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Insulin Federalism

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ARTICLE

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INTRODUCTION

In April 2019, U.S. Food and Drug Administration (FDA) Commissioner Scott Gottlieb decreed interchangeable insulin poised for market entry within the next few years.[1] If this projection holds true, this would make insulin the first biologic to achieve interchangeable biologic status.[2] Insulin, relatively "simpler" than more complex biologics and with a substantial amount of real-world evidence supporting its safety and efficacy, is a natural choice for interchangeable biologic status.[3] The Association for Accessible Medicines (AAM) notes that brand-to-brand switches of insulin products regularly occur at the direction of providers, and "the risk of diminished safety or efficacy from a transition is minimal or not present" due to the nature of insulin products.[4] Interchangeable status for insulin promises a tremendous impact on costs because it will allow insulin to be dispensed at retail pharmacies, subject to state interchangeable biologic substitution laws.[5]

The FDA has regulated insulin since it was first used to treat diabetes almost one hundred years ago.[6] Insulin, which maintains the conversion of glucose to energy in those with diabetes, is life-saving and expensive.[7] Insulin products have historically been subject to FDA regulation as a drug, which mandates

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[1] Zachary Brennan, *Updated: Interchangeable Biosimilars: FDA Finalizes Guidance*, REG. AFFS. PROF. SOC'Y: REG. FOCUS (May 13, 2019), https://www.raps.org/news-and-articles/news-articles/2019/5/interchangeable-biosimilars-fda-finalizes-guidance [https://perma.cc/8QM7-UDX7].

[2] *Id.*

[3] *See* Ass'n for Accessible Med. Biosimilars Council, Comment Letter on Proposed Rule: The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Biosimilar and Interchangeable Insulin Products 4 (May 31, 2019), https://www.regulations.gov/contentStreamer?documentId=FDA-2019-N-1132-0326&attachmentNumber=1&contentType=pdf [https://perma.cc/96A7-G6WC].

[4] *Id.* at 5.

[5] *See id.*

[6] Insulin products are often marketed as combination products, consisting of both the insulin and the delivery device. *See* 21 C.F.R. § 3.2(e)(1) (2019); *see also* FOOD & DRUG ADMIN., FREQUENTLY ASKED QUESTIONS ABOUT COMBINATION PRODUCTS (Apr. 9, 2020), https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products#examples [https://perma.cc/5LLL-GDLM].

[7] *See* Tiffany Stanley, *Life, Death, and Insulin*, THE WASH. POST (Jan. 7, 2019), https://www.washingtonpost.com/news/magazine/wp/2019/01/07/feature/insulin-is-a-life-saving-drug-but-it-has-become-intolerably-expensive-and-the-consequences-can-be-tragic [https://perma.cc/J3T7-VXEF].

rigorous clinical trials.[8] Due to incremental innovation in the technology required, no insulin product has entered the market as a generic drug.[9] Also, given the natural characteristics of insulin and its batch-to-batch variability, satisfying the statutory and regulatory "bioequivalence" threshold for traditional generic drug approval is difficult, leading to the use of the new drug approval pathway to market.[10] The persistently high cost of insulin restricts universal access, causes some patients to dangerously ration their supply,[11] and fuels the broad interest of "do-it-yourself" groups who develop their own unapproved versions.[12] State responses to skyrocketing insulin costs include legislation that puts a cap on monthly insulin prices.[13]

In March 2020, the FDA began regulatory transition of insulin products originally approved as "new drugs" to "biological products" subject to Public Health Service Act (PHSA) requirements.[14] In accordance with PHSA amendments furnished by the Biologics Price Competition and Innovation Act of 2010 (BPCIA), this regulatory shift gives insulin status as a "reference product" in determining whether other biological products meet the unique evidentiary threshold for either a "biosimilar" or "interchangeable" classification.[15] Significantly, a biologic product's "interchangeability" implies that a FDA-approved product may be substituted for insulin without prescriber involvement under state law.[16] Nearly every state has interchangeable biologic substitution laws in place, which

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[8] *See* FOOD & DRUG ADMIN., DEVELOPMENT & APPROVAL PROCESS: DRUGS (Oct. 28, 2019), https://www.fda.gov/drugs/development-approval-process-drugs [https://perma.cc/376K-SGKV].

[9] Lutz Heinemann, *Biosimilar Insulin and Costs: What Can We Expect?*, 10 J. DIABETES SCI. & TECH, 457, 458 (2016).

[10] *See* David R. Owens et al., *The Emergence of Biosimilar Insulin Preparations–A Cause for Concern?*, 14 DIABETES TECH. & THERAPEUTICS, no. 11, at 989, 989-990, 993-94 (2012).

[11] *See* Stanley, *supra* note 7.

[12] Jenna E. Gallegos & Jean Peccoud, *After a Century, Insulin is Still Expensive– Could DIYers Change That?*, THE CONVERSATION (Sept. 13, 2018, 10:32 AM EDT), https://theconversation.com/after-a-century-insulin-is-still-expensive-could-diyers-change-that-99822 [https://perma.cc/FUZ3-5J9K].

[13] Colorado and Illinois both cap the monthly cost of insulin at one hundred dollars. 2019 Colo. Sess. Laws 2418; Pub. Act 101-0625, 2019 Ill. Comp. Stat. Ann. Adv. Legis. Serv. 667 (LexisNexis).

[14] *FDA Works to Ensure Smooth Regulatory Transition of Insulin and Other Biological Products*, FDA (Feb. 20, 2020), https://www.fda.gov/news-events/press-announcements/fda-works-ensure-smooth-regulatory-transition-insulin-and-other-biological-products [https://perma.cc/8UHM-EQ9Q].

[15] *See* Public Health Service Act of 1944 §§ 262(i)(1–2), 42 U.S.C. § 262(i); Owens et al., *supra* note 10 at 994. These classifications are explored in Part II.A.

[16] *See* 42 U.S.C. § 262(i)(3).

differ from generic drug substitution laws.[17] This article explores the implications of this current variation in state legislation for patients, prescribers, and pharmacists.

The article proceeds in five parts. Utilizing a hypothetical scenario, Part I identifies five concrete problems arising out of the current regulatory and legal landscape pertaining to biologic products. The article then explains the foundational structures, laws, regulations, and common law that give rise to these problems. Part II explores the insulin market, focusing particularly on cost considerations and characteristics of insulin that make it the likely candidate to achieve the title of first interchangeable biologic product. This part also assesses the difference between drug and biologic approval and explains the importance of the March 2020 regulatory transition (or "switch") of insulin products from drug status to biologic status. Part III analyzes and compares two types of state laws impacting the insulin marketplace: interchangeable substitution laws and insulin price caps. State provisions under assessment regarding interchangeable substitution include requirements for physician notations on scripts, physician notification procedures upon pharmacist substitution, and patient product notification requirements. Recent insulin price cap laws are also assessed as an accelerating trend and a direct lever on costs.

