed many insulins, including some analog products, most human insulin products, and all animal insulin products from the market. Meanwhile, the prices of available insulins have skyrocketed. Newer products such as Lantus and Humalog have doubled in price in only a handful of years, and the older products that remain are orders of magnitude more expensive than when they were released.[1]

It is possible that the discontinuation of older insulin products could be attributed to safety or effectiveness concerns, or to the overwhelming benefits of newer products. This article demonstrates, however, that such a justification falls short. Analyzing discontinuation of all 62 insulin products over the past several decades, this article found that not a single discontinuation occurred for safety or effectiveness reasons.

Moreover, although newer products offered advantages, the clinical benefits produced were generally small. Newer advancements may be scientifically significant in terms of mass production, more sophisticated delivery devices, and adherence for some patients, but they offer only marginal clinical benefits for many patients. Instead, the most striking difference between trailing-edge products and their newer counterparts is the price. For example, the average price of human insulin products still on the market is less than half that of newer insulin analog products.[2] Given the higher prices of newer insulin products, the discontinuation of trailing-edge products serves to push patients toward more expensive products and reduce access to affordable alternatives.

Access to the leading edge of insulin innovation—the full bells and whistles—is important for patients who want and can afford the most advanced products available. For many patients financially burdened by rising prices, however, trailing-edge products offer a more affordable and still effective treatment solution.

Once patents have expired, where there is a willing buyer and a willing seller, the manufacture and sale of trailing-edge insulin products should be actively facilitated. Today, the potential for that willing exchange between buyers and sellers is blocked. Steps should be taken to ensure that such discontinued products can eventually be made by another manufacturer even if the original manufacturer has shifted focus to newer products.

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1 *See infra* Part IV.C.

2 Hannah McQueen & Diane Li, *How Much Does Insulin Cost? Here's How 31 Brands and Generics Compare*, GoodRx (May 8, 2023), https://www.goodrx.com/healthcare-access/research/how-much-does-insulin-cost-compare-brands.

One need not ascribe nefarious motives to industry participants. Nor does the article attempt to demonstrate that industry participants are engaging in behavior that would be actionable under antitrust laws. The point is simply that the intersection of industry behavior and regulatory processes are operating to narrow the potential for wider consumer choice and market entry.

Part II of this article gives an overview of the modern insulin market and its trailing edge. Part III considers the scientific and medical impact of transitions between the different forms of insulin produced in the past several decades. Part IV, by examining historical data as well as individual cases, analyzes insulin products that have been discontinued in recent decades, and the resulting limitation of patient access to clinically comparable and often cheaper products. Based on this analysis of the use of voluntary discontinuations to shepherd patients toward more expensive drug products with minimal clinical benefits, Part V focuses on a key stumbling block for those who would make trailing-edge drug products: access to a supply of the brand drug. This section explains that discontinuing a biologic drug from the market effectively blocks potential biosimilars from obtaining the necessary supply for FDA-required studies and suggests a means to remedy this issue. Specifically, policy makers could require that at the time of FDA approval, biosimilar companies must provide the FDA or an independent third party with a supply of the product that could be used as a comparison pool for future products. Such an approach would allow the development of trailing-edge markets in insulin and all biosimilars, where willing sellers could meet the needs of willing buyers for whom such products would provide affordable access to life-saving drugs with clinical viability. Sometimes, a patient does not need all the bells and whistles, but rather a simple but effective product.

## II. OVERVIEW OF THE MODERN INSULIN MARKET

A hundred years after its discovery, insulin has become critically important to millions of American patients, but one that remains unaffordable to many of those who need it. Of the 30 million patients managing diabetes in the USA, nearly a quarter require daily insulin.[3] Despite this massive need for insulin and the century-long interval since its discovery, insulin spending remains a serious cost burden for many patients. According to Yale researchers, 14 per cent of US patients purchasing insulin spend more than 40 per cent of their 'postsubsistence income' on the drug.[4] Moreover, many avoid or ration their treatment because of the high cost. In a 2018 survey, 45 per cent of patients managing diabetes reported having intentionally foregone insulin treatment for a period because of the financial burden.[5]

These high costs are in stark contrast to the philanthropic intent of the scientists who discovered insulin. Frederick Banting and John MacLeod, the physicians who received a Nobel Prize for the innovation of animal insulin products for human medical treatment,

3 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.

4 *Id.*

5 Alexa Lardieri, *Study: Almost Half of Diabetics Skip Care Because of High Cost*, U.S. News & World Rep. (June 18, 2018, 1: 47 PM), https://www.usnews.com/news/health-care-news/articles/2018-06-18/study-almost-half-of-diabetics-skip-care-because-of-high-cost.

refused to be listed on the patent for their discovery because they believed that insulin should be globally accessible and that patenting insulin would violate the Hippocratic oath.[6] Their non-physician colleagues, Charles Best and James Collip, were listed on the patent application, but they sold all rights to the University of Toronto for $1 to increase accessibility and lower cost-barriers.[7] Despite the best efforts of its discoverers, insulin did not become the universally available and affordable treatment they envisioned. Instead, newer insulins have become the poster child for pharmaceutical price increases and the financial burden of healthcare in the USA.

The high price of insulin is in large part due to the significant number of patents and exclusivities that are still active on insulin products, constraining the market even a century after the initial patent was granted.[8] These patents and exclusivities are obtained by gradual improvements made to the drug, entitling manufacturers to additional protections that extend their market monopoly. Some of the product modifications indeed have had significant health benefits. In the 1970s, for example, a new process emerged for refining animal insulin, the only insulin then marketed. The new process produced fewer impurities in the resulting insulin product, reducing immunogenicity and allergic reactions for patients.[9]

Today, many of the unexpired insulin patents and exclusivities are not for improvements to the active ingredient of the insulin product at issue. Instead, these patents are granted for non-active ingredients or variant formulations (known as 'secondary patents'[10]) or for delivery devices (known as 'tertiary patents'[11]). In fact, the patents on the active ingredients for most insulin drugs on the market have expired.[12] Secondary patents on insulin drugs, and particularly tertiary patents on wave after wave of delivery systems, allow manufacturers to maintain exclusive control of the market long past the expiration of the patent on the original innovation.[13] Given the additional patents and exclusivities that have resulted from the proliferation of insulin products, three manufacturers (sometimes called the 'Big Three') have held near-total control of the insulin market for decades: Sanofi, Novo Nordisk, and Eli Lilly.[14]

As newer products are introduced, older products are frequently discontinued from the market, focusing consumer demand on the latest and greatest. Animal insulin, the initial product of Banting's work, is no longer on the market at all, replaced by 'human' insulin. Most human insulins have been replaced by insulin 'analogs'. In fact, as of 2019, sixty-two insulin products had been removed from the market across time. For

6 Robert A. Hegele, *Insulin affordability*, 5 Lancet 324, 324 (2017).

7 *Id.*

8 *See* Jing Luo & Aaron S. Kesselheim, *Evolution of insulin patents and market exclusivities in the USA*, 3 Lancet 835, 836 (2015).

9 Jeremy A. Greene & Kevin R. Riggs, *Why is There No Generic Insulin? Historic Origins of a Modern Problem*, 372 New Eng. J. Med. 1171, 1172 (2015).

10 *See* Robin Feldman, *May your drug price be evergreen*, 5 J. L. & Biosciences 590, 632–34 (2018).

11 *See* Reed F. Beall & Aaron S. Kesselheim, *Tertiary patenting on drug-device combination products in the United States,* 36 Nat Biotechnol 142, 142 (2018).

12 Ryan Knox, *Insulin Insulated: Barriers to Competition and Affordability in the United States Insulin Market*, 7 J.L. & Biosciences, 1, 11 (2020).

13 *Id.* The proliferation of new and modified insulin products over the years has been so great that insulin has become more of a 'family of products' than a single drug with multiple forms. *See* Greene & Riggs, *supra* note 9, at 1173.

14 Knox, *supra* note 12, at 7.

perspective, only 46 insulin products remained available as of that year.[15] In many cases, however, the older products have clinically comparable outcomes for most patients and were sold at a lower price than the newer products. Such discontinuation of older products to make room for newer products often forces patients to transition to a more expensive treatment that may not be meaningfully better than the original.

One might imagine that doctors could help their patients navigate the cost maze, but most doctors are insulated from the out-of-pocket cost to the patient. Current prescription systems for doctors generally do not show the cost of the drug to that patient under the patient's plan, nor do they necessarily offer cost information about alternatives.[16] In addition, with less-expensive drugs frequently discontinued, the choices are more limited.

Considerable literature exists regarding what is known as a 'hard product hop', in which companies remove products from the market and replace them with newer, more expensive ones.[17] Alternatively, a so-called soft product hop involves leaving an older product on the market but using marketing or contracting techniques to convince doctors, health plans, or patients to prefer the more expensive drug.[18] Commentators have argued that product-hopping either constitutes or should constitute anticompetitive behavior under the antitrust laws.[19] Although product-hopping behavior may be a component of some of the behavior discussed below, this article describes a broader issue. Irrespective of whether any particular anticompetitive behavior could be alleged or proven, the intersection of industry behavior and regulatory processes are operating to narrow the potential for wider consumer choice and market entry. This market problem can be remedied without resorting to antitrust laws.

Lack of access to effective older-generation insulin treatment constrains choice in a way that is not seen in other industries outside pharmaceuticals. Consider, for example, iPhones. Consumers who want to buy the latest version can buy the iPhone 14 Plus, which features two more gigabytes of memory along with improved dual cameras that have a wider aperture and larger pixel size.[20] Consumers who do not wish to have the dual cameras, extra memory, and other features can buy an iPhone 12, for one-third less. And those with more limited budgets can still purchase a new iPhone 8 from other sellers for almost 90 per cent less than the latest iPhone. If the number of camera lenses on cellphones continues to grow, at some point in the future, a segment of consumers may decide that although six camera lenses on a phone is nice, they can do just fine with five lenses at a lower price.

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15 *Orange Book Data Files*, U.S. Food & Drug Admin. (last accessed 2019) (data available upon request from author) [hereinafter *Orange Book Data Files*].

16 Robin Feldman, Natalie Feldman & Enrique Seoane-Vazquez, *A Patient Price Guide for Prescription Medication*, 175 Ann Intern Med. 885, 885 (2022).

17 *See, eg*, Robin Feldman, Rethinking Patent Law 175–77 (Harv. Univ. Press 2012).

18 *See, eg*, Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 Notre Dame L. Rev. 167 (2016); Robin Feldman & Evan Frondorf, Drug Wars: How Big Pharma Raises Prices and Keeps Generics Off the Market 69–71 (Cambridge Univ. Press 2017) (discussing the marketing and contracting techniques used by companies to convince doctors, patients, and insurers to prescribe the more expensive drug, such as offering 'significant rebates and discounts to insurers' or 'woo[ing patients] with copay discounts or rebates').

19 *See, eg*, Carrier & Shadowen, *supra* note 18; Vikram Iyengar, *Should Pharmaceutical Product Hopping Be Subject to Antitrust Scrutiny?*, 97 J. Pat. & Trademark Off. Soc'y 663 (2015); Jessie Cheng, Note, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 Colum. L. Rev. 1471 (2008).

20 Axel Nash, *iPhone 12 vs. iPhone 14: Should You Upgrade?*, Wondershare (May 24, 2023), https://mobiletrans.wondershare.com/phone-review/iphone-12-vs-iphone-14.html.

Of course, features of the delivery system for a life-saving medication may be of weightier importance than the features of a cellphone. A so-called 'smart' insulin pen with a built-in app that tracks insulin doses and provides reminders and alerts may improve treatments by helping patients calculate the right dose at the right time.[21] Nevertheless, for older patients who may find the technology confusing or for any patient whose budget is seriously constrained, the added cost of an app-based insulin device may not be the desired choice. The availability of trailing-edge technology options with comparable clinical effectiveness helps a consumer access the product that is the best fit.

In short, giving patients access to the *leading* edge of technological innovation provides access to new and improved products. Giving patients access to the *trailing* edge of the insulin market—the older but effective products that manufacturers often discontinue—can give consumers facing financial challenges access to perfectly effective treatments at more affordable prices. Together, the two types of drugs offer the most robust set of consumer choices.

### II.A. Historic Development of Insulin Types

Advances in the insulin market over the last four decades represent remarkable scientific achievement in greater sophistication of mass production of insulin drug products, as well as modernization of devices for delivering insulin. The clinical difference among the various products may be less dramatic, however, particularly for some patients.

Until the 1970s, animal insulin was the only form of insulin available. In 1978, scientists succeeded in genetically engineering human insulin in a laboratory, and the FDA approved the first human insulin product in 1982.[22] This feat was accomplished by inserting chemically created, synthetic sequences that mimic human insulin genes into the DNA of bacteria to create recombinant bacteria capable of producing insulin.[23] The insulin could then be harvested and purified into a usable human insulin drug product. As used herein, 'human insulin' refers to any human insulin product synthesized through genetic engineering, but not to insulin analogs, which will be described later. Observations of human insulin, as compared to animal insulin, found lower insulin resistance and fewer instances of rare negative side effects. In addition, the capacity to synthesize these products in a laboratory made them easier to mass produce, a benefit for production and distribution of the drug.[24] Nevertheless, as described in detail below,[25] animal insulin remained a viable treatment option, and some patients found it to have a less variable effect on blood sugar.[26] Soon after the emergence of human insulin, however, animal insulin products were withdrawn from the market in the USA.

21 *What Is a Smart Insulin Pen?*, Am. Diabetes Ass'n, https://diabetes.org/tools-support/devices-technology/smart-insulin-pen (last visited Jan. 25, 2023).