Turning to state common law, Part IV examines the potential impact of state law on tort liability based on federal preemption case law across the FDA-approved product spectrum. While the Supreme Court has addressed drug and device preemption, it has not addressed biologic preemption, except in the limited context of vaccines.[18] Addressing the inconsistencies between state interchangeable biologic substitution laws and state tort liability case law pertaining to biologics is imperative to protect patients. Part V sets forth several recommendations to address the problems stemming from state law and federal preemption jurisprudence from a patient safety and public health perspective.

I. FORECASTING PUBLIC HARMS IN THE INTERCHANGEABLE INSULIN REALM

Consider the following hypothetical in the context of a future interchangeable insulin market:

A patient with Type 1 Diabetes consults their physician, complaining about a side effect of their current short-acting insulin product. The physician determines that the proper course of action is to switch the patient to a recently-approved rapid-acting insulin product. The physician writes a script for the rapid-

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[17] Forty-five states and Puerto Rico have interchangeable biologic substitution laws. Sarah Beth S. Kuyers, MINTZ, *Forty-Five States Now Have Biosimilar Substitution Laws*, 9 NAT'L L. REV., no. 42, 2019, at 1, 1-2, https://www.natlawreview.com/article/45-states-now-have-biosimilar-substitution-laws [https://perma.cc/6XGA-DXEL].

[18] *See* Bruesewitz v. Wyeth, 562 U.S. 223, 223-243 (2011) (regarding awards paid out of National Childhood Vaccine Injury Act's compensation fund as preemptive to all other design-defect claims against vaccine manufacturers).

acting insulin product and hands it to the patient, who then travels to a pharmacy to fill the prescription. What the patient may not realize, nor the physician, is that depending on the state, there may be significant differences in outcomes because of legislation setting forth varying procedures for the substitution of interchangeable biologic products. Recent laws establishing price caps for insulin will also introduce variability by state. This patient description is purely hypothetical, for the reasons identified below, although the general scenario will inevitably play out in the future. The potential harms to patients arising from such a scenario is significant, and raises five core problems that the current regulatory and legal system have yet to address. Each problem is explored below.

A. Biological Products Are Not Generics

Biological products will never have "generic" versions due to their characteristics and the statutory framework overseeing their market entry. Biological products are never "the same" as the innovator product.[19] On the other hand, because chemically synthesized drugs can be engineered to closely mimic the innovator drug, the state generic substitution laws are triggered with market entry of any generic drug product, without intervention from the Food & Drug Administration (FDA) as to that substitution decision.[20] Generic drug substitution laws have been in play for decades following enactment of Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act). All drugs approved by the FDA through the new drug approval process are eligible to serve as reference products for generic versions if the FDA deems the two products to be bioequivalent, which for all practical purposes means nearly identical.[21]

Though generic drug substitution laws vary state-by-state, they often share commonalities in the context of interchangeable biologic laws, as many states used preexisting regulatory schemes to guide drafting of their own interchangeable biologics legislation.[22] The generic drug substitution laws either mandate or permit pharmacists to dispense the generic drug when a physician prescribes the reference brand drug, except if explicitly directed otherwise by the physician.[23] When the physician or other prescribing entity indicates on the script that the drug is not to be substituted—typically with "may not substitute," "dispense

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[19] *See* Owens et al., *supra* note 10, at 990.

[20] *See* Aaron S. Kesselheim & Jonathan J. Darrow, *Hatch-Waxman Turns 30: Do We Need a Re-Designed Approach for the Modern Era?*, 15 YALE J. HEALTH POL'Y L. & ETHICS, 293, 311–14 (2015) (chronicling evolution of state generic substitution laws and interface with FDA).

[21] Drug Price Competition and Patent Term Restoration Act of 1984, 21 USC § 505(j).

[22] *See id.* at 312.

[23] *Id.*

as written," or similar language—the pharmacist may not dispense a generic.[24] If no 'brand-only' notation is indicated by the prescriber, thirty-six states have laws allowing generic substitution, while the remaining fourteen mandate generic substitution.[25] Some states, such as New Jersey, have "positive formulary" laws, whereby generics that may be substituted are identified in a formulary; other states, such as Minnesota, have "negative formulary" laws, whereby drugs that cannot be substituted are identified in the formulary.[26] Many laws also require patient notification or consent to the substitution, or that the drug dispensed by the pharmacist is less or equal price to the prescribed drug.[27]

A more comprehensive exploration of state generic drug substitution laws is unnecessary. The reality is that generic drug substitution laws are more uniform in nature; states fall into broad categories with predictable outcomes depending on the provisions. They are well-established laws, patients and prescribers are aware of their scope and function, and insurance providers have developed practices over decades to establish coverage and reimbursement actions.[28] Perhaps most importantly, chemical compounds regulated as drugs are nearly identical, save for miniscule variations allowable within the FDA's bounds of "bioequivalence." When adverse events or harmful products do surface, there are longstanding regulatory mechanisms to swiftly address them. There is also Supreme Court case law dealing with state tort law applicability, as discussed in Part IV.

Biologics are by their very nature not identical, with the potential for significant variation given their biological rather than chemically derived source, their size, and their structural complexity. The scientific community, the FDA, and Congress all recognize that two biologic products cannot be identical or "same" products. Rather, Congress has set forth the comparison as one measuring whether they are "highly similar" instead, leaving much of the evidentiary requirement setting to the FDA.[29] This is evidenced by the requirement that a biological product be "highly similar" to the reference innovator product to achieve "biosimilar status," an evidentiary standard not required of generic

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[24] *See State Laws or Statutes Governing Generic Substitution by Pharmacists* (illustration), Epilepsy.com (Apr. 25 2007), http://professionals.epilepsy.com/page/statutes_by_pharmacists.html, *reprinted in* U.S. DEP'T HEALTH & HUM. SERVS., OFF. ASSISTANT SEC'Y FOR PLAN. & EVALUATION, ASPE ISSUE BRIEF: EXPANDING THE USE OF GENERIC DRUGS 7 app. a (2010).

[25] *See id.*

[26] Jesse C. Vivian, *Generic-Substitution Laws*, U.S. PHARM., Sept. 2008, at 30, 32-33 (2008).

[27] *See* Kesselheim & Darrow, *supra* note 21, at 312.

[28] *See, e.g.*, Vivian *supra* note 26.

[29] *See* Aaron S. Kesselheim & Jonathan J. Darrow, *Hatch-Waxman Turns 30: Do We Need a Re-Designed Approach for the Modern Era?*, 15 YALE J. HEALTH POL'Y L. & ETHICS, 293, 311–14 (2015) (chronicling evolution of state generic substitution laws and interface with FDA).

drugs.[30] Moreover, "interchangeable" status does not require "bioequivalence," but rather "biosimilar" status, such that the product "can be expected to produce the same clinical result as the reference product in any given patient" and, additionally, "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[31] Thus, the heightened status of interchangeability requires that the product is both biosimilar and that the FDA has determined that product can be automatically substituted at the pharmacy.[32]

As noted earlier, once the FDA approves an interchangeable product, it is up to individual states to determine as a matter of state law whether an interchangeable product may be substituted for a reference biologic and what requirements are associated with that substitution, leading to the 45 statutes discussed in Part III. The inconsistency in the state interchangeable substitution laws, and the uncertainty in the case law on state tort law causes of action against manufacturers, make for a potentially frustrating future for patients receiving interchangeable biologics.[33]

B. Lack of Patient and Prescriber Awareness

Most American consumers are unaware of the regulatory differences between drugs and biologics. Both types of products are therapeutics that are prescribed or administrated by physicians or other medical specialists, with uniform formatting in their labels and promotional materials as regulated by the FDA. However, whether a product enters the market through the new drug approval process, the generic drug approval process, or through mechanisms for biological products, has profound implications for the abbreviated routes to market available, state substitution laws, and federal preemption of state tort law for manufacturer liability. Likewise, public understanding of the recently added biosimilar and interchangeable pathways to market for biologic products is practically nonexistent.[34] Unfortunately, there is accumulating evidence that prescribers also do not have a firm grasp on regulatory aspects and their implications.[35] The FDA implementation contributes to this lack of awareness, as without standardized procedures for both pre-market and post-market evaluations of biosimilar products, there is bound to be confusion among pharmacists, physicians, patients, and healthcare providers.[36]

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[30] 42 U.S.C. § 262(i)(2).

[31] § 262(i)(3); § 262(k)(4)(A)(ii).

[32] *See id.*

[33] *See* discussion *infra* Parts III, IV.

[34] *See infra* Section IV C.

[35] *See* Sean McGowan, *Five Years On, Biosimilars Need Support From All Healthcare Players*, STAT NEWS (Mar. 6, 2020), https://www.statnews.com/2020/03/06/biosimilars-in-us-turn-five/ [https://perma.cc/Q286-FFDP].

[36] *See* discussion *infra* p. 20.

Recently, the FDA and Federal Trade Commission (FTC) targeted some aspects of labeling and advertising to address consumer perceptions and awareness. In February 2020, the two agencies issued a joint statement announcing efforts to support competition and deter anti-competitive behaviors in the biologic arena.[37] These measures include: (1) policing false and misleading statements comparing innovator biologics to biosimilar versions; (2) facilitating public outreach and coordination with industry, academic, and government agencies to address industry behaviors that stifle competition and obscure information; and (3) publishing draft guidance on promotional activities and labeling to ensure clear comprehension of the product characteristics.[38] These measures respond to calls from industry and consumer groups to address misinformation in the biosimilar market.[39] In addition, the FTC intends to review patent settlement agreements between reference product and biosimilar manufacturers to ensure that they are void of anticompetitive reverse payments that slow or defeat the introduction of lower-priced medicines, including biosimilars.[40] The FDA also intends to develop educational materials to inform the public and healthcare professionals about trusted safety and efficacy of FDA-approved biosimilars.[41] The FTC and FDA held a joint workshop to educate stakeholders about U.S. biosimilar markets and FDA approval process, enforcement activities by the FDA and FTC, the benefits of competition, and improving stakeholder engagement.[42]

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[37] *FDA and FTC Announce New Efforts to Further Deter Anti-Competitive Business Practices, Support Competitive Market for Biological Products to Help Americans*, FDA (Feb. 3, 2020), https://www.fda.gov/news-events/press-announcements/fda-and-ftc-announce-new-efforts-further-deter-anti-competitive-business-practices-support [https://perma.cc/VJ5L-3U7R].

[38] *Id.*; *see* FDA, DRAFT GUIDANCE, PROMOTIONAL LABELING AND ADVERTISING CONSIDERATIONS FOR PRESCRIPTION BIOLOGICAL REFERENCE AND BIOSIMILAR PRODUCTS QUESTIONS AND ANSWERS GUIDANCE FOR INDUSTRY (Feb. 2020), https://www.fda.gov/media/134862/download [https://perma.cc/46Q4-HLMS].

[39] *See* Zachary Brennan, *Biosimilar Forum Calls for FDA Guidance to Address Misinformation*, REG. AFFS. PRO. SOC'Y: REG. FOCUS (Dec. 3, 2018), https://www.raps.org/news-and-articles/news-articles/2018/12/biosimilars-forum-calls-for-fda-guidance-to-addres [https://perma.cc/YG5U-WRPF]; *see also* Zachary Brennan, *Industry Groups Call on FDA to Dispel Biosimilar Misinformation*, REG. AFFS. PRO. SOC'Y: REG. FOCUS (Feb. 28, 2019), https://www.raps.org/news-and-articles/news-articles/2019/2/industry-groups-call-on-fda-to-dispel-biosimilar-m [https://perma.cc/6LWT-KUP2].

[40] STEPHEN M. HAHN, FDA & JOSEPH J. SIMONS, FTC, JOINT STATEMENT OF THE FOOD & DRUG ADMINISTRATION AND THE FEDERAL TRADE COMMISSION REGARDING A COLLABORATION TO ADVANCE COMPETITION IN THE BIOLOGIC MARKETPLACE 6 (Feb. 3, 2020) https://www.ftc.gov/system/files/documents/public_statements/1565273/v190003fdaftcbiologicsstatement.pdf [https://perma.cc/DP8A-N45R].

[41] *Id.* at 5.