22 Arthur Riggs, *Making, Cloning, and the Expression of Human Insulin Genes in Bacteria: The Path to Humulin*, 42 Endocrine Rev. 374, 379 (2021) (describing Eli Lilly's Humulin as the first human insulin product approved).

23 *Id.* at 375.

24 Irl B. Hirsch et al., *The Evolution of Insulin and How it Informs Therapy and Treatment Choices*, 41 Endocrine Rev. 733, 736 (2020) (describing the benefits of the development of human insulin).

25 *See infra* Part III.B.

26 *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.

Insulin analogs emerged in the late 1990s. Production of insulin analogs begins with the genetically engineered human insulin. The molecular structure of the human insulin is then modified to more closely resemble the insulin released in the human body.[27] Although insulin analogs more closely mimic the behavior of insulin in the healthy human body than human insulin,[28] the actual benefits of the change from human insulin to insulin analog are disputed, particularly for patients with type 2 diabetes.[29] Type 2 diabetes is far more common in the USA than type 1 diabetes is. As of 2018, 90–95 per cent of US patients diagnosed with diabetes were diagnosed with type 2 diabetes; fewer than 6 per cent of diagnosed patients were diagnosed with type 1 diabetes.[30] All patients with type 1 diabetes require insulin, but not all patients with type 2 diabetes do.[31] Nevertheless, the vast majority of patients on insulin are being treated for type 2 diabetes.[32]

Since the inception of insulin analogs, most human insulin products have been discontinued. Insulin analogs are the dominant form of active insulin products, and their prices are considerably higher than those of non-modified human insulin products—up to 10 times so by some estimations.[33] That is a hefty price increase, particularly for patients managing type 2 diabetes, for whom there is little of evidence of improved clinical benefit.

### II.B. Patent Protection for Product Transitions

Many new insulin patents are not directed to new chemical entities. Instead, they cover alternative formulations, dosages, or delivery devices for drugs containing a preexisting active ingredient. The patents on a drug's active ingredient—which are usually the drug's initial patents—are known as 'primary' patents.[34] These provide an initial period of monopoly to reward manufacturer innovation. Patents are called 'secondary' when they cover different forms, uses, or combinations of existing active ingredients

27 Karla F. S. Melo et al., *Short-Acting Insulin Analogues versus Regular Human Insulin on Postprandial Glucose and Hypoglycemia in Type 1 Diabetes Mellitus: a Systematic Review and Meta-analysis*, 11 Diabetol Metab Syndr, no. 2, 2019, at 1, 2.

28 Hirsch et al., *supra* note 24, at 738–39.

29 Kasia J. Lipska, *Insulin Analogues for Type 2 Diabetes*, 321 J. Am. Med. Ass'n 350, 350 (2019).

30 *See* University of Iowa, *Current rates of diagnosed type 1 and type 2 diabetes in American adults*, Sci. Daily (Sept. 17, 2018), https://www.sciencedaily.com/releases/2018/09/180917191843.htm.

31 Hannah Nichols, *What are the differences between type 1 and type 2 diabetes?*, Med. News Today (May 24, 2023), https://www.medicalnewstoday.com/articles/7504.

32 In 2018, 7.4 million patients managing diabetes reported using insulin. In 2020, the CDC reported that 1.4 million patients with type 1 diabetes were using insulin. Since nearly 97 per cent of diabetes cases are type 1 or type 2, with only some rare other cases, we can conclude that the vast majority of the remaining 6 million patients managing diabetes are suffering from type 2 diabetes. *See* William T. Cefalu et al., *Insulin Access and Affordability Working Group: Conclusions and Recommendations*, 41 Diabetes Care 1299, 1300; *see also National Diabetes Statistics Report: 2020*, Ctrs. For Disease Control & Prevention (Feb. 14, 2020), https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf; University of Iowa, *supra* note 30.

33 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.

34 María José Abud, Bronwyn Hall & Christian Helmers, *An Empirical Analysis of Primary and Secondary Patents in Chile*, 10 PLoS One, no. 4, 2015, at 1, 3.

instead of any new chemical compounds.[35] 'Tertiary' patents refer to patents on drug delivery systems and devices for an existing drug.[36] These terms are not formally codified, but they are commonly used in academic and regulatory discussions.

Instead of representing significant innovation, some incremental patents merely serve to extend the market monopoly of the innovation that was rewarded with the initial patent.

Obtaining a large number of secondary and tertiary patents increases the obstacles to generic or biosimilar entry.[37] One can think of patents as a wall of protection. Some patents make the wall longer, increasing the end date for the last coverage. Some patents make the wall thicker, increasing the number of protections a potential competitor would have to review and consider challenging to enter the market. Together, they form a barrier with layers of protection to ward off potential competition.

One basic example of these layers of patents is NovoLog, a rapid-acting insulin analog created by Novo Nordisk. The primary patent, issued in 1998, covered the actual chemical formula of the drug.[38] However, a secondary patent was issued in 1999 for a formulation of the drug with fairly minimal alterations, purportedly intended to achieve greater chemical stability.[39] Then in 2018, two decades after the first patent for NovoLog was issued, Novo Nordisk received a tertiary patent for a NovoLog injection device.[40] All told, the protection for NovoLog spanned three decades. The subjects of the later patents may have added some value for consumers. Nevertheless, they demonstrate the power of secondary and tertiary patents to extend the effective market monopoly of a drug.

Another prominent example of patent layering is Lantus, a long-acting insulin analog produced by Sanofi. Since its launch in 2000, the number of patent applications for the drug has skyrocketed to 74, the vast majority of which were filed after the drug was already on the market.[41] This patent collection has allowed Sanofi to maintain some degree of market protection through the year 2031, into the fourth decade of the drug's marketing.[42]

Device patents have come to dominate the insulin market over the past several decades. In particular, manufacturers have begun to focus on prefilled delivery systems, regulated by the FDA as drug–device combination products.[43] Such drug–device combination products consist mainly of prefilled insulin pens, intended to reduce the complexity of insulin delivery. Many patients prefer these devices, which can be important for patient compliance, although there is no clinical difference between pens

35 Feldman, *supra* note 10, at 632–34.

36 Beall & Kesselheim, *supra* note 11, at 142.

37 *See* Chie Hoon Song & Jeung-Whan Han, *Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry*, 5 SpringerPlus, 2016, at 1, 6.

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

39 U.S. Patent No. 5,866,538 (filed Jun. 20, 1997).

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

41 *Overpatented, Overpriced Special Edition: Lantus (Insulin Glargine)*, Initiative for Meds., Access & Knowledge 4–5 (Oct. 30, 2018), http://www.i-mak.org/wp-content/uploads/2018/10/I-MAK-Lantus-Report-2018-10-30F.pdf.

42 *Id* at 5.

43 *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.

and the syringes they replace.[44] Since pens and delivery devices for insulin are not standardized, a manufacturer looking to compete with an existing insulin drug is forced to design its own pen without infringing on the many device patents held by established manufacturers.[45] The requirement to enter multiple markets can increase barriers to entry in certain circumstances, even with complementary products.[46] Unsurprisingly, insulin pens are notably more expensive than insulin in vials.[47] Moreover, just as manufacturers may obtain new patents for minor changes in drug formulation, so too can companies obtain new patents for minor changes in delivery devices.[48]

The ascendancy of drug–device combination products is illustrated by Sanofi's Toujeo, a more concentrated version of Lantus. Toujeo was launched in 2015, but only through Toujeo Solostar, a prefilled pen.[49] Toujeo itself is innovative only in its concentration, not in its ingredients or clinical effects. The fact that it was offered only as a prefilled pen, an expensive delivery method, signifies the dominance of insulin drug–device combination products, despite their high costs. Like insulin analogs and human insulins before them, prefilled insulin pens represent a small clinical change in relation to the large jump in pricing. In short, the insulin market often rewards minor changes with major price increases.

## III. PRODUCT TRANSITIONS: WHAT WAS GAINED AND WHAT WAS LOST

New products in the insulin product market have brought advances in mass production and delivery devices. Nevertheless, some studies indicate that the relative benefits of newer products may be smaller than suggested by manufacturers and significant for only a minority of patients managing diabetes. It is important to note that some patients may prefer newer products for reasons that may be clinically minor but increase the convenience or comfort of the treatment. This preference may increase the patient's adherence to treatment, an unquestionably positive result. However, for patients who do not exhibit such a preference, or for whom cost is the primary factor affecting adherence, more minor clinical benefits may not be a reason to transition such patients to new products and away from older, effective ones. The following section considers what has been gained and what has been lost as insulin products march forward.

### II.A. Insulin Analogs Versus Human Insulin

Insulin analogs, the newest generation of insulin, have become the dominant form of insulin in the market since their emergence in the late 1990s, eclipsing human insulin, the previous generation of insulin products. Presented as clinically superior, insulin analog products are generally far more expensive than their human insulin predeces-

44 Andrew Ahmann et al., *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); *see also* Henry Howard Goldstein, *Pen Devices to Improve Patient Adherence With Insulin Therapy in Type 2 Diabetes*, 120 Postgraduate Med. 172 (2008).

45 Markus Reitzig, *Strategic Management of Intellectual Property*, 45 MIT Sloan Mgmt. Rev. 35, 39 (2004).

46 *See, eg*, Robin Feldman, *Defensive Leveraging in Antitrust,* 87 Geo. L.J. 2079 (1999).

47 Amy Honebrink, Chelsea Peters & David Bright, *Insulin Pens vs. Vials and Syringes: The Pharmacist's Role in Individualizing Therapy*, 26 Consultant Pharmacist 491, 492 (2011).

48 *See* Reitzig, *supra* note 45, at 38–39.

49 *Sanofi Receives FDA Approval of Once-Daily Basal Insulin Toujeo*, Sanofi (Feb. 25, 2015), https://www.news.sanofi.us/2015-02-25-Sanofi-Receives-FDA-Approval-of-Once-Daily-Basal-Insulin-Toujeo.

sors. However, recent scholarship has called into question the clinical superiority of insulin analogs, indicating that the relative benefit compared to human insulin may not be significant for many patients managing diabetes.

Some scholars argue that there is no compelling reason at all for any patients managing type 2 diabetes to use insulin analogs.[50] Those who argue that insulin analogs do offer comparative benefits focus on patients managing type 1 diabetes.[51] For patients with type 2 diabetes, there is little evidence that the more expensive insulin analogs offer a meaningful benefit or risk reduction.[52] Thus, the innovation of insulin analogs was of value, but not necessary of value to all patients, especially in the context of the higher price tag.

Four Cochrane Database systematic reviews between 2016 and 2021 reviewed available studies to examine the comparative merits of insulin analogs and human insulin. The reviews separately studied the relative benefits of both short-acting and long-acting insulins, and for patients with type 1 and type 2 diabetes. For patients with type 1 diabetes, studies showed that short-acting analogs conferred a 'minor benefit' regarding glycemic control as compared with short-acting human insulin, with no clear benefits regarding hypoglycemia or health-related quality of life.[53] When considering type 1 use of basal insulin—longer-acting insulin taken to cover non-mealtime periods of the day—studies found 'no clear differences for all main outcomes' between insulin analogs and human insulin, among 26 studies with nearly 9000 participants.[54] For patients with type 2 diabetes, studies found 'no clear benefits' for short-acting analogs over human insulin,[55] and a minor reduction in hypoglycemia for long-acting analogs over human basal insulin with 'no clear difference' in other complications or glycemic control.[56] Overall, studies showed minor benefits for patients managing type 1 diabetes with insulin analogs, but minimal clinical differences between human insulin and insulin analogs for patients managing type 2 diabetes, who comprise the vast majority of patients using insulin.[57]

These studies indicate that insulin analogs are preferable as a treatment for type 1 diabetes (although human insulin is still a viable option) but may not offer significant relative benefits compared to human insulin for patients managing type 2 diabetes, which is much more common. Despite this, insulin analogs achieved dominance in the insulin market and have been permitted to push some older human insulin products off of the market. The 2019 Orange Book listed only five human insulin products approved after 1996, as opposed to 45 approved insulin analog products,[58] demonstrating a

50 *See, eg*, Mayer B. Davidson, *Insulin Analogs—Is There a Compelling Case to Use Them? No!*, 37 Diabetes Care 1771, 1773 (2014).

51 *See, eg*, Melo et al., *supra* note 27, at 12.

52 Peart, *supra* note 33.

53 Birgit Fullerton et al., *Short-Acting Insulin Analogues versus Regular Human Insulin for Adults with Type 1 Diabetes Mellitus*, Cochrane Database Syst Rev, no. 6, June 30, 2016, at 1, 2.

54 Bianca Hemmingsen, Maria-Inti Metzendorf & Bernd Richter, *(Ultra-)Long-Acting Insulin Analogues for People with Type 1 Diabetes Mellitus*, Cochrane Database Syst Rev, no. 3, Mar. 4, 2021, at 1, 3.

55 Birgit Fullerton et al., *Short-Acting Insulin Analogues versus Regular Human Insulin for Adult, Non-pregnant Persons with Type 2 Diabetes Mellitus*, Cochrane Database Syst Rev, no. 12, Dec. 17, 2018, at 1, 2.

56 Thomas Semlitsch et al., *(Ultra-)Long-Acting Insulin Analogues versus NPH Insulin (Human Isophane Insulin) for Adults with Type 2 Diabetes Mellitus*, Cochrane Database Syst Rev, no. 11, Nov. 9, 2020, at 1, 3.

57 *See supra* note 32.

58 *See Orange Book Data Files, supra* note 15.

definitive transition from human insulin to insulin analogs despite marginal clinical differences for most patients.