[42] *Public Workshop: FDA/FTC Workshop on a Competitive Marketplace for Biosimilars*, FDA (March 9, 2020), https://www.fda.gov/drugs/news-events-human-drugs/public-

C. Anticompetitive Business as Usual

In addition to concerns specific to biologics discussed above, the biologic industry also engages in typical monopolistic behaviors prevalent in the pharmaceutical realm. The pharmaceutical industry has long-been criticized for its use of anticompetitive tactics that effectively increase profits and stifle competition.[43] These tactics include shifting demand to a modified form of an existing brand drug (often called "product hopping") where the modified product has a longer patent life,[44] allowing authorized generics of innovator products through agreements with other manufacturers to retain market share,[45] frivolously filing citizens petitions to the FDA in order to delay generic market entry,[46] and entering into reverse payment settlements to keep generic drugs off the market during their 180 day exclusivity period (otherwise known as pay-for-delay settlements).[47]

A persistent opponent to the use of these tactics, the FTC routinely invokes antitrust and unfair competition law to frame legal challenges. In fact, the 2013 Supreme Court case *Federal Trade Commission v. Actavis* examined pay-for-delay settlements entered into between new drug application (NDA) patent holders and generic applicants, holding that the settlement agreements were not per se illegal but subject to a rule-of-reason analysis.[48] Many are now pointing to brand pharmaceutical manufacturers use of Risk Evaluation and Mitigation Strategies as the latest anticompetitive tactic, where drug sponsors are patenting methods of use to assure safe use of the product and refusing to allow generic

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workshop-fdaftc-workshop-competitive-marketplace-biosimilars-03092020-03092020 [https://perma.cc/RF8L-MAFK].

[43] This discussion excerpted from Jordan Paradise, *REMS as A Competitive Tactic: Is Big Pharma Hijacking Drug Access and Patient Safety?*, 15 HOUS. J. HEALTH L. & POL'Y 43, 46-47 (2015).

[44] *See generally*, M. Sean Royall, Ashley E. Johnson & Jason C. McKenney, *Antitrust Scrutiny of Pharmaceutical "Product Hopping"*, 28 ANTITRUST L. & ECON. REV. 71, 71-77 (2013).

[45] *See generally,* FTC, AUTHORIZED GENERIC DRUGS: SHORT-TERM EFFECTS AND LONG-TERM IMPACT (Aug. 2011).

[46] *See generally,* Matthew Avery, William Newsom & Brian Hahn, *The Antitrust Implications of Filing "Sham" Citizens Petitions with the FDA*, 65 HASTINGS L. J. 113, 113-152 (2013).

[47] *See generally,* FTC, PAY-FOR-DELAY: WHEN DRUG COMPANIES AGREE NOT TO COMPETE https://www.ftc.gov/news-events/media-resources/mergers-competition/pay-delay [https://perma.cc/5FKD-H6P6].

[48] FTC v. Actavis, 570 U.S. 136, 156 (2013). Since the Supreme Court's decision, several additional cases have arisen questioning the scope of pay-for-delay settlements. *See, e.g.*, In Re: Wellbutrin XL Antitrust Litig. Indirect Purchaser Class, 868 F.3d 132, 138 (3d Cir. 2017).

products to copy those methods for use with their own product.[49] As Part II explores, the biologic industry (with many of the same players) is also exhibiting these anticompetitive tactics as the biosimilar, and eventual interchangeable, marketplace expands. The FDA and FTC collaboration noted above is currently examining the extent and competitive impact of these activities.

D. Nonuniformity in Dispensing Outcomes

Depending on the state in which a patient resides, the outcome may vary regarding which interchangeable biologic product that patient is dispensed and the scope and timing of the notification that the patient and physician receive about that substitution. Relatedly, recent state legislation establishing price caps on insulin products will also produce variable results. Using insulin as a case study, Part III will discuss the varying state interchangeable biologic substitution laws and compare the potential outcomes for patients.

E. Variability in Legal Liability and Remedies

Likewise, depending on the state in which the patient resides, and the product ultimately dispensed to the patient, state common law liability and remedies may also vary given the particular jurisdiction. There are two levels to this common law variability. The first is connected directly to the product the patient receives from the pharmacist, whether there is liability immunity within the state substitution law, and the scope of that immunity. This article will not explore that level of variability. The second level of variability results from the range of case law governing federal preemption of state tort liability in the context of medical products. Whether a patient receives the innovator biologic or an interchangeable version may impact the availability of a legal remedy. Part IV assesses the case law regarding state tort liability and federal preemption, highlighting that there is a pressing need to protect patient and public health through various legal and regulatory mechanisms.

II. REGULATING THE INSULIN MARKETPLACE

A. Scope of Products and Magnitude of Costs

Insulin is a hormone naturally produced within the pancreas that functions to convert glucose from sugars and starches into energy.[50] The inability to produce insulin and thus control blood sugar levels leads to several forms of diabetes

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[49] ALEX BRILL, MATRIX GLOB. ADVISORS, LOST PRESCRIPTION DRUG SAVINGS FROM USE OF REMS PROGRAMS TO DELAY GENERIC MARKET ENTRY 2 (2014), http://getmga.com/wp-content/uploads/2017/02/REMS_Study_July.pdf [https://perm.cc/UN8D-3SPF].

[50] Valencia Higuera, *Everything You Need to Know About Insulin*, HEALTHLINE (May 7, 2019), https://www.healthline.com/health/type-2-diabetes/insulin [https://perma.cc/TEC4-7E2Y].

mellitus, which left unmanaged can be fatal.[51] In the United States, over 30 million people are afflicted with diabetes and 7.4 million of those utilize insulin.[52] The Centers for Disease Control and Prevention has identified diabetes as the "largest and fastest growing chronic disease" in the U.S.[53] For those who are uninsured, the costs range from $120 to $400 out of pocket each month.[54] For those who are insured, coverage is complicated and variable depending on, among other things: the type of insulin, the use of rebates and discounts, formulary determinations by pharmacy benefit managers (PBMs), and the type of health plan.[55]

The lifesaving potential of therapeutic insulin dates to 1921 when active insulin was extracted from animal pancreas by researchers from the University of Toronto and later delivered via injection into a 14-year-old patient.[56] The patient's clinical outcomes vastly improved with successive injections.[57] Now, one hundred years later, the insulin market has experienced a consistently evolving range of innovations resulting in a complex spectrum of insulin products available.[58] Following the successful extraction of insulin in 1921, the University of Toronto partnered with Eli Lilly to manufacture the product.[59] The research team patented the method of production and Eli Lilly was granted the ability to patent improvements to the process, yet the university retained the patent rights and licensed the rights.[60] Incremental advancements over the next 50 years led to longer duration of insulin action, combination of products to allow for single daily injections, and improvements in the safety profile of insulin products.[61]

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[51] These are Type 1 diabetes (typically, though not always, childhood onset), Type 2 diabetes (adult onset), and gestational diabetes. There is also a recognized condition called "prediabetes." CDC, WHAT IS DIABETES? (June 11, 2020), https://www.cdc.gov/diabetes/basics/diabetes.html [https://perma.cc/YP6C-FTEW].

[52] William T. Cefalu et al., *Insulin Access and Affordability Working Group: Conclusions and Recommendations*, 41 DIABETES CARE 1299, 1299-1230 (2018), https://care.diabetesjournals.org/content/diacare/41/6/1299.full.pdf [https://perma.cc/9C39-T6AS].

[53] NAT'L CONF. OF STATE LEGISLATORS, DIABETES HEALTH COVERAGE: STATE LAWS AND PROGRAMS (Jan. 10, 2016), https://www.ncsl.org/research/health/diabetes-health-coverage-state-laws-and-programs.aspx [https://perma.cc/CMX6-JECC]

[54] Jeremy A. Greene & Kevin R. Riggs, *Why Is There No Generic Insulin? Historical Origins of A Modern Problem*, 372 N. ENG. J. MED. 1171, 1171 (2015).

[55] *See generally* Cefalu et al., *supra* note 52.

[56] C.H. Best & D.A. Scott, *The Preparation of Insulin*, 57 J. BIOL. CHEM. 709, 711-12 (1923).

[57] Louis Rosenfeld, *Insulin: Discovery and Controversy*, 48 CLIN. CHEM. 2270, 2278 (2002).

[58] *Types of Insulin for Diabetes Treatment*, WEBMD (July 17, 2020), https://www.webmd.com/diabetes/diabetes-types-insulin [https://perma.cc/6STW-B5LE].

[59] Greene & Riggs, *supra* note 54, at 1171.

[60] *Id.* at 1172.

[61] *Id.*

Accompanying each of these advancements were patents, though many have long expired.

In 1978, Stanley Cohen and Herbert Boyer utilized recombinant DNA (rDNA) techniques to genetically engineer human insulin.[62] Shortly thereafter, Genentech began manufacturing Humulin, a synthetic human insulin and the first biotechnology product approved by the FDA in 1982.[63] The utilization of rDNA technology introduced vast potential to alter the genetic code in the production of insulin, leading to the development of insulin analogs.[64] The first insulin analog entered the market in 1996, with competition following shortly.[65] The current insulin market includes both synthetic human insulin, which is identical to the structure of human insulin (like Humulin), and insulin analogs, which are laboratory grown and genetically altered with minor structural changes resulting from amino acid sequencing revisions that enhance their functioning in various ways.[66] Differences in the structure of human insulin and insulin analogs impact the interactions within the human body, leading to alterations in binding properties and intracellular signaling.[67] Improvements in delivery mechanisms and absorption rates are typically attributed to insulin analogs.[68]

The most recent innovations and improvements in insulin analogs enjoy patent protection, which is one factor resulting in high prices.[69] The insulin industry is criticized for anticompetitive behaviors prevalent in the pharmaceutical drug realm, such as aggressive tactics to extend patent life with inconsequential changes to a product that nevertheless achieve patent protection.[70] Medical experts also urge that given the constant innovation in the insulin realm, drug companies have not thought it worthwhile to attempt a generic version of a product that may quickly become obsolete.[71] However, patent protection and innovation cycles are not the only factors contributing to high prices. Manufacturing complexities abound as problems of impurities, variation across batches, bacteria or yeast strain used, degradation and denaturation, and storage condition limitations make production expensive.[72] These complexities in production also

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[62] *Id.*

[63] *Humulin N, NPH, Human Insulin (Recombinant DNA Origin) Isophane Suspension*, NAT'L MUSEUM OF AM. HIST., BEHRING CTR. (last visited Oct. 11, 2020), https://americanhistory.si.edu/collections/search/object/nmah_1000967 [https://perma.cc/8NWE-Q8DT].

[64] Greene & Riggs, *supra* note 54, at 1172.

[65] *Id.*

[66] *See* NAT'L MUSEUM OF AM. HIST., BEHRING CTR., *supra* note 63.

[67] Lutz Heinemann & Marcus Hompesch, *Biosimilar Insulins: Basic Considerations*, 8 J. DIABETES SCI. & TECH. 6, 6 (2014).

[68] Greene & Riggs, *supra* note 54, at 1172.

[69] *See, id.*

[70] *Id.* at 1172 – 73.

[71] *Id.* at 1174.

[72] *See* Owens et al., *supra* note 10, at 990.

impact antigenicity, bioavailability, and stability of the product,[73] and introduce potential for immunogenic responses to insulin products.[74] Larger molecule biologic drugs, like insulin, are just more complex and introduce additional manufacturing challenges, which result in higher costs to produce.[75] The historical legal framework for review and approval of insulins is also a contributing factor to high prices.

There are five basic aspects of insulin products relevant to availability and cost. First is the time of onset, or how quickly the insulin product acts on the body.[76] Second is the peak, or the time of the maximum impact of the insulin product.[77] The third is the duration of the effect of the insulin.[78] The fourth is the concentration; in the U.S. the concentration is a standardized 100 units/ml or U100 although other concentrations are available.[79] Fifth is the method of delivery: either subcutaneously by injection, intravenously by infusion under medical supervision, or by inhalation.[80] Insulin products are classified on the market into the following categories: short-acting, intermediate-acting, rapid-acting, long-acting, or ultra-rapid-acting.[81] Human insulin is typically characterized as short-acting, intermediate-acting, or fast-acting, while the newer insulin analogs are characterized as rapid-acting or long-acting.[82] The most recent products to enter the market are the ultra-rapid insulin analogs delivered though inhalation.[83] As the classifications indicate, insulin is not a single FDA-approved product, but rather a family of products.

The average cost of insulin therapy tripled between the years of 2003 and 2014, and increased by 55% between 2014 and 2019.[84] The costs of insulin to individual patients can vary tenfold depending on the type of insulin, the delivery method, the dosage, and the formulation.[85] Three manufacturers - Sanofi, Eli

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[73] Heinemann & Hompesch, *supra* note 67, at 8.

[74] Owens et al., *supra* note 10, at 990.

[75] Greene & Riggs, *supra* note 54, at 1172-1173.

[76] *See Insulin Basics*, AMERICAN DIABETES ASSOCIATION, https://www.diabetes.org/diabetes/medication-management/insulin-other-injectables/insulin-basics [https://perma.cc/EG2U-DK2P] (last visited Oct. 11, 2020).

[77] *Id.*

[78] *Id.*

[79] *Id.*

[80] Rima B. Shah et al, *Insulin Delivery Methods: Past, Present and Future*, 6 INT. J. PHARM. INVESTIG. 1, 1 (2016).