The demand for human insulin has not evaporated. With Humulin, a human insulin product that remains on the market, Eli Lilly reported higher revenues in 2021 than in 2001.[59] Nonetheless, many human insulin products have been discontinued to make way for even more profitable insulin analog products.

Casting further doubt on this transition, the World Health Organization as of 2018 continued to recommend human insulin as the primary treatment for adults who are dependent on insulin in 'low-resource settings', including in high-income countries.[60] This was based on an expert panel's judgment that the limited benefits of insulin analogs are outweighed by the large price differential.[61] Many US patients managing diabetes fit within this recommendation; some Americans spend 40 per cent or more of their post-subsistence income on insulin,[62] and nearly half of patients managing diabetes surveyed in 2018 reported having foregone treatment for financial reasons.[63] Moreover, studies have found that for patients with type 2 diabetes, switching from insulin analogs to human insulin does not produce clinically relevant differences, but does produce 'improved adherence' due to lower costs.[64] One of these studies, led by Dr Jing Luo, observed that such results 'add to a growing body of literature suggesting that human insulins may result in similar clinical outcomes compared with insulin analogues for many patients with type 2 diabetes'.[65] Since the vast majority of patients who are dependent on insulin suffer from type 2 diabetes, this indicates that insulin analogs may be unnecessary for some patients who are dependent on insulin.

### III.B. Human Insulin Versus Animal Insulin

Although human insulin preceded insulin analogs, it was the subject of a similar and even more comprehensive transition away from the first generation of insulin products: animal insulin. Animal insulin, extracted from porcine and bovine pancreatic tissue, was the only form of insulin from the time of insulin's initial use by Banting and his colleagues until 1982, when the FDA approved Humulin, the first genetically engineered

59 *Lilly Announces Fourth-Quarter Earnings per Share of $.60, Excluding One-Time Charges*, Eli Lilly & Co. (Jan. 24, 2002), https://investor.lilly.com/static-files/f725f3fb-132d-4c98-a3b8-7d237d1f7fdd (announcing 2001 fourth quarter global Humulin sales of $267.8 million); *Lilly Reports Solid Fourth-Quarter and Full-Year 2021 Financial Results, Recent Late-Stage Pipeline Successes Set Up Next Wave of Innovative Medicines for Patients*, Eli Lilly & Co. (Feb. 3, 2022), https://investor.lilly.com/news-releases/news-release-details/lilly-reports-solid-fourth-quarter-and-full-year-2021-financial (noting 2021 fourth quarter global Humulin sales of $298.8 million).

60 Gojka Roglic & Susan Norris, *Medicines for Treatment Intensification in Type 2 Diabetes and Type of Insulin in Type 1 and Type 2 Diabetes in Low-Resource Settings: Synopsis of the World Health Organization Guidelines on Second- and Third-Line Medicines and Type of Insulin for the Control of Blood Glucose Levels in Nonpregnant Adults With Diabetes Mellitus*, 169 Ann Intern Med. 394, 394 (2018).

61 *Id.* at 396.

62 *See* Locklear, *supra* note 3.

63 *See* Lardieri, *supra* note 5.

64 Kyunghwa Park, Angela Eng Jeong & Eric Guenther-Gleason, *Impact of Switching Analogue Insulin to Human Insulin in Diabetes*, 25 Evidence-Based Diabetes Mgmt., no. 10, Sept. 27, 2019, https://www.ajmc.com/view/impact-of-switching-analogue-insulin-to-human-insulin-in-diabetes; *see also* Jing Luo et al., *Implementation of a Health Plan Program for Switching From Analogue to Human Insulin and Glycemic Control Among Medicare Beneficiaries With Type 2 Diabetes*, 321 J. Am. Med. Ass'n 374 (2019).

65 *See* Luo et al., *supra* note 64, at 383.

insulin product.[66] The innovation of Humulin was a significant scientific achievement, demonstrating the power of genetic engineering and allowing insulin to be produced in a laboratory instead of extracted in large quantities from animal pancreases.

However, human insulin may not have offered clinical improvement of the same magnitude as the scientific progress it represented, at least, not for all patients. Dr Henry Miller, the FDA official assigned to manage Humulin, stated in 1982 that no broad clinical advantages compared to animal insulin had been found, although Humulin was shown to be 'safe and effective'.[67] Moreover, later scholarship has questioned whether human insulin is meaningfully superior to animal insulin as a therapeutic product in many circumstances. A widely cited[68] Cochrane Database systematic review of studies comparing animal and human insulins found 'no significant differences' between the clinical outcomes of animal insulin and human insulin treatments.[69] The review analyzed 45 studies with 2156 total participants and found no meaningful differences in blood sugar control, hypoglycemia, or insulin antibody development.[70]

Antibody development can be a sign of the immunogenicity, the 'tendency to trigger an unwanted immune response', of a drug.[71] Lower immunogenicity was projected to be a benefit of human insulin over animal insulin, and it was suggested that this lower immunogenicity would be clinically advantageous.[72] Indeed, some studies showed 'slightly lower immunogenicity' of human insulin compared to certain animal insulins, although a 1993 analysis deemed the clinical relevance of that difference 'questionable' in many circumstances.[73] The analysis recommended that human insulin should be preferred for patients with insulin allergies and those newly diagnosed with type 1 diabetes, but that there is no reason to switch well-controlled patients to it.[74]

Indeed, some studies indicated disadvantages of transitioning patients from animal insulin to human insulin. The transition was found to temporarily reduce blood sugar control for a period of months.[75] Other studies indicated a loss of warning symptoms of hypoglycemia for patients transitioning to human insulin, reducing their ability to self-regulate and prevent hypoglycemic events.[76] Based on retrospective analysis of patients

66 *See* Riggs, *supra* note 22, at 375.

67 Lawrence K. Altman, *A New Insulin Given Approval for Use in U.S.*, N.Y. Times, Oct. 30, 1982, at 1, 16.

68 Sarah Ndegwa, Amanda Hodgson & Melissa Severn, *Efficacy and Safety of Human versus Animal Insulins*, Canadian Agency for Drugs & Techs. Health 1, 3 (Aug. 3, 2007), https://www.cadth.ca/sites/default/files/pdf/htis/Efficacy%20and%20Safety%20of%20Human%20versus%20Animal%20Insulins.pdf (citing the 2005 version of the Richter & Neises Cochrane systematic review); *see also* Greene & Riggs, *supra* note 9, at 1174–75 (citing the 2002 version of the Richter & Neises Cochrane systematic review).

69 Bernd Richter & Gudrun Neises, *'Human' Insulin versus Animal Insulin in People with Diabetes Mellitus*, Cochrane Database Syst Rev, July 21, 2003, at 3.

70 *Id.* at 6.

71 Zuben E. Sauna, *Immunogenicity of Protein-based Therapeutics*, U.S. Food & Drug Admin. (June 23, 2020), https://www.fda.gov/vaccines-blood-biologics/biologics-research-projects/immunogenicity-protein-based-therapeutics.

72 *See* Richter & Neises, *supra* note 69, at 3 (describing the unsupported projections that human insulin would benefit patients with reduced immunogenicity).

73 Guntram Schernthaner, *Immunogenicity and Allergenic Potential of Animal and Human Insulins*, 16 Diabetes Care 155, 161–62 (1993).

74 *Id.* at 162.

75 *Id.* at 161 (describing a temporary reduction of glycemic control in patients switching to human insulin).

76 Willi Berger et al., *Warning Symptoms of Hypoglycaemia during Treatment with Human and Porcine Insulin in Diabetes Mellitus*, 333 Lancet 1041, 1042 (1989); *see also* Arthur Teuscher & Willi Berger, *Hypoglycaemia Unawareness in Diabetics Transferred from Beef/Porcine Insulin to Human Insulin*, 330 Lancet 382, 382–84 (1987).

transitioning to human insulin, some scholars concluded that the transition presented an increased risk of severe hypoglycemia due to loss of warning symptoms,[77] and called for animal insulin to remain available as a safe alternative 'in all convenient forms'.[78] The FDA even went so far as to request 'an obligatory warning' of potential changes in warning symptoms of hypoglycemia for all human insulin products.[79] Nonetheless, human insulin quickly came to dominate the insulin market, contravening the norm to refrain from moving well-controlled patients to new treatments simply because something newer has arrived on the scene.[80]

The real advantage offered by human insulin concerned production methods. Animal insulin is synthesized from the pancreatic tissue of pigs and cows whose other parts are being used for food,[81] and is therefore dependent on the availability of such animals as sources of insulin.[82] In contrast, recombinant human insulin is produced synthetically from genetically engineered bacteria,[83] allowing for mass production without resource limitation.[84] This has the advantage of improving supply and mass-production. Indeed, the use of animal insulin presents unique challenges with respect to purity and standardization,[85] challenges that genetically engineered insulins can resolve to a greater extent. Some of these challenges, such as transmission of retroviruses and diseases such as Bovine Spongiform Encephalopathy, emerged long after

77 Arthur Teuscher, *Human Insulin 1992: a Significant Independent Risk Factor for Sudden Hypoglycaemia?*, 9 Pract Diabetes 174, 175 (1992).

78 Matthias Egger, George Davey Smith & Arthur Teuscher, *Human Insulin and Unawareness of Hypoglycaemia: Need for a Large Randomised Trial,* 305 British Medical J. 351, 354 (1992).

79 *See* Teuscher, *supra* note 77, at 175.

80 *See* Egger, Smith & Teuscher, *supra* note 78, at 354.

81 *See* Smithsonian, *Insulin* (last visited Nov. 1, 2023), https://www.si.edu/spotlight/insulin-and-diabetes-management/insulin (stating that for commercial production of insulin, scientists used pancreases of pigs and cattle supplied by slaughterhouses); *see also* Diane Wendt, National Museum of American History, *Two Tons of Pig Parts: Making Insulin in the 1920s* (Nov. 1, 2013), https://americanhistory.si.edu/blog/2013/11/two-tons-of-pig-parts-making-insulin-in-the-1920s.html (describing the pancreases of pigs and cows used for insulin as a 'waste product of the meatpacking industry'); *see also* Lawrence K. Altman, *The Tumultuous Discovery of Insulin: Finally, Hidden Story is Told,* N.Y. Times, Sept. 14, 1982, at C1 (stating that experts had forecasted a shortage of animal insulin due to the rate of increase of diabetes outpacing the rate of increase in meat consumption).

82 Wolfgang Landgraf & Juergen Sandow, *Recombinant Insulins: Clinical Efficacy and Safety in Diabetes Therapy*, 12 Eur. Endocrinology 12, 12 (2016).

83 *See* Riggs, *supra* note 22, at 377–78.

84 *See* Hirsch et al., *supra* note 24.

85 *See,* eg, Health Canada, *Frequently Asked Questions: Animal-Sourced Insulin* (Oct. 15, 2010), https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/activities/fact-sheets/questions-answers-animal-sourced-insulin.html (recognizing that production of animal insulin has become more complex as a result of bovine spongiform encephalopathy ('BSE') and transmissible spongiform encephalopathy ('TSE') issues arising out of the use of raw animal tissues); Jacques Verdrager, *Risk of Transmission of BSE via Drugs of Bovine Origin*, 354 Lancet 1304, 1304–05 (1999) (indicating that humans may be exposed to BSE through 'injectable pharmaceutical drugs' and citing 'bovine pancreas-derived insulin' as an example of such drug); Walid Heneine et al., *No Evidence of Infection with Porcine Endogenous Retrovirus in Recipients of Porcine Islet-Cell Xenografts*, 352 Lancet 695, 695 (1998) (noting the potential for infection with xenogeneic agents and porcine endogenous retrovirus as a major concern for patients receiving porcine-sourced insulin); V. Mohan, *Which Insulin to Use? Human or Animal?*, 83 Curr Sci 1544, 1545 (2002) (describing clinical complications associated with impurity of insulin preparations and finding that improved processes of purification in past decades has resulted in significant improvements in purity of commercially available insulin).

the shift from animal insulin to human insulin, but they would create impediments to offering acceptable animal insulins today.[86]

Other production advantages exist in the modern context. Environmentalists have raised concerns about using animal stock as a food source and its accompanying environmental impact. In theory, these concerns could spill over into the use of those same animal stocks for insulin production. Animal rights groups also might raise ethical concerns about the use of animals for human medical treatment when alternatives exist.[87] Finally, one has to consider how modern patients might react to the notion of purchasing an animal product when a so-called 'human' product exists.[88]

As a result of these constraints, this article does not suggest the reintroduction of animal insulin into the US market as a solution to high insulin prices. Nevertheless, understanding the shift from animal insulin to human insulin is an important part of understanding the history of product shifts in the insulin market.

Of particular note, human insulin was introduced at a price far above the price of animal insulin. That price has continued to climb steeply across time. In 1982, a vial of the human insulin Humulin sold for $14,[89] although Eli Lilly stated that 'the ultimate aim is to make it cheaper'.[90] Instead, the cheapest 10-ml vial of Humulin today costs around $185, an increase of more than 1300 per cent, or close to 7 per cent per year for 40 years.[91]

These transitions between categories of insulin—from animal insulin to human insulin and then to insulin analogs—differ from the standard notion of a product hop. Instead of just discontinuing a product and replacing it with a newer version, which also occurred, insulin manufacturers were able to produce industry-wide shifts to new generations of products, despite the limited relative clinical benefits of the newer products.

It is possible that the broad shifts across the market are facilitated by the dominance of the Big Three insulin manufacturers. When all three push a new type of product, they can shift the entire market, not just a single product line. As noted above, however, this article will examine ways to facilitate competitive market entry regardless of whether anticompetitive behavior has occurred or could be proven.

## IV. THE ROLE OF PRODUCT DISCONTINUATION IN INSULIN PRODUCT TRANSITION

This article set out to examine the role product discontinuations have played in insulin product transitions, particularly any discontinuations that were not based on safety or effectiveness reasons. To do so, the study used an archived version of the Orange Book

86 *See, eg*, sources cited *supra* note 85.

87 Cf. Science Learning Hub, *Ethics of Pig Cell Transplants* (Oct. 20, 2016), https://www.sciencelearn.org.nz/resources/911-ethics-of-pig-cell-transplants (describing ethical concerns over raising and killing piglets for pig cell transplants to treat type 1 diabetes and other diseases).

88 *See infra* text accompanying note 136 (positing that if post-animal insulins had been described as 'bacterially derived' insulin rather than 'human insulin', patients might not have been as easily persuaded to switch).

89 Irl B. Hirsch, *Insulin in America: A Right or a Privilege?*, 29 Diabetes Spectr 130 (2020) (describing the growth in the prices of insulin products over the past four decades and the resulting crisis).

90 *See* Altman, *supra* note 67.

91 McQueen & Li, *supra* note 2.

from 2019, before insulin's 2020 transition to biologics.[92] The discontinued section of this archived Orange Book listed 62 discontinued insulin products.[93] Analyzing these 62 discontinuations first required separating out any products discontinued for safety or effectiveness reasons to look further at those products discontinued purely for business reasons.

If the FDA makes a determination that a drug was 'withdrawn from sale' (ie discontinued from marketing) for safety or effectiveness reasons, that drug is removed from the Orange Book, including from the discontinued drug product list.[94] Otherwise, a discontinued drug will continue to be listed in the Orange Book, designated as discontinued.[95] The FDA *may* make this determination at any time, but *must* make it when a citizen petition or an application for generic approval has been submitted.[96] Any person may file a citizen petition seeking a determination as to whether that drug was withdrawn from sale for safety or effectiveness reasons.[97] If, in response, the FDA determines that the drug was withdrawn from sale for safety or effectiveness reasons, then the drug is removed from the Orange Book, including from the discontinued list, and the FDA publishes a notice in the Federal Register.[98] Research for this article found no such notices in the Federal Register for the 62 discontinued insulin drugs.[99]

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92 Orange Book data files, including the annual edition, are made available for download by the FDA. The 2019 archived version of the Orange Book that was used for the study is available upon request from the author. *See Orange Book Data Files, supra* note 15. The data was obtained by inserting 'insulin' into the Orange Book's online search tool and downloading the results as a spreadsheet. This process took place in late 2019 and before the shift of insulin drugs from the Orange Book to the Purple Book.

93 *Id.*

94 *See Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. Dep't Health & Hum. Servs., U.S. Food & Drug Admin. vi (40th ed. 2020) [hereinafter *Orange Book*]; 21 C.F.R. § 314.162(a) (1992); *see also* 21 C.F.R. § 314.161(e) (1992).

95 *See Orange Book*, *supra* note 94, at xxiv.

96 *See* 21 C.F.R. § 314.161(a)(1)–(3) (1992). The determination as to whether a withdrawal from sale was for reasons for safety or effectiveness 'may' be made 'at any time', but 'must' be made (1) before an abbreviated new drug application ('ANDA') that refers to the drug has been approved, (2) whenever ANDAs that refer to the drug have been approved, and (3) when a citizen petition for such a determination has been submitted. *Id.*

97 Under subsection (c) of 21 C.F.R. § 314.150, the FDA cannot grant a request to withdraw approval of an application if the conditions of subsection (a) or (b) apply, which include that the drug is not safe or effective. However, even if the FDA grants a request to withdraw approval under subsection (c), a citizen petition may still be filed seeking an express determination by FDA as to whether the drug was withdrawn from sale for safety or effectiveness reasons. *See* 21 C.F.R. § 314.161(b) (1992).

98 21 C.F.R. § 314.162(b) (1992). *See, e.g.*, Determination That CERNEVIT–12 (Multivitamins for Infusion) Was Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 12,760 (Mar. 17, 2010).

99 Additional support for the notion above arises to the extent that the FDA has granted a request to withdraw approval under 21 C.F.R. § 314.150(c). *See supra* note 97. If the discontinued drug was a drug whose approval was withdrawn under 21 C.F.R. § 314.150(c), one can tell at least that the company itself did not claim safety or effectiveness reasons, nor was the agency aware of safety or effectiveness reasons at that time.Of the insulin products that entered the discontinued list prior to 2012, 49 out of 50 were also products whose approval was withdrawn under 21 C.F.R. § 314.150(c). This suggests further support for the notion that there were no safety or effectiveness reasons for those 49 products. With respect to the 12 insulin products that entered the discontinued list after 2012 (and for the one that entered before 2012), for some reason there is no record that any of those products had approval withdrawn under 21 C.F.R. § 314.150(c). With respect to the 49 products that did have approval withdrawn, one could hypothesize that applicants, when discontinuing their insulin products, stopped requesting withdrawal of approval under 21 C.F.R. § 314.150(c), or that the FDA stopped granting such requests, in anticipation of the eventual shifting of all insulin drugs to the biologic regulatory regime. This timing is plausible given that the Biosimilars Price Competition and Innovation Act or BPCIA (which laid out the transition of insulin to being considered a

Of the 62 discontinued insulin products listed in the Orange Book, not a single one has been treated as discontinued for safety or effectiveness reasons.[100] There remains some small possibility of manufacturers making retroactive claims of discontinuation for safety or effectiveness reasons,[101] but barring such an outcome, this article will treat these products, as the FDA does, as having been discontinued for reasons other than safety or effectiveness. The voluntary discontinuation of these products has played a key role in moving the market toward more expensive products. In using the term 'voluntary discontinuation', this article refers to the unprompted withdrawal of drug products from the market, for reasons other than safety or effectiveness, that are then moved to the FDA's list of discontinued products. This term does not, however, refer to voluntary withdrawals determined to be for safety or effectiveness reasons, or withdrawals requested by the FDA for such reasons.[102]

### IV.A. Documentation of Discontinuations

The majority of drugs fall into a category known as small-molecule drugs. These are relatively simple molecules made up of mere tens of atoms, and they can be chemically replicated. In contrast, biologic drugs are substances such as proteins and nucleic acids. They are produced in processes that use living cells and can consist of thousands or even tens of thousands of atoms in complex structures that are difficult to fully identify or replicate. Information related to small-molecule drugs is listed in the FDA's Orange Book, which is named for the color of the cover page when the publication originally appeared in print.

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biologic as of 2020) was enacted in 2010, with the FDA working through provisions in the subsequent years. This secondary method of support for the notion above is not relevant for the 13 insulin products that were discontinued but whose approval was not withdrawn by the FDA, but in none of those 13 cases has the FDA determined a drug product to have been discontinued for safety or effectiveness reasons. One should note that, according to some practitioners, if the FDA receives a request to withdraw approval under 21 C.F.R. § 314.150(c), the agency's practice is not to conduct an independent inquiry but to grant the withdrawal of approval—on the assumption that the withdrawal from sale did not involve safety or effectiveness—and wait for someone to submit a citizen petition or an ANDA.

100 *See supra* note 99.

101 It appears to be possible to make retroactive claims of discontinuation for safety or effectiveness reasons since the FDA often makes no determination at the time, but it is unclear whether this strategy can actually be effective. In 2012, ISTA Pharmaceuticals claimed retroactively that their product, Xibrom, was discontinued for safety or effectiveness reasons when a generic drug was approved, in an attempt to challenge the ANDA approval. However, ISTA lost their case, and the DC Circuit's decision noted that 'ISTA never indicated that Xibrom was unsafe or ineffective', implying that the failure to indicate such at the time of discontinuation was evidence against a retroactive claim of discontinuation for safety or effectiveness reasons. ISTA Pharm., Inc. v. FDA, 898 F. Supp. 2d 227, 232 (D.D.C. 2012).

102 Note that although the FDA requires notice of both health-related and non-health-related discontinuations, only the latter appear on the FDA's list of discontinued products. In evaluating voluntary discontinuation as a strategy employed by manufacturers, we are concerned only with discontinuations unprompted by FDA intervention or evidence of safety or effectiveness concerns. Center for Drug Evaluation & Research ('CDER'), *Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format Guidance for Industry*, U.S. Dep't Health & Hum. Servs., U.S. Food & Drug Admin. 2 (Aug. 2020), https://www.fda.gov/media/120095/download; *see also Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format; Guidance for Industry; Availability*, 85 Fed. Reg. 48,541, 48,542 (Aug. 11, 2020) (noting that Section 506I, mandating advance notice of withdrawal, was added in 2017 via the FDA Reauthorization Act of 2017).

If a small-molecule drug becomes unavailable for sale, companies are required to notify the FDA so that the drug can be shifted to a 'Discontinued Drug Product List'.[103] Unless a drug is discontinued for reasons of 'safety or effectiveness',[104] a discontinued drug will be moved to the 'discontinued section' of the FDA Orange Book.[105]

Insulin is a biologic substance whose molecule is more complicated than most small-molecule drugs. However, until March 2020, insulin drug products were grouped with small-molecule drugs and listed in the FDA's Orange Book.[106] Since generics must prove bioequivalence, which is nearly impossible for biologics, generic insulin was a virtual impossibility. In light of a provision in the Biologics Price Competition and Innovation Act (BPCIA), the FDA moved insulin from the small-molecule realm to that of biologics, effective March 23, 2020,[107] and all active insulin products are now treated as biologics.[108]

Unlike the Orange Book, which lists all discontinued small-molecule drugs in the same place, the Purple Book for biologics does not list discontinued biologics together. Instead, drugs that are discontinued remain listed in the Purple Book, but the fact of their discontinuation appears in either of two other lists, kept by separate FDA centers, which split custody of biologic drug products.[109] Moreover, although the FDA has

103 The Discontinued Drug Product List can be found in the FDA's Orange Book. *See, eg*, *Orange Book*, *supra* note 94. The requirement applies to both drugs approved via a new drug application (NDA) or abbreviated new drug application (ANDA). CDER, *supra* note 102, at 2. For holders of NDAs or ANDAs, the FDA requires notification 180 days before withdrawal from sale. *Id.* In addition, if a drug will not be marketed within 180 days of approval, the FDA requires notification within that 180-day period. *See id.*, at 2. Even if the company does not notify the FDA that marketing has stopped, the FDA may still determine that a drug company has discontinued its distribution of a drug, and can, therefore, consider the drug withdrawn from the market. *See id.*, at 3.

104 On occasion, the FDA specifically requests discontinuation for reasons of safety or effectiveness. *See, e.g.*, *FDA requests withdrawal of bacitracin for injection from market*, U.S. Food & Drug Admin. (Jan. 31, 2020) https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-bacitracin-injection-market (announcing in 2020 that the FDA requested manufacturers of bacitracin for injection to withdraw their product from the market).

105 Discontinued drugs for reasons of safety or effectiveness are removed from the Orange Book entirely, while other discontinued drugs are moved to the discontinued list of the Orange Book. *See* CDER, *supra* note 102, at 2–3.

106 Manufacturers seeking approval for insulin products had to file NDAs under the Federal Food Drug and Cosmetic Act (FD&C Act). Most other biologics were, by contrast, approved via biologics license applications (BLAs) under the Public Health Service Act (PHS Act). *See 'Deemed to be a License' Provision of the BPCI Act*, U.S. Food & Drug Admin. (Apr. 2, 2020), https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act [hereinafter *BPCIA*].

107 *Id.* Moreover, any existing approved NDA or ANDA for an insulin product was 'deemed to be' an approved BLA, except those for which the FDA had withdrawn approval. *See id.* (describing NDAs and ANDAs deemed to be BLAs); *List of Withdrawn Applications for Biological Products That Were Removed From FDA's Orange Book on March 23, 2020*, U.S. Food & Drug Admin. (Apr. 2, 2022), https://www.fda.gov/media/136420/download (showing biological withdrawals).

108 *BPCIA*, *supra* note 106 (noting the two types of BLA: the 'stand-alone' BLA under section 351(a) of the PHS Act and the 'biosimilar' BLA under section 351(k) of the PHS Act).

109 In 2003, the FDA transferred some therapeutic biologics from the Center for Biologics Evaluation and Research (CBER) to the CDER, including 'therapeutic proteins' such as insulin, and therapeutic biologics remain divided between CBER and CDER. *See Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, U.S. Food & Drug Admin. (Mar. 7, 2022), https://www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research (describing transfer of certain therapeutics); Jeen S. Min, *Dear Colleague Letter*, U.S. Food & Drug Admin. 3 (May 2, 2022), https://fda.report/media/158118/FY+2023+PDUFA+Dear+Colleague+Letter.pdf (describing the continuing division of

created a subsection of the Orange Book listing discontinued small-molecule drugs, the FDA has not created an analogous subsection listing discontinued biologic products within the Purple Book.[110] This gap in information has not gone unnoticed. A bill introduced in the Senate in May 2022 proposes to duplicate the requirement that small-molecule applicants notify the FDA of any discontinuation of their products and apply this to biologics applicants, as well.[111]

This article confines itself to discontinuation data from before the 2020 transition of insulin to the realm of biologics. The limitation permits use of the Orange Book as a data source, particularly the discontinued section, while avoiding the current information gaps of post-2020 biologics. Using pre-2020 discontinuation data will cover most of the history of voluntary discontinuation of insulin products.

### IV.B. Analyzing Insulin Discontinuations

Of the 62 voluntary discontinuations listed in the Orange Book discontinued section from 2019, 33 were animal insulin products, 16 were human insulin products, including two inhaled insulin products, and 13 were insulin analog products.[112] Although the delivery and development of inhaled insulin differs from that of other insulin products, inhaled insulin products used human insulin in powder form,[113] so the article categorizes them as human insulin products.