[81] AMERICAN DIABETES ASSOCIATION, *supra* note 76.

[82] *Id.*

[83] *Id.*

[84] Benita Lee, *How Much Does Insulin Cost? Here's How 23 Brands Compare* GOODRX (Aug. 23, 2019), https://www.goodrx.com/blog/how-much-does-insulin-cost-compare-brands/ [https://perma.cc/B8YQ-YGCR].

[85] *Id.*

Lilly, and Novo Nordisk - dominate the global $27 billion insulin market.[86] While pricing for traditional short-and intermediate-acting insulin has decreased, prices of modern rapid- and long- acting insulin continue to rise, which is attributable to the heightened difficulties in production and their ability to more effectively regulate blood-sugar levels.[87] The method of delivery is also a relevant factor in pricing, with the most utilized choices being subcutaneous syringe and vial, disposable or reusable pens, or portable pumps.[88] The retail prices of rapid-acting insulins are about 30% higher if a patient opts for pens instead of vials as delivery methods.[89] Figures 1-3 identify reported insulin retail pricing across over two dozen brands in the second quarter of 2019 based on the type of insulin.[90]

Figure 1: Retail Prices of Traditional Human Insulin[91]

	Dispenser Price	**Insulin Unit Price**
Short-term acting		
Novolin R vial (10 mL)	$ 93 per vial	$0.09 per unit
Humulin R vial (10 mL)	$185 per vial	$0.19 per unit
Humulin R vial (20 mL, 500 units/mL)	$183 per vial	$0.18 per unit
Humulin R KwikPen (3 mL, 500 units/mL)	$352 per pen	$0.23 per unit
Intermediate-acting		
Novolin N vial (10 mL)	$92 per vial	$0.09 per unit
Humulin N vial (10 mL)	$183 per vial	$0.18 per unit
Humulin N KwikPen (3 mL)	$117 per pen	$0.39 per unit

Figure 2: Retail Prices of Rapid-Acting Insulin Analogs[92]

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[86] *The Issue with Interchangeable Insulin*, HEAT (Oct. 31, 2019), https://heatinformatics.com/posts/issue-interchangeable-insulin [https://perma.cc/5MUC-ZEFC].

[87] Lee, *supra* note 84.

[88] Shah et al, *supra* note 80, at 16.

[89] Lee, *supra* note 84.

[90] One unit of insulin is generally the amount of insulin it takes to reduce blood glucose levels by 50 mg/dL, with the caveat that individual response rates vary. *See id.*

[91] *Id.*

[92] *Id.*

	Dispenser Price	**Insulin Unit Price**
Insulin lispro (generic insulin)		
Generic insulin lispro vial vial (10 mL)	$180 per vial	$0.18 per unit
Generic insulin lispro KwikPen (3 mL)	$72 per pen	$0.24 per unit
Admelog vial (10 mL)	$291 per vial	$0.29 per unit
Admelog SoloStar pen (3 mL)	$187 per pen	$0.37 per unit
Humalog vial (10 mL)	$332 per vial	$0.33 per unit
Humalog KwikPen (3 mL)	$133 per pen	$0.44 per unit
Humalog KwikPen (3 mL, 200 units/mL)	$264 per pen	$0.44 per unit
Humalog cartridge (3 mL)	$132 per cartridge	$0.44 per unit
Humalog junior KwikPen (3 mL)	$129 per pen	$0.43 per unit
Insulin aspart		
Novolog vial (10 mL)	$351 per vial	$0.35 per unit
Novolog FlexPen (3 mL)	$134 per pen	$0.45 per unit
Novolog cartridge (3 mL)	$130 per cartridge	$0.47 per unit
Fiasp vial (10 mL)	$348 per vial	$0.35 per unit
Fiasp FlexTouch pen (3 mL)	$136 per pen	$0.45 per unit
Insulin glulisine		
Apidra vial (10 mL)	$362 per vial	$0.36 per unit
Apidra SoloStar pen (3 mL)	$143 per pen	$0.48 per unit
Inhaled insulin		
Afrezza cartridge (4 units)	$4.42 per cartridge	$1.11 per unit

Figure 3: Retail Prices of Long-Acting Insulin Analogs[93]

	Dispenser Price	**Insulin Unit Price**
Insulin detemir		
Levemir FlexTouch pen (3 mL)	$113 per pen	$0.38 per unit
Levemir vial (10 mL)	$397 per vial	$0.40 per unit
Insulin glargine		
Basaglar KwikPen (3 mL)	$81 per pen	$0.27 per unit
Lantus vial (10 mL)	$340 per vial	$0.34 per unit
Lantus SoloStar pen (3 mL)	$168 per pen	$0.34 per unit
Toujeo pen (1.5 mL, 300 units/mL)	$160 per pen	$0.35 per unit
Toujeo Max pen (3 mL, 300 units/mL)	$315 per pen	$0.35 per unit
Soliqua 100/33 SoloStar pen (3 mL)	$173 per pen	$0.58 per unit
Insulin degludec		
Tresiba vial (10 mL)	$417 per vial	$0.42 per unit
Tresiba FlexTouch pen (3 mL)	$124 per pen	$0.41 per unit
Tresiba FlexTouch pen (3 mL, 200 units/mL)	$248 per pen	$0.41 per unit
Xultophy pen (3 mL)	$254 per pen	$0.85 per unit

There is a robust insulin market, yet competitors almost always enter the market at higher prices than the existing market price (except for short-acting, traditional human insulin products).[94] Innovation in the formulation and delivery

[93] *Id.*

[94] *Insulins: Prices, Rebates, and Other Factors Influencing Costs*, PHARMACEUTICAL CARE MANAGEMENT ASSOCIATION (May 8, 2018), https://www.pcmanet.org/insulins-prices-rebates-and-other-factors-influencing-costs/ [https://perma.cc/K853-EGNQ]. One notable exception was Basaglar, introduced in December 2016 as the first follow-on long-acting insulin. *Id.* With the introduction of more follow-on insulins like Basaglar, competing options for

routes of insulin analogs is contributing to pricing increases, with more recent products deemed more effective.[95] While the cost of and demand for traditional human insulin has decreased, insulin analog costs are escalating, chiefly tied to patent protections achieved for the innovations.[96] As one scholar notes "[t]he main reason why no generic insulin has become available over the past decades is that incremental innovation has repeatedly precluded the formation of a generic insulin industry in North America when earlier patents expired."[97] Most insulin products are subject to protection in the form of patents covering the active ingredient, formulation, and/or delivery device.[98] There is a growing literature critiquing the insulin patent landscape.[99] In addition, innovator biologic manufacturers may also employ trade secret protections for certain crucial manufacturing techniques, forcing biosimilar competitors to attempt to reverse-engineer them.[100] Without access to production methods, biosimilar sponsors may fail to fully understand the biologic's characterization and allow the trade secret to continue indefinitely.[101]

The actualization of lower biologic costs alongside implementation of the biosimilar and interchangeable pathways to market has been elusive. While some economists predicted cost savings like that resulting from the generic drug approval process, others cautioned that the reduction in prices would not be as profound given the differences in regulatory requirements and costs associated

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consumers may drive costs down. *See id.* There are currently only three follow-on biologic insulin products on the market. Cefalu, et al, *supra* note 52, at 1308.