In order to appropriately characterize the 62 insulin product discontinuations, the article examines them in the three categories mentioned above: animal insulin, human insulin, and insulin analogs. Animal insulins were discontinued as human insulins became dominant, and many human insulin products were then discontinued as insulin analogs rose to prominence.[114] These discontinuations have come to be a fixture of the insulin market, as established products without safety or effectiveness issues are frequently withdrawn from the market, forcing patients to switch to products with minimal relative benefit for most patients.

Analysis of these discontinuations revealed that they generally remove clinically viable products from the market, constraining patient choice and pushing patients toward newer products that are often more expensive. The following subsections will analyze how voluntary discontinuation has been employed by manufacturers and the harm that stems from these strategies.

#### *IV.B.1 Human Insulin Discontinuations*

Human insulin is the generation of insulin products that preceded the more modern insulin analogs. Although some human insulin products remain available in the USA,[115] many human insulin products have been discontinued since the emergence of insulin analogs, despite continuing clinical effectiveness for many patients.[116] In total,

biologic products). As a result, CBER has one list of discontinued biologic products, and CDER has another. *See id.*

110 As noted *supra* note 109, CBER and CDER each has a list of discontinued biologic products.

111 S. 4302, 117th Cong. § 2 (2022).

112 *See Orange Book Data Files, supra* note 15.

113 Seán M. Cunningham and David A. Tanner, *A Review: The Prospect of Inhaled Insulin Therapy via Vibrating Mesh Technology to Treat Diabetes*, 17 Int'l J. Env't. Rsch. & Pub. Health 5795, 5799 (2020).

114 *See Orange Book Data Files, supra* note 15.

115 *Id.*

16 human insulin products appear in the 2019 Orange Book discontinued section, and 10 appear in the active section.[117] In other words, more human insulin products have been discontinued than are currently on the market.

Most of the discontinued human insulin products were simply removed from the market, but a handful of human insulin products were removed and replaced with similar drugs under the same proprietary names, but with different purification processes.[118] This article uses the label 'replacement' to refer to discontinued products replaced by products with the same active ingredient, manufacturer, and type of delivery (eg vial and syringe, prefilled pen, reusable pen) although the delivery device or amounts in the device may have varied. Of the 16 discontinued human insulin products, five were replaced: four Novolin products and one Velosulin product, all made by Novo Nordisk.[119] These product replacements with minor changes introduced a discontinuation strategy of product replacement which would recur, in the following decades, with the discontinuation of insulin analog products.[120]

After the first insulin analog was approved in 1996, human insulin innovation ground nearly to a halt; only a handful of human insulin drugs entered the market, even though 1996 was a mere 14 years after Humulin's approval.[121] Moreover, although some human insulins did remain on the market, the majority were discontinued, limiting options for patients seeking to continue using human insulin for treatment.[122] Today, although human insulin has not fully disappeared, the human insulin category is a shell of its former self, with most human insulin products voluntarily discontinued in the market.

These discontinuations exemplify both the simple discontinuation of older products and the strategy of discontinuation with replacement. Both strategies persisted as insulin analog products established dominance over the market and then began in part to be discontinued themselves in favor of newer formulations and delivery devices.

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116 *Id. See supra* notes 50–57 and accompanying text (discussing scholarship questioning clinical superiority of insulin analogs in comparison to human insulin products for most patients).

117 *Id.*

118 *Id.* (listing the only difference between the discontinued products and some of the replacement human insulins as some being 'purified' and some being 'not purified', a difference this article understands to reference differences in the purification process used in synthesizing these insulin products).

119 Novolin L, Novolin R, Novolin N, and Novolin 70/30 were approved between 1983 and 1986, but were soon followed by four products of the same names, all approved in 1991. The original four drugs were then discontinued at dates not listed in the 2019 Orange Book, and the FDA withdrew its approval of all four NDAs between 1996 and 1997. The fifth drug discontinued with replacement, Velosulin BR, was approved in 1986 but was discontinued in 2001 after the 1999 approval of a second Velosulin BR. *See Orange Book Data Files, supra* note 15 (noting the approval and discontinuation dates of the four Novolin products as well as the two Velosulin BR products, the second of which was discontinued in 2003, not long after the first).

120 Due to limitations in Medicare Part D pricing data, this article was not able to determine whether these slightly modified human insulin products were more expensive than those they replaced.

121 *Orange Book Data Files, supra* note 15 (noting only a handful of human insulin pen products entering the market after 1996 along with Myxredlin, an IV infusion insulin product, and a few inhaled insulin products made using human insulin); *see also* Anuradha L. Puttagunta & Ellen L. Toth, *Insulin Lispro (Humalog), the First Marketed Insulin Analogue: Indications, Contraindications and Need for Further Study,* 154 Can. Med. Ass'n J. 506, 507 (1998).

122 *Orange Book Data Files, supra* note 15.

### *IV.B.2. Insulin Analog Discontinuations*

Insulin analogs, like human insulin products, appear in both the active and discontinued sections of the 2019 Orange Book.[123] There are 45 active insulin analogs, with 13 insulin analog products discontinued. Eight of these were discontinued completely, and five were discontinued with replacement.

Many of the insulin analog products that have been discontinued in the USA remain available in European countries, emphasizing their continued viability. Nearly 90 per cent—seven out of eight—of the insulin analogs completely discontinued in the USA remained available in Europe.[124] The seven discontinued insulin analogs that remain available in Europe were all Novo Nordisk products. The eighth, Sanofi's Apidra 300-U/3-ml vial, is not currently available in Europe.[125] With that product, the company kept an older vial on the market that contained a larger amount of insulin.[126] In other words, all of the eight simply discontinued insulin analogs were available either in Europe or in a slightly different form, which supports the notion that they all remained viable products from a clinical standpoint.[127]

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123 *Id.*

124 NovoLog is marketed outside the USA under the name NovoRapid. *See* Neil Reynolds & Antona Wagstaff, *Insulin Aspart: A Review of its Use in the Management of Type 1 or 2 Diabetes Mellitus*, 64 Drugs 1957, 1960 (2004). The NovoRapid FlexTouch and NovoRapid InnoLet both remain available in Europe, products identical to those discontinued in the United States. *See NovoRapid*, Eur. Meds. Agency (Mar. 22, 2023), https://www.ema.europa.eu/en/medicines/human/EPAR/novorapid (listing NovoRapid as available in Europe with both the FlexTouch and InnoLet as delivery options); *see also Class 4 Medicines Defect Information: Novo Nordisk Limited, NovoRapid® FlexTouch® 100 units/ml, Saxenda® FlexTouch® (liraglutide) 6 mg/ml, EL(22)A/33*, Meds. & Healthcare Prods. Regul. Agency (July 21, 2022), https://www.gov.uk/drug-device-alerts/class-4-medicines-defect-information-novo-nordisk-limited-novorapid-r-flextouch-r-100-units-slash-ml-saxenda-r-flextouch-r-liraglutide-6mg-slash-ml-el-22-a-slash-33 (describing a defect in specific batches of NovoRapid FlexTouch, indicating that it is still available in the UK at least as of mid-2022). Ryzodeg 70/30 and NovoLog Mix 50/50 remain available in Europe under the near-identical names 'Ryzodeg' and 'NovoMix 50'. *See Ryzodeg*, Eur. Meds. Agency (Sept. 23, 2021), https://www.ema.europa.eu/en/medicines/human/EPAR/ryzodeg (listing Ryzodeg as available in Europe despite its discontinuation in the USA); *see also NovoMix*, Eur. Meds. Agency (Aug. 29, 2023), https://www.ema.europa.eu/en/medicines/human/EPAR/novomix (listing NovoMix, equivalent to NovoLog Mix 50/50, as available in Europe despite its discontinuation in the United States). Finally, Levemir Penfill remains available in Europe under the exact same name, and NovoLog Mix 70/30 Penfill products remain available in Europe as 'NovoMix 30 Penfill', identical to the discontinued US products.

125 This Apidra vial was the only insulin product of Sanofi's on the discontinued list. All other discontinued insulin products, either simply discontinued or discontinued with replacement, were products from Novo Nordisk and Eli Lilly. *See supra* notes 118–119 and accompanying text (describing the discontinuation with replacement of five human insulin products made by Novo Nordisk); *see also infra* note 128 and accompanying text (describing the discontinuation with replacement of five insulin analog prefilled pen products, three by Eli Lilly and two by Novo Nordisk).*See Orange Book Data Files, supra* note 15.

126 *Id.* (noting as still active a 1000-U/10-ml Apidra vial, approved 1 year before the smaller 300-U/3-ml vial that was eventually discontinued).

127 The eight insulin analog products that were simply discontinued were NovoLog FlexTouch, NovoLog InnoLet, NovoLog Mix 50/50, Ryzodeg 70/30, two Novolog Mix 70/30 Penfill products, Levemir Penfill, and an Apidra 300-U/3-ml vial. For two of the drugs, a similar product from the company remains on the market. *See Orange Book Data Files, supra* note 15 (listing the NovoLog FlexTouch and NovoLog InnoLet as discontinued, both NovoLog prefilled pen products, another of which—the NovoLog FlexPen—remains on the market. Despite this, neither discontinued product should be considered replaced: the NovoLog FlexPen was approved before either the FlexTouch or the InnoLet and outlived both, so it did not replace either). Although it is possible that the company anticipated that patients would switch from the discontinued ones to the continued ones, they are not included in the count of replacements because the

Beyond simple discontinuations, five insulin analog products were discontinued and replaced, all of which were prefilled insulin pens. In other words, the medication, form, and dosage did not change, but the replacement delivery device had different features.[128] For example, in explaining the transition from Levemir FlexTouch to FlexPen, Novo Nordisk explained that FlexTouch and FlexPen 'have different features and functions, and will require patients to adopt new Instructions For Use [but] the active medicine will not change with the conversion from FlexTouch to FlexPen, and it will not affect the efficacy and safety profile'.[129] These particular replacements reflect the shift in focus in recent decades from active ingredient innovation to device innovation.[130]

Overall, of the 13 discontinued insulin analogs, five were directly replaced and seven remained available in Europe. Only one of the 13 discontinuations falls outside of this category—the Apidra vial, for which a larger version remained available on the market.

### *IV.B.3. Animal Insulin Discontinuations*

Although many human and analog insulin products have been discontinued, one can find some forms of these types of products on the market today.[131] In contrast, animal insulin has entirely disappeared from the US market. Today, animal insulin products appear only in the discontinued section of the 2019 Orange Book—all 33 having been discontinued.[132] The complete removal of this category was not prompted by safety or effectiveness concerns, but rather by the entry of human insulin, a form of treatment that offered limited relative clinical benefits to many patients.[133]

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product that is on the market now was on the market before the discontinued product was approved. *See id.* (noting that the NovoLog FlexPen remained active as of 2019); *see also supra* Part IV.B.1 (restricting the label 'replacement' for the purposes of this article to 'discontinued products replaced by products with the same active ingredient, manufacturer, and type of delivery (e.g., vial and syringe, prefilled pen, reusable pen)'). Future researchers, however, might choose to group them differently, depending on the purpose of the analysis.In some circumstances, a biosimilar may be able to use a foreign product (regardless of whether that product is licensed in the USA) to demonstrate biosimilarity. *See Questions and Answers on Biosimilar Development and the BPCI Act*, U.S. Food & Drug Admin., Sept. 2021, at 7–8 (Q&A I.8.), https://www.fda.gov/media/119258/download (explaining requirements for using animal or clinical data related to a non-US-licensed product to demonstrate biosimilarity). The requirements, however, can be difficult to meet. Even this limited solution would only be available in the subset of cases in which the drug that has been discontinued in the USA remains on the market in another country.

128 The discontinued products were the Levemir FlexPen, the Levemir InnoLet, the Humalog Pen, the Humalog 75/25 Pen, and the Humalog 50/50 Pen. The Levemir FlexPen and Levemir InnoLet were discontinued respectively in 2016 and 2012, and a new product, the Levemir FlexTouch, was approved in 2013 (roughly at the same time as the discontinuations) and quickly became the only Levemir prefilled pen on the market. The other three pens discontinued with replacement, the Humalog Pen, the Humalog 75/25 Pen, and the Humalog 50/50 Pen, made by Eli Lilly, were all discontinued in 2012, five years after the 2007 approval of three near-identical products: the Humalog KwikPen, the Humalog 75/25 KwikPen, and the Humalog 50/50 KwikPen. These marked the first discontinuations with replacement by Eli Lilly, joining Novo Nordisk in the use of the practice. *See Orange Book Data Files, supra* note 15.

129 *Levemir*, Novo Nordisk, https://www.novomedlink.com/diabetes/products/treatments/levemir.html (last visited Sept. 29, 2023).

130 *See supra* notes 44–48 and accompanying text (describing the recent shift in focus to device innovation).

131 *Orange Book Data Files, supra* note 15.

132 *Id.*

133 *See* Richter & Neises, *supra* note 69.

It is interesting to note that animal insulin continued to be available in other nations, long after it disappeared from the USA. Porcine insulin remained available in the United Kingdom as of 2021[134] and in Canada as recently as 2014.[135]

To some extent, the complete switch from animal to human insulin may be a product of clever marketing and scientific nomenclature. What patient would not want a 'human' product over an 'animal' product? If the insulin product had been described as 'bacterially derived insulin', patients might not have been so easily persuaded to switch, particularly at higher prices.[136]

Regardless, as more human insulins entered the market, animal insulin products were eventually discontinued in a gradual process extending into the 2000s.[137] By 2009, every animal insulin had been voluntarily discontinued from the US market.[138] As described above, scholarship questioned whether human insulin offered more than marginal, if any, clinical benefits over animal insulin for many patients—although human insulin provided distinct advantages in production and distribution. Nevertheless, these discontinuations pushed all consumers toward newer and ever-more-expensive products.