[95] Philip W. Lavori, Randall S. Stafford, & Todd H Wagner, *New, but Not Improved? Incorporating Comparative-Effectiveness Information into FDA Labeling*, 361 NEW ENG. J. MED. 1230, 1230 (2009). Note that prior products are not then removed from the market with entry of a more effective one and that the FDA does not engage in comparative effectiveness as part of its review.

[96] Heinemann, *supra* note 9, at 458.

[97] *Id.*

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

[99] *See, e.g.,* Lutz Heinemann, *Biosimilar Insulins*, 12 EXPERT OP. ON BIOLOGICAL THERAPY 1009, 1009 (2012); Luo & Kesselheim, *supra* note 98, at 835-37 (2015). One scholar offers that "[h]uman insulin is off patent, is relatively simple to manufacture, and WHO recently included it in its list of essential medicines in preference to analogue insulin. Generic biosynthetic human insulin would bring down the price of insulin, and several companies have the capacity to produce it, but progress has been confounded by claims that branded analogue insulins—which are typically two to four times the cost of branded human insulin—are better treatment." Edwin A.M. Gale, *Commentary: Politics of Affordable Insulin*, 343 BRITISH MED. J. (2011).

[100] W. Nicholson Price & Arti K. Rai, *Are Trade Secrets Delaying Biosimilars*, 348 SCI. 188, 189 (2015); Luo & Kesselheim, *supra* note 98, at 837.

[101] Price & Rai, *supra* note 100, at 188-189.

with biologic products.[102] With a current market that includes 29 FDA-approved biosimilar products as of March 1, 2021,[103] the impact on innovator pricing yet remains unclear, but some urge that the savings have not materialized.[104] In addition, there is accumulating evidence that commercial health plans rarely prefer biosimilars to their brand-name counterpart.[105] In fact, one analysis found that of seventeen of the largest plans in the U.S., the health plans required that patients try a biosimilar before gaining access to the innovator only 14 percent of the time.[106] Similarly, health plan decisions to assign preferred formulary status to the innovator biologic rather than a biosimilar has garnered attention as well. UnitedHealthcare's preferred formulary status of Amgen's Neulasta over biosimilar versions of pegfilgrastim in exchange for a substantial rebate is one prime example.[107] In order for biosimilars including Nivestym, Zarxio, and Granix to be covered, UnitedHealthcare must provide prior authorization.[108] UnitedHealthcare's policy does allow for a switch in the event that a treatment fails or the patient is intolerant to the reference drug.[109] The Association for Accessible Medicines denounced the move as "a step backwards in patient care."[110] Despite this particular example, the payer community lacks a uniform strategy for the coverage of biosimilar products.[111]

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[102] Heinemann, *supra* note 9, at 459.

[103] FDA, BIOSIMILAR PRODUCT INFORMATION: FDA-APPROVED BIOSIMILAR PRODUCTS (December 17, 2020) https://www.fda.gov/drugs/biosimilars/biosimilar-product-information [https://perma.cc/S82V-LFTA].

[104] Ed Silverman, *Biosimilars Got the Cold Shoulder from Health Plans When It Came to Preferred Coverage*, STAT PHARMALOT (May 20, 2020), https://www.statnews.com/pharmalot/2020/05/20/biosimilars-biologics-health-coverage-drug-prices/ [https://perma.cc/55T7-X7R6].

[105] *See* James D. Chambers et al., *Coverage for Biosimilars vs Reference Products Among U.S. Commercial Health Plans*, 323 J. AM. MED. ASS'N 1972, 1972 (2020).

[106] *Id.* The analysis involved 535 coverage decisions from 2019 for nine biosimilar products. *Id.*

[107] Cathy Kelly, *UnitedHealthcare Coverage Policy Undercutting Neulasta Biosimilars Draws Concerns*, THE PINK SHEET, June 17 2019, at 1.

[108] *Medical Benefit Drug Policy: White Blood Cell Colony Stimulating Factors*, UNITEDHEALTHCARE (April 1, 2020), https://www.uhcprovider.com/content/dam/provider/docs/public/policies/medicaid-comm-plan/white-blood-cell-colony-stimulating-factors-cs.pdf [https://perma.cc/URM7-G58F].

[109] *Id.*

[110] *AAM and the Biosimilars Council Statement on UnitedHealthcare Announcement to Reverse Course on Biosimilars*, BIOSIMILARS COUNCIL (May 30, 2019), https://biosimilarscouncil.org/news/statement-reverse-course-biosimilars/ [https://perma.cc/U7MM-MFD6].

[111] McGowan, *supra* note 35.

B. The Significance of the "BLA" Switch

Historically, the FDA has regulated insulins as drugs even though insulins fall within the statutory definition of a biological product. Through intra-agency agreements, several types of products that technically fall within the definition of biologic have been regulated as drugs by the FDA, including proteins (such as insulin) for therapeutic use, monoclonal antibodies, growth factors and enzymes, and non-vaccine therapeutic immunotherapies.[112] The FDA began the transition of insulin products originally approved under a new drug application to be deemed licensed under the Public Health Service Act as a biological product in March 2020.[113] Following this move, these products may be used as reference products for biosimilar or interchangeable insulin products.[114] A brief explanation of the statutory and regulatory differences is warranted here.

Conventional pharmaceutical drugs are small chemical molecules that are relatively simple to characterize and synthesize.[115] The Food, Drug and Cosmetic Act (FDCA) defines a "drug" as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; articles intended to affect the structure or function of the body; and any articles intended for use as components.[116] The statute also defines a "new drug" which implicates the new drug approval process for drugs not generally recognized as safe and effective prior to market entry.[117] New drugs are reviewed by the FDA and approved for the market through an investigational new drug and new drug application (NDA) process, the abbreviated drug application (ANDA, also known as generic) process, or the "505(b)(2)" process which involves reference to a prior data set or publication by another to support a showing of safety and efficacy.[118] The Center

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[112] *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research*, FDA (Feb. 2, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/transfer-therapeutic-products-center-drug-evaluation-and-research-cder [https://perma.cc/WM6D-67GQ].