### IV.C. Pricing

At the outset of any discussion of insulin pricing, one should note that the marginal cost of producing insulin has consistently landed far below its pricing. For example, the cost to produce a 1000-unit vial of regular human insulin was estimated to be $2.28 as of 2018,[139] but a 1000-unit vial of the regular insulin product Humulin R cost $52 in 2009 and $163 in 2018.[140] Even after the price cuts announced by insulin manufacturers in early 2023, prices will remain orders of magnitude higher than the cost of production.[141]

134 *Hypurin Porcine Insulin,* Wockhardt UK (June 21, 2021), https://www.wockhardt.co.uk/medicines/hcp/hypurin/.

135 Agnes V. Klein et al., *The Role of Animal-Sourced Insulin in the Treatment of Type 1 Diabetes and its Availability*, 34 Chronic Diseases & Injs. Can. 169, 170 (2014).

136 As explained above, human insulin is made by inserting chemically created, synthetic DNA sequences that mimic human genes into bacteria to stimulate the creation of insulin *See* Riggs, *supra* note 22, at 375.

137 *See Orange Book Data Files, supra* note 15.

138 *Id.*

139 Dzintars Gotham, Melissa Barber & Andrew Hill, *Production Costs and Potential Prices for Biosimilars of Human Insulin and Insulin Analogues*, 3 Brit. Med. J. Global Health, no. 5, Sept. 25, 2018, at 5.

140 These prices are according to Medicare Part D pricing data purchased from the Center for Medicare and Medicaid Services (CMS). A 1000-unit vial of Humulin R is 10 ml in volume, a vial sometimes referenced as 1000 U/10 ml.

141 These price reduction announcements were likely in response to the removal of a cap on mandatory Medicaid rebates and other, political pressures. A previous cap on Medicaid rebates at 100 per cent of average manufacturer price was removed in the 2021 American Rescue Plan as of Jan. 1, 2024. American Rescue Plan Act of 2021, Pub. L. No. 117-2, 135 Stat. 4, 216 (2021). In March 2023, Eli Lilly, Novo Nordisk, and Sanofi all announced large price cuts of some of their most prominent products. *Lilly Cuts Insulin Prices by 70% and Caps Patient Insulin Out-of-Pocket Costs at $35 Per Month*, Eli Lilly & Co. (Mar. 1, 2023), https://investor.lilly.com/news-releases/news-release-details/lilly-cuts-insulin-prices-70-and-caps-patient-insulin-out-pocket [hereinafter *Eli Lilly Press Release*]; *Novo Nordisk to lower U.S. prices of several pre-filled insulin pens and vials up to 75% for people living with diabetes in January 2024*, Novo Nordisk (Mar. 14, 2023), https://www.novonordisk.com/news-and-media/latest-news/lowering-us-list-prices-of-several-products-.html [hereinafter *Novo Nordisk Press Release*]; *Press Release: Sanofi cuts U.S. list price of Lantus®, its most-prescribed insulin, by 78% and caps out-of-pocket Lantus costs at $35 for all*

Of course, the cost of production constitutes only part of the full cost of a drug; one must also consider research and development costs. Although estimates vary widely concerning the cost to research and develop a drug, the numbers are large, with one recent study estimating the median cost to develop a drug at over $1 billion.[142] Nevertheless, Humulin R was approved in 1982,[143] so the company should have had ample time to recoup its research and development costs in the 40 years since the drug was approved. Given that the length of time the drug has been on the market, the prolonged and expansive profit margin is likely not from the need to recoup research and development costs of those drugs.

As a general matter, the price of insulin products overall have risen steeply in recent years. For example, the list price of a vial of Lantus grew from $131 in 2012 to $248 in 2014, nearly doubling the list price in 2 years.[144] A GoodRx pricing analysis found that the average cash price of all insulins rose a startling 54 per cent from 2014 to 2019.[145] Many of these price increases were seen to occur in lockstep between the Big Three insulin manufacturers: Sanofi, Novo Nordisk, and Eli Lilly.[146] These synchronized price increases are enabled by lack of competition in the industry, as well as driven by the need to offer ever-larger rebates to pharmacy benefit managers.[147]

Prices after rebate for several flagship insulin products have not seen the rapid growth that list prices have, at least not in recent years.[148] For example, one study found that although prices after rebates for long-acting insulins rose 26 per cent a year from 2012 to 2016, they declined 8 per cent a year from 2015 to 2019.[149] Of course, 4 years of small declines in net prices have not erased the prior years of larger declines. Moreover, rising list prices have resulted in increased out-of-pocket costs for some patients.

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*patients with commercial insurance*, Sanofi (Mar. 16, 2023), https://www.sanofi.com/en/media-room/press-releases/2023/2023-03-16-20-06-43-2629188 [hereinafter *Sanofi Press Release*]. These price cuts were widely attributed to the Medicaid cap removal, which would have resulted in insulin manufacturers paying Medicaid rebates larger than the cost of each dose dispensed of some drugs. This is due to the previously large list-to-net price bubble and the consistent price increases in excess of inflation since these products entered the market. Oriana González, *Pharma lowers insulin costs to save money*, Axios (Mar. 17, 2023), https://www.axios.com/2023/03/17/sanofi-insulin-price-cap-rebate-medicaid.

142 Oliver Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018*, 323 J. Am. Med. Ass'n 844, 845 (2020).

143 *See Orange Book Data Files, supra* note 15.

144 Staff of S. Comm. on Fin., 116th Cong., Rep. on Insulin: Examining the Factors Driving the Rising Cost of a Century Old Drug 3 (Comm. Print 2021).

145 McQueen & Li, *supra* note 2.

146 Colo. Dep't of L., Prescription Insulin Drug Pricing Report, at 36–37 (2020), https://coag.gov/app/uploads/2020/11/Insulin-Report-102020.pdf.

147 Staff of S. Comm. on Fin., *supra* note 144, at 80.

148 Sean Dickson, Nico Gabriel, Walid Gellad & Inmaculada Hernandez, *Estimated Changes in Insulin Prices and Discounts After Entry of New Insulin Products, 2012–2019*, 4 J. Am. Med. Ass'n Health F., no. 6, June 16, 2023, at 3–5 (finding that although prices after rebates for long-acting insulins rose 26 per cent a year from 2012 to 2016, they declined 8 per cent a year from 2015 to 2019); *see also* Adam Fein, *Five Top Drugmakers Reveal List vs. Net Price Gaps (Plus: The Trouble With Insulin Prices)*, Drug Channels (Aug. 11, 2020), https://www.drugchannels.net/2020/08/five-top-drugmakers-reveal-list-vs-net.html (noting that net prices reported by Eli Lilly and Sanofi were decreasing as of 2019, while list prices rose).

149 Dickson, Gabriel, Gellad & Hernandez, *supra* note 148, at 3–5.

Many private plan beneficiaries are better shielded from price increases,[150] particularly if their plan requires only a copay. However, those whose private plans require a co-insurance payment, which can be based on a percentage of list price, have felt a greater impact from rising list prices.[151] In addition, one report shows that even in private insurance plans, 18 per cent of patients rationed their insulin due to cost.[152] Finally, Medicare Part D insulin patients have suffered the most, with out-of-pocket costs rising significantly from 2007 to 2020.[153]

As referenced above, all three major insulin manufacturers recently announced significant price cuts for certain insulin products, including Lantus, Humalog, NovoLog, Levemir, and Humulin.[154] Eli Lilly also announced a copay assistance program capping out-of-pocket costs at $35 per month, and Sanofi announced a similar program capping the out-of-pocket cost of Lantus at $35 per month.[155] Eli Lilly's price cuts take effect gradually through 2023,[156] and the others take effect January 1, 2024,[157] the same day that a cap will be lifted on Medicaid rebates.[158] Without the new price cuts, the combination of these rebates would have required insulin manufacturers to potentially pay Medicaid a significant sum for every dose of certain drugs dispensed to Medicaid beneficiaries.

The insulin price reductions also demonstrate the importance of competitive pressures. The state of California has announced plans to produce state-label insulins that would be interchangeable with several well-established insulin products on the market: Lantus, Humalog, and NovoLog.[159] Although the Medicaid rebates are certainly a

150 Amir Meiri et al., *Trends in Insulin Out-of-Pocket Costs and Reimbursement Price Among US Patients With Private Health Insurance, 2006–2017*, 180 J. Am. Med. Ass'n Internal Med. 1010, 1011 (2020) (reporting that according to company data from 2006 to 2017 private plan out-of-pocket insulin costs remained roughly flat).

151 Sherry Glied & Benjamin Zhu, *Not So Sweet: Insulin Affordability over Time*, Commonwealth Fund (Sept. 25, 2020), https://www.commonwealthfund.org/publications/issue-briefs/2020/sep/not-so-sweet-insulin-affordability-over-time (noting in a report on insulin affordability that '[f]or those with private insurance, the structure of that insurance matters a great deal. Enrollees in copayment-only plans are better protected than are those who pay coinsurance for drugs').

152 Kelsey Waddill, *How Insulin Costs Vary Across Medicare, Medicaid, Private Plans, Uninsurance*, TechTarget (Jan. 4, 2023), https://healthpayerintelligence.com/news/how-insulin-costs-vary-across-medicare-medicaid-private-plans-uninsurance.

153 Juliette Cubanski & Anthony Damico, *Insulin Out-of-Pocket Costs in Medicare Part D*, Kaiser Fam. Found. (July 28, 2022), https://www.kff.org/medicare/issue-brief/insulin-out-of-pocket-costs-in-medicare-part-d/ (analyzing and presenting rising out-of-pocket insulin costs for Part D overall, per beneficiary, and per prescription).

154 *See Eli Lilly Press Release, supra* note 141; *Novo Nordisk Press Release, supra* note 141; *Sanofi Press Release, supra* note 141.

155 *Eli Lilly Press Release, supra* note 141; *Sanofi Press Release, supra* note 141.

156 *Eli Lilly Press Release, supra* note 141.

157 *Novo Nordisk Press Release, supra* note 141; *Sanofi Press Release, supra* note 141.

158 The Medicaid rebate is a 'best price' rebate on the list-to-net price bubble, as well as an inflation rebate on price increases in excess of inflation. Beth Mole, *Here's why slashing insulin prices will actually save Big Pharma money*, Ars Technica (Mar. 14, 2023, 10:25 PM), https://arstechnica.com/science/2023/03/heres-why-slashing-insulin-prices-will-actually-save-big-pharma-money/amp/ (describing the calculus of Medicaid rebates and noting that price cuts fully take effect at the same time as the rebate cap is lifted). These Medicaid rebates are separate from the inflation rebates for *Medicare* created by the Inflation Reduction Act of 2022. *See* Inflation Reduction Act of 2022, Pub. L. No. 117–169, § 11,101–11,102, 136 Stat. 1818, 1865–77 (2022).

159 Six months before insulin companies announced their price cuts, the California legislature authorized $100 million for the state to produce generic-label drugs at affordable prices, specifically naming insulin. See

major driver of the price reductions, one should not discount California's impending competitive entry into the market.

Although programs that help with out-of-pocket costs may lower a patient's cost at the time of purchase, that outlay represents only part of the cost of the product. The plan pays the larger portion of the drug cost—an amount that remains unaffected by out-of-pocket protections. Costs to the plan itself can filter through to increased premiums for all patients, including those suffering from diabetes. Thus, although reducing the out-of-pocket burden for patients is desirable, these programs may serve to mask the ongoing systematic costs of expensive insulin drugs.

List price reductions for certain insulin drugs will be beneficial for patients without insurance, and copay assistance programs may help control out-of-pocket costs. Nevertheless, these price reductions will not return products to anywhere near their original prices, nor will they return access to products already removed from the market. Many of these discontinued products could potentially pave the way for competitors to enter the market and challenge the dominant market players.

One should also note that the newest products from each insulin manufacturer are not included in the price reductions. These newer products face much more limited Medicaid inflation rebates, given that they have not been on the market long enough to experience significant price increases over the initial entry price. Elimination of pressure from the Medicaid rebate changes reduces the incentive for any price reductions, although it may have a disciplining effect on further price increases. Moreover, since these products will not see significant price reductions imminently, manufacturers could once again guide patients and providers to these newer, more expensive products.

To evaluate the hypothesis that discontinuations have redirected patients toward more expensive products on a more granular level, this article specifically examined the insulin analog products discontinued with replacement, to determine whether these discontinuations pushed patients toward more expensive alternatives. By looking at discontinuations with replacement, one can observe transitions and price trends on an individual level, not just between categories of products. Thus, this article analyzed all Medicare Part D claims for 1 million beneficiaries for four of the insulin analog products discontinued with replacement, over the period of 2006 to 2018, using claims and pricing data purchased from the Center for Medicare and Medicaid Services (CMS).[160] Part D contains all claims related to self-administered prescription drug use, the setting in which insulin is administered to patients managing diabetes. The prices used to conduct this analysis are those paid by Medicare plans on behalf of beneficiaries managing diabetes.

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S.B. 154, 2022 Leg., Reg. Sess. (Cal. 2022) (appropriating funds 'to support the development of three low-cost interchangeable biosimilar insulin products and a California-based insulin manufacturing facility' to increase availability and affordability of insulin in the state). After the price cut announcements had begun, the state announced that it had signed a contract with a non-profit drug manufacturer to make three insulin interchangeable products, to be made available for less than $30 for a 10-ml vial. *Governor Newsom Announces $30 Insulin Through CalRx*, Off. of Governor Gavin Newsom (Mar. 18, 2023), https://www.gov.ca.gov/2023/03/18/governor-newsom-announces-30-insulin-through-calrx/; *see also California Selects Civica Rx as Its Insulin Manufacturing Partner*, Civica (Mar. 18, 2023), https://civicarx.org/california-selects-civica-rx-as-its-insulin-manufacturing-partner/.

160 The Levemir InnoLet did not appear in CMS Medicare Part D data, indicating it was either not covered by Medicare Part D or not marketed in the USA during the 2006 to 2018 period.

Analysis of the prices of four insulin analog products discontinued with replacement over time revealed that in all four cases, the discontinuation with replacement was followed by a steep rise in price. Three Humalog pens were discontinued in 2012, soon after three replacement products entered the market, and over the following 6 years the average price of a Humalog pen rose by a remarkable 120 per cent.[161] One Levemir pen was discontinued in 2016, after the 2013 approval of a replacement product which launched at a higher price. By 2018, the replacement pen was priced at double the 2013 cost of the prior Levemir pen.[162] All four products saw discontinuations with replacement accompanied by significant price increases, with the cost of a Humalog or Levemir pen doubling in a handful of years.

For patients using the older insulin prefilled pens who wanted to continue using prefilled Humalog or Levemir pens for treatment, the only option became the newer and ever more expensive pens. Here, voluntary discontinuations are seen to drive patients toward newer and more expensive products on an individual level, in addition to on the large scale. By removing the older pen products from the market, Novo Nordisk and Eli Lilly redirected consumers toward specific newer products, which saw rapid price increases following the discontinuations. The upcoming price reductions of some of these products come with their own caveats and do not resolve the basic issue of loss of access to the older, cheaper products.

## V. SOLUTIONS

As demonstrated in the sections above, voluntary discontinuations are responsible for constraining choice of treatment for patients managing diabetes. These discontinuations have removed most human insulin products from the market, as well as numerous

161 The Humalog pens (standard, 75/25, and 50/50) are listed along with their replacements in Part D data; the data does not differentiate between the Pen and the KwikPen for the duration of their overlap. So, to gain insight into the effect of Humalog discontinuations with replacement, this article considers the prices relative to the product approval and discontinuation dates. All three discontinued Humalog pens were discontinued in 2012, and their replacements—the Humalog KwikPen, the Humalog 75/25 KwikPen, and the Humalog 50/50 KwikPen—were all approved in 2007. In 2006, the prices of the Humalog Pen, the 75/25 Pen, and the 50/50 Pen were $54, $47, and $28, respectively. From 2007 to 2012, while both the Pen and the KwikPen were on the market, only the 50/50 pens saw price increases, rising to $48 at an annualized rate of nearly 10 per cent (from 2006). The Humalog and Humalog 75/25 pens, on the other hand, cost $50 and $48 in 2012, with essentially no change since 2006. However, once the Humalog Pen, the Humalog 75/25 Pen, and the Humalog 50/50 Pen were discontinued in 2012, the prices of the KwikPen surged. By 2018, the Humalog KwikPen, the Humalog 75/25 KwikPen, and the Humalog 50/50 KwikPen were all priced at $109 for a 3-ml pen, a roughly 14 per cent annualized price increase from 2012 for all three products. Here, the price increases appear to have been sparked by the discontinuation of the old products, rather than the introduction of new products, since prices did not rise until the older pens were removed from the market. Nonetheless, this data indicates that discontinuation with replacement may be a relevant factor in driving price increases of affected insulin products.

162 The Levemir FlexPen, which was discontinued in 2016 after the 2013 approval of the Levemir FlexTouch, had nearly halved in price from 2006 to 2013 before the FlexTouch sparked a series of price increases. In 2006, the Levemir FlexPen was priced at $91 for a 3-ml pen, and by 2013 this price had fallen to $52. Then, in 2014, the Levemir FlexTouch appeared in Part D data at a price of $73 per 3-ml pen, and the Levemir FlexPen jumped to $65. The Levemir FlexTouch continued to increase in price as the Levemir FlexPen was discontinued in 2016, and by 2018 the Levemir FlexTouch was priced at $90, nearly twice the 2013 cost of the Levemir FlexPen. Although this discontinuation with replacement was one among numerous factors driving price increases, it is of note that Levemir pen prices began to increase immediately after the introduction of the Levemir FlexTouch.

insulin analog products that often remained available abroad or were replaced with more expensive versions.[163] This issue has persisted over time and through each generation of insulin products. Its effects have become more pronounced in recent years because of the rising costs of insulin,[164] and some have called for shifting patients to older products, when possible,[165] to reduce the economic burden of diabetes treatment.[166]

Moreover, a recent piece of legislation could further incentivize manufacturers' adverse behavior going forward. A section of the Inflation Reduction Act, passed in 2022, applies mandatory rebates to Medicare Part B and Part D drugs for price increases exceeding the rate of inflation.[167] Essentially, if a drug price increase exceeds inflation for a given 12-month period, the manufacturer must pay back to Medicare the excess amount multiplied by the quantity dispensed to Medicare patients.[168] This compounds the existing Medicaid inflation rebates.[169] Although the new law does not affect the private market, the mandatory inflation rebates for a payer as large as Medicare represents a significant blow to the profitability of price increases.

This provision will significantly restrict manufacturers' ability to raise prices of existing products, especially at the rate seen in the insulin market; for example, the list price of a vial of Lantus grew from $131 in 2012 to $248 in 2014, nearly doubling the list price in 2 years.[170] On the flip side, it will encourage manufacturers to introduce new drugs at very high prices. After all, a higher initial price reduces the pain of restricting price increases to the rate of inflation.

### V.A. What Blocks the Trailing-Edge?

If patent rights have expired, why are not trailing-edge insulin products available? After all, if willing buyers exist, and the cost of production is far below the price, one might expect markets to develop to serve those consumers. In the case of trailing-edge insulin products, regulatory processes inadvertently create a key stumbling block for the maintenance of the trailing edge.

The problem arises in the approval process required for insulin products, in light of the complexity of biologic medicines such as insulin. Most drugs on the market are what are known as small-molecule or chemical drugs.[171] These include familiar

163 Although far less likely to return to the US market, voluntary discontinuation also resulted in all animal insulin products being withdrawn, erasing an entire category of treatment.

164 *See* McQueen & Li, *supra* note 2.

165 Elizabeth Bashoff, *Human Insulin may be a Lower-Cost Option for some People with Diabetes*, Harvard Health Blog (June 6, 2019), https://www.health.harvard.edu/blog/human-insulin-may-be-a-lower-cost-option-for-some-people-with-diabetes-2019060316747.

166 *See supra* notes 4–5 and accompanying text (describing the severe economic burden of insulin treatment for many American patients managing diabetes).

167 Inflation Reduction Act of 2022, Pub. L. No. 117–169, § 11,101–11,102, 136 Stat. 1818, 1865–77 (2022).

168 *Id.*

169 *See generally supra* note 141 (describing the existing Medicaid rebates).

170 Staff of S. Comm. on Fin., *supra* note 147, at 3.

171 Joshua Cohen, *Inflation Reduction Act Favors Biologics Over Small-Molecules: In the Long Term, This Could Partly Undermine Bill's Effort to Contain Costs*, Forbes (Jan. 15, 2023, 9:25 AM), https://www.forbes.com/sites/joshuacohen/2023/01/15/inflation-reduction-act-favors-biologics-over-small-molecules-in-the-long-term-this-could-partly-undermine-bills-effort-to-contain-costs/?sh=4582e568500d (noting that 90 per cent of all pharmaceuticals are small-molecule drugs).

medicines such as aspirin, antihistamines, and other common household drugs.[172] Small molecule drugs have relatively simple structures and light molecular weight, allowing them to be chemically defined and replicated with relative ease.[173] With small-molecule drugs, companies who wish to make generic versions of the drug after patents have expired can rely fully on the safety or effectiveness data of the brand company and need only show bioequivalence.[174] If samples of the drug are no longer available, generic applicants may be able to demonstrate bioequivalence using chemical structure comparison.[175]

Biologic drugs are entirely different. Biologics drug products are produced through the use of living cells, and they are far more complex in structure than small-molecule drugs.[176] Biologic drug products are highly sensitive to all aspects of the manufacturing process; small changes in the method or materials used can affect the purity, safety, and efficacy of the medicine.[177] Thus, the creation of later versions of medications is more difficult, and the regulatory approval process is more extensive.

Later versions of biologic medicines are called biosimilars, rather than generics. Although biosimilar applicants may rely to some extent on the safety or effectiveness data of the brand biologic, a biosimilar applicant must engage in additional testing to show that their product will be at least bio*similar* rather than the generic's bio*equivalence* to the original product.[178]

Moreover, some biosimilar applicants may try to obtain interchangeable status, which provides the potential for pharmacists to substitute the less-expensive biosimilar, when the prescription was written for the brand, without contacting the doctor for permission.[179] For interchangeable status, a biosimilar must complete a switching study demonstrating that switching a patient from the biologic to the interchangeable and vice versa does not result in any clinical difference for the patient.[180]

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172 Veronica Salib, *Comparing Small Molecule and Biologics Drug Development Challenges*, TechTarget (May 9, 2023), https://pharmanewsintel.com/news/key-differences-in-small-molecule-biologics-drug-development.

173 *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.

174 21 U.S.C. § 355; *see also* Jing Luo, Aaron Kesselheim & Ameet Sarpatwari, *Insulin Access and Affordability in the US: Anticipating the First Interchangeable Insulin Product*, 8 Lancet Diabetes & Endocrinology 360 (2020).

175 21 C.F.R. § 320.22 (2002) (describing the circumstances in which *in vitro* evidence may be substituted for *in vivo* evidence to establish bioequivalence).

176 Favour Makurvet, *Biologics vs. Small Molecules: Drug Costs and Patient Access*, 9 Med. Drug Discovery 1, 1 (2021); *see also Frequently Asked Questions, supra* note 173.

177 Makurvet, *supra* note 176, at 1.

178 Anne Park Kim & Ross Jason Bindler, *The Future of Biosimilar Insulins,* 29 Diabetes Spectr 161, 163 (2016).

179 42 U.S.C. § 262(i)(3) (noting that a biosimilar must be deemed interchangeable to be substituted without direction from a provider). Note that although the BPCIA provides for automatic substitution of interchangeable biosimilars, this is dependent on state substitution laws, which not all states have passed. Even in states that have such laws, greater requirements are often placed on interchangeable substitution than on generic substitution, such as requiring physicians to be notified of the substitution. Adriana Lee Benedict, *State-level legislation on follow-on biologic substitution*, 2014 J. L. & Biosciences 190, 199 (2014); *see also* 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).

180 *See* 42 U.S.C. § 262(k)(4)(B) (noting that in addition to demonstrating 'no clinically meaningful differences in terms of safety, purity, and potency', an interchangeable biosimilar must demonstrate that switching or

Although with generics and small-molecule drugs, one could, in theory, directly compare the chemical structure of each, such is not possible with biosimilars. Potential FDA waivers of *in vivo* bioequivalence demonstration apply only to abbreviated new drug applications (ANDAs), not to 351(k) biosimilar applications.[181] Demonstrating biosimilarity requires that the biosimilar manufacturer have the actual drug to compare. And of course, for interchangeability, one could not conduct a switching study without using the actual biologic drug itself.

When biologic companies remove a product from the market, there is no supply of the product available for comparison. Thus, removing a trailing-edge product effectively blocks biosimilar competitors from gaining the necessary licensing to enter the market.

### V.B. Comparison Pools for Future Products

Finding a solution to the discontinuation problem would be important, not just for insulin products, but for all biologics in which products have been discontinued that might still be of interest to consumers. Regardless of the type of medicine, once patents have expired on discontinued products, such access should be facilitated. When there is a willing buyer and a willing seller, clinically effective products can be made available for sale.

The obstacles created by voluntary discontinuation compound other reported problems with access to drug samples. Some pharmaceutical companies have directly refused to sell samples to generic manufacturers.[182] Even amid the Covid-19 pandemic, many researchers developing new vaccine methods have been unable to access Covid-19 vaccine samples.[183] Access limitations impede the development of later versions of drugs as well as new, innovative products building on previous discoveries.

The issue of access to the drug also applies to discontinued products whose patents have yet to expire. Patent laws provide that patented products may be used for experimentation, or even in some cases drug development, without violating the innovator's patents. Specifically, although the Patent Act gives patent holders 'the right to exclude others from making, using . . . or selling' an invention,[184] exceptions exist to this broad right of exclusion.[185] Particularly relevant for human insulin and insulin analog

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alternating between the reference product and biosimilar does not produce more risk for a patient than remaining on the reference product); Tony Hagen, *The Difference Between an Interchangeable Biosimilar and One That Isn't*, Am. J. Managed Care: Ctr. for Biosimilars (May 5, 2021), https://www.centerforbiosimilars.com/view/the-difference-between-an-interchangeable-biosimilar-and-one-that-isn-t.

181 21 C.F.R § 320.22(a) (2002) (describing the waivers of in vivo evidence of bioequivalence as possible specifically for ANDA applicants).

182 Feldman & Frondorf, *supra* note 18, at 81–82 (discussing the refusal of drug manufacturers to sell samples to generic manufacturers, sometimes based on drug safety plans, and describing *Actelion Pharm. v Apotex*, a case in which a brand-name manufacturer was sued for refusing to provide samples to generic manufacturers).

183 Benjamin Mueller, *The End of Vaccines at 'Warp Speed'*, N.Y. Times (Nov. 18, 2022), https://www.nytimes.com/2022/11/18/health/covid-nasal-vaccines-warp-speed.html.

184 35 U.S.C. § 154.

185 For example, the 'experimental use exception' permits the use of a patented invention 'for philosophical inquiry, curiosity, or amusement', although some scholars argue for a narrow interpretation of this exception. *See* Elizabeth A. Rowe, *The Experimental Use Exception to Patent Infringement: Do Universities Deserve Special Treatment?*, 57 Hastings L.J. 921 (2006) (arguing against the notion that the experimental use exception should protect university research from patent infringement claims).

products, 35 U.S.C. section 271 offers a statutory exception to patent infringement for developing recombinant, genetically engineered products to submit information to the regulating federal agency.[186] That pathway is a dead end, however, with discontinuations. If the drug is no longer available, companies could not develop a later version that will satisfy the biosimilarity required by the FDA. And without biosimilarity, the streamlined entry process created by the Biosimilars Act is moot.

All of this, in theory, should begin well before the patent rights expire, so that a biosimilar can hit the ground running as soon as the patent rights end. That carefully crafted runway is useless, however, without the drug itself. Thus, the competitive barriers created by discontinuation of viable drugs affect both products still on patent and those whose patents have expired.

No company should be asked to shoulder the burden of continuing to produce a product or device it no longer wishes to provide to the market, no matter the reason for the discontinuation. Nor will any company appreciate being asked to maintain supplies of a product over time. That solution might be unhelpful, in any event, given that the life of a drug company is not necessarily endless. In contrast, deposit of a comparison pool creates reference points for future product-makers, thereby satisfying regulatory approval requirements without unduly burdening drug companies.

### *V.B.1. Creating a Comparison Pool*

To ensure access to a supply of discontinued but safe and effective products, policy makers could require companies to provide the FDA or an independent third party a supply of the product in the event of discontinuation. The depository could then distribute part of the supply to researchers and manufacturers developing products or projects.

Pathways already exist for depositing biologic products for regulatory processes—pathways that could be modified, adapted, or used as an analogy for creating a similar system. For example, the Patent Act requires that an applicant provide 'a written description of the invention in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use it'.[187] Given the impossibility of accurately describing a biologic product in writing with sufficient fullness and specificity, the Federal Circuit has ruled that depositing a sample of the product can help satisfy the written description.[188]

Another potential mechanism for ensuring a supply of biologic products is the Budapest Treaty.[189] The Treaty, which the USA has signed, provides that for purposes of 'patent procedure'[190] signatory countries must recognize deposits made with

186 35 U.S.C. § 271.

187 35 U.S.C. § 112.

188 *See, eg*, Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 963–65 (Fed. Cir. 2002) (describing a federal circuit case affirming that sample deposits of genetically engineered products may serve as a substitute for the written descriptions of genetic sequencing that would otherwise be required for such a patent); *see also* 37 C.F.R. § 1.802(a) ('Where an invention is, or relies on, a biological material, the disclosure may include reference to a deposit of such biological material.').

189 Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, Apr. 28, 1977, 32 U.S.T. 1241, 1861 U.N.T.S. 361 (as amended Sept. 26, 1980) [hereinafter *Budapest Treaty*].

190 *Id.* art. 2(iii) (defining 'patent procedure' as 'any administrative or judicial procedure relating to a patent application or a patent').

any depository approved by the World Intellectual Property Organization (WIPO) (referred to as an 'international depositary authority' in the Treaty).[191] Crucially, a deposit made pursuant to the Treaty must be stored by the international depositary authority for at least 5 years after the most recent request for a sample or 30 years after the date of the deposit, whichever is later.[192] Therefore, provided that the issue of access is properly addressed,[193] deposits made pursuant to the Budapest Treaty could help applicants satisfy the written description requirement imposed by U.S. patent law.[194] Under U.S. regulations, depositors are further required to replace any Budapest Treaty sample that becomes corrupted during the life of the patent, at the risk of losing their ability to enforce the patent.[195] For the public to access samples, the Budapest Treaty defers to the regulations of the signing member, requiring the industrial property office—the USPTO—to certify *inter alia* that the requesting party has a right to the sample under the local law governing patent procedure before that office.[196] Where patent applications have been granted, the Treaty provides that the USPTO 'may'—but is not required to—communicate to the international depositary authority a list of the deposits referred to in said granted patent applications.[197] Where such a communication has been made, the Treaty reflects US regulations, which provide that the public must be granted access to the deposited material.[198]

Patentability deposits will not help biosimilar companies, however. The actual product that makes its way to the shelves will have been developed, refined, and adapted along the way, and it is the actual product to which the biosimilar must compare itself. Nevertheless, the Budapest Treaty system, with its network of third-party depositories and existing procedures and regulations, could be adapted to the needs of maintaining

191 *Id.* art. 3.

192 Regulations under the Budapest Treaty, Rule 9.1, WIPO, (as amended July 22, 2022), https://www.wipo.int/wipolex/en/text/283813 (last visited Sept. 15, 2023).

193 For technicalities regarding access and the lack of a requirement for communications between the USPTO and international depositary authorities, see Ex Parte Hildebrand, 15 U.S.P.Q.2d 1662 (Bd. Pat. App. & Int. 1990). *See also* Manual of Patent Examining Procedure, § 2404.01, https://www.uspto.gov/web/offices/pac/mpep/s2404.html (last visited Oct. 12, 2023) [hereinafter USPTO Manual].

194 *See* USPTO Manual, *supra* note 193, § 2402, https://www.uspto.gov/web/offices/pac/mpep/s2402.html (last visited Sept. 15, 2023) (specifying acceptability of the Budapest Treaty depositories); *see also Budapest Treaty*, USPTO, https://www.uspto.gov/ip-policy/patent-policy/budapest-treaty (last visited Sept. 15, 2023) (explaining the Budapest Treaty in brief).

195 *See* 37 C.F.R. § 1.805(d) (describing when a Budapest Treaty sample requires replacement and noting that failure to replace a deposit that is no longer viable will result in the patent being treated 'as if no deposit were made').

196 *See* Budapest Treaty Regulations, Rules 11.3(a) and (a)(iii) (noting that samples shall be provided to any authority, natural person, or legal entity that 'has a right to a sample of the microorganism under the law governing patent procedure before that office and, where the said law makes the said right dependent on the fulfillment of certain conditions, that that office is satisfied that such conditions have actually been fulfilled').

197 *See* Budapest Treaty Regulations, Rule 11.3(b).

198 *See id.* (providing that in respect of granted patents where the industrial property office has communicated to the international depositary authority lists of the accession numbers referred to in said granted patents, the international depositary authority 'shall, on the request of [the requesting party], furnish to it a sample of any microorganism . . . the [industrial property office] shall not be required to provide the certification referred to in Rule 11.3(a)'); *see also* 37 C.F.R. § 1.808(a)(2) ('all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent', subject to certain procedural regulations).

sufficient supply of a drug to allow comparisons for companies who wish to make biosimilar versions of the drug.

As another model, intellectual property protection for plant varieties also establishes a depository system for biological products. Plant varieties can receive three forms of protection: an ordinary patent (known as a utility patent), a plant patent, and plant variety protection through the U.S. Department of Agriculture (USDA).[199] Under the USDA's plant variety protection program, those receiving an intellectual property certification must deposit a seed or plant tissue deposit for protected sexually and tuber-propagated varieties with the National Laboratory for Genetic Resources Preservation.[200] The deposits are not publicly available during the period of protection, but after protection ends, the deposits are transferred to the USDA Genebank, becoming publicly available.[201] Thus, the USDA plant system offers a model for US government regulatory agencies to collect, preserve, and manage the distribution of the deposits. Given federal budgetary constraints, a program that piggybacks on the network of third-party depositories in the Budapest Treaty system, rather than asking the FDA to set up a depository, may be more appealing.

Although this article's proposal is directed at approval barriers for biosimilars, one could argue that generics could benefit from such a process as well. Occasionally, generic companies have complained that the brand has refused to cooperate in providing samples that could be used for the generic to obtain approval.[202] Requiring non-biologic drug companies to deposit samples for all drugs might create more of a burden on companies and on the system than is warranted by current evidence of the extent of the problem with generic drugs. In addition, as described above, generic companies generally are more easily able to develop the product, and they may be able to find workarounds when the brand is no longer available. No such workarounds exist for biosimilars, however, making the proposal particularly appropriate in the biologics realm.

Any such reform would work best if coupled with better disclosure of manufacturing processes and clinical study details. The ability of brand companies to avoid providing such information, all of which is essential for production and approval of later versions of the drug, continues to be an obstacle to competition and to the effectiveness of the Biosimilars Act.[203] Similarly, the ability of brand companies to pile protections onto existing drugs also delays competitive entry for many medications.[204] Nevertheless, even the company with the most determined legal department must eventually face the end of its patent cliff. In the current insulin environment, many such versions exist.

199 *See PVPO Program Requirements*, USDA, https://www.ams.usda.gov/services/plant-variety-protection/pvpo-requirements (last visited Sept. 15, 2023).

200 *See id.*

201 *See id.*

202 Feldman & Frondorf, *supra* note 18, at 81–82 (discussing the refusal of drug manufacturers to sell samples to generic manufacturers, sometimes based on drug safety plans, and describing *Actelion Pharmaceuticals v Apotex*, a case in which a brand-name manufacturer was sued for refusing to provide samples to generic manufacturers).

203 *See generally* Robin Feldman, *Trade Secrets in Biologic Medicine: The Boundary with Patents*, 24 Colum. Sci. & Tech. L. Rev. 1 (2022).

204 *See* Feldman, *supra* note 10.

### *V.B.2. Timing of Deposits*

As noted above, a deposit at the time of patenting will be of little use for the FDA process, given that the material will have been developed, refined, and adapted along the way. Understandably, the FDA will require biosimilarity and, if appropriate, switching studies, in relation to the brand product that was approved for sale. Thus, for an effective system, the actual product itself must be deposited.

But when should that deposit take place? Potential timing moments for the brand company to deposit a supply of the drug include when the brand company receives approval for the drug and when the brand company decides to discontinue the drug. Requiring deposit when the brand discontinues the drug has the virtue of creating less burden on companies and on the system as a whole. In addition, the product may have experienced some drift across time, making the moment of discontinuation more appropriate for comparison studies—although one could require that a deposit be refreshed if the product is withdrawn.

However, the FDA has little leverage over a company that is discontinuing a drug, given that one does not need approval to *stop* making a drug. If the company declined to participate, enforcement would be a messy process. And if the company experienced a catastrophic event or simply shut down, the government would have no recourse. It is perhaps for reasons such as these that other deposit programs—specifically, the deposit of biological materials for patent approval and deposit of plant variety materials for USDA intellectual property protection—require a deposit to obtain the relevant regulatory approval. Thus, with drug approvals, requiring a deposit to obtain FDA approval to enter the market provides the best timing. The desire to obtain entry naturally ensures all the cooperation the agency would need.

Over time, it is possible that the samples in the pool could age and lose viability. For this reason, the Budapest Treat deposit system as applied in the USA, for example, requires that companies refresh their samples, if the samples become corrupted.[205] A similar requirement could be enacted for the period during which a drug is marketed, but that would not address the fact that samples may lose viability after the drug has been discontinued. To remedy this problem, later companies entering the market using those supplies could be asked to contribute to the sample pool themselves, by providing their own supplies. This would ensure that the pool remains fresh and updated. The more time that passes before any later company wishes to make a product, the less likely it is that the product is still viable in the market, with willing buyers and sellers. Thus, if the pool degrades with no replacement, the market may have spoken.

In short, requiring companies to provide a supply of discontinued products would help lay the groundwork for potential future, biosimilars, or related products. This solution is broadly applicable, beyond just insulin, to ensuring continued access to trailing-edge versions of all biologic products.

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205 *See* 37 C.F.R. § 1.805 (1997) (describing when a Budapest Treaty sample requires replacement and noting that failure to replace a deposit that is no longer viable will result in the patent being treated 'as if no deposit were made'); *see also* Budapest Treaty, USPTO, https://www.uspto.gov/ip-policy/patent-policy/budapest-treaty (last visited Aug. 23, 2023) (explaining the Budapest Treaty in brief).

## VI. CONCLUSION

With each new generation of insulin products that has appeared over the past several decades, voluntary discontinuation of insulin products has emerged as a consistent and significant trend. These discontinuations have removed many viable products from the market, limiting treatment options for patients managing diabetes and preventing biosimilars of those products from being developed. Moreover, insulin discontinuations have served to push patients toward more expensive treatments, both by discontinuing older classes of products in favor of new generations and by replacing specific products with more expensive versions. With the steep rise in insulin costs in recent years, patients are more affected than ever by the loss of access to cheaper, older products, which in many cases were clinically comparable to their successors.

In concert with efforts to reduce the prices of newer insulin products, policy makers must take steps to increase patient access to older but effective treatments—trailing edge insulin products—which have been decimated by voluntary discontinuations. Patients should certainly have access to the newest and most updated insulin products, but for the many patients managing diabetes with budget constraints, the older and cheaper products must remain available as well, allowing patients to enjoy the potential for access for as long as they remain clinically viable. Otherwise, patients are forced to pay ever-increasing prices for waves of innovation that may offer minimal clinical benefits for many.

If consumers want a product that the original manufacturer no longer wants to produce, another manufacturer should be permitted to step in to meet the demand. Simply put, if there is a willing buyer and a willing seller for a product for which patent rights have expired, that product should be available for sale.

## ACKNOWLEDGEMENTS

This article was supported by a grant from the Commonwealth Fund, beginning in 2021 and ending in 2023. No other external funding supported this project.