[113] 21 C.F.R. § 601 (2019).

[114] U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, QUESTIONS AND ANSWERS ON BIOSIMILAR DEVELOPMENT AND THE BPCI ACT (2018); U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FDA, CENTER FOR DRUG EVALUATION AND RESEARCH, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, NEW AND REVISED DRAFT Q&AS ON BIOSIMILAR DEVELOPMENT AND THE BPCI ACT (REVISION 2), CENTER FOR DRUG EVALUATION AND RESEARCH (2018).

[115] *See* Jordan Paradise, *The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the United States Healthcare System*, 41 AM. J. L. & MED. 49, 68 (2015).

[116] 21 U.S.C. § 321(g)(1).

[117] 21 U.S.C. § 321(p); 21 U.S.C. § 355.

[118] 21 U.S.C. § 355(b)(1); § 355(b)(2); § 355(j).

for Drug Evaluation and Research (CDER) oversees drug review and approvals.[119]

> Biologics are larger macromolecules derived from living sources such as microorganisms, animals, and humans. Biologics are defined according to their source as:
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> > a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.[120]

The FDA groups biologics generally as allergenics, blood and blood products, cellular and gene therapy products, proteins (as of March 23, 2020), tissue and tissue products, vaccines, and xenotransplantation.[121] Biologic approval is overseen by either the Center for Biologic Evaluation and Research (CBER) or CDER depending on the product type.[122] Because biologics are governed by the Public Health Service Act (PHSA) rather than the FDCA, review and approval for biologics proceed through an investigational application and biologic license application, or BLA, based on "safety, purity, and potency."[123]

Unlike the FDCA with intricate, rigorous requirements provided within the statute itself, the PHSA provides very general language and discretion to the agency to fill in the details of BLA requirements through rulemaking or policy. Congress by legislation brought the new drug and biologic approval processes into harmonization in 1997 to require demonstrations of safety and efficacy through clinical trials and similar measures of product information submission.[124] There are important distinctions between the NDA and BLA process that are outside the scope of this article. Ultimately, a BLA is issued by the FDA after finding that product is safe, pure, and potent as assured through manufacturing practices; it also incorporates classical FDCA provisions and structures

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[119] *Center for Drug Evaluation and Research*, FDA, https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder [https://perma.cc/8ZZV-DQBF].

[120] 42 U.S.C. § 262(j). The word "protein" was added by the Biologics Price Competition and Innovation Act as part of the larger Patient Protection and Affordable Care Act. This addition is the trigger for the shifting of insulin, a protein, from regulation as a drug to regulation as a biologic. Approval Pathway for Biosimilar Biological Products, Pub. L. No. 111–148, § 7002(b), 124 Stat. 814.

[121] *What Are "Biologics" Questions and Answers*, FDA (Feb. 6, 2018), https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers [https://perma.cc/DKA5-JHD5]

[122] FDA, *supra* note 119.

[123] 42 U.S.C. § 262(a)(2)(C)(II).

[124] *See* 42 U.S.C. § 262(a) & note (2006) (Amendments).

of NDAs, including clinical trial requirements, post-market requirements, and enforcement mechanisms for violations of the statute or regulations.[125]

Biologics have enjoyed lucrative returns, with prices vastly exceeding that of small molecule drugs. In 2018, most of the top-selling therapeutic products were biologics, with Abbvie's Humira (adalimumab) grabbing the top slot with $21 billion in sales and Amgen's Enbrel (etanercept) at $7.3 billion in third.[126] As of May 2020, there are five approved biosimilar versions of Humira (adalimumab) and two for Enbrel (etanercept). The twenty-nine approved biosimilars mimic the following innovator products: Humira (six), Herceptin (five), Remicade (four), Neulasta (four), Enbrel (two), Rituxan (three), Avastin (two), Neupogran (two), and Epogen (one).[127] As noted earlier, Neulasta has responded to biosimilar competition by offering rebates to health plans in return for preferred formulary status.

As insulin is now transitioning to a biologic product, competitors will be able to pursue the biosimilar or interchangeable route to market established in the BPCIA. Biosimilar status requires that the product is "highly similar" to the reference biologic notwithstanding any minor differences in the clinically inactive components of the product and that there are no clinically meaningful differences between the two products in terms of safety, purity, and potency.[128] The heightened status of interchangeability requires that the product is biosimilar and that the product can be substituted for the reference product without intervention from the prescriber.[129] The statutory provisions again give discretion to the Secretary of the Department of Health and Human Services, delegated to the FDA, to issue guidance regarding standards and criteria and implement approval processes utilizing public comment rather than notice and comment rulemaking. This is notably divergent from the notice and comment rulemaking required in

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[125] *See* 42 U.S.C. §262(j); Public Health Service Act §351(j). ("The Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.], including the requirements under sections 505(*o*), 505(p), and 505–1 of such Act [21 U.S.C. 355(*o*), (p), 355–1], applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act.").

[126] *Top Best Selling Drugs in 2018*, BOC SCIS. BLOG (Jan. 23, 2018), https://www.bocsci.com/blog/index.php/top10-best-selling-drugs-in-2018/ [https://perma.cc/4J8M-44EC].

[127] *Biosimilar Product Information: FDA-Approved Biosimilar Products*, FDA (Dec. 17, 2020) at https://www.fda.gov/drugs/biosimilars/biosimilar-product-information [https://perma.cc/BE8W-BHHK].

[128] 42 U.S.C. §262(i)(2); Public Health Service Act §351(i)(2).

[129] 42 U.S.C. §262(i)(3); Public Health Service Act §351(i)(3).

the FDCA for implementation of new drug requirements and innovator biologic requirements.[130] On this point, one commentator offers:

> To be clear, Congress has provided that the FDA can issue extensive regulations with far-reaching economic effects over a period of ten years using only guidance-plus documents, which ostensibly have no binding legal effect. Such guidance-plus documents cannot be considered mere policy documents. Scholars and the Congressional Budget Office expect the guidances to have billion-dollar consequences. [citation omitted][131]

In addition, the statute creates a process for resolution of patent disputes distinct from the process set forth in the Hatch-Waxman Act for generic drug products. Patent protection prohibits biosimilar market entry until the patent expires or a competitor is successful in the complicated patent process laid out in the statute. Rather than a public posting of innovator patents in the Orange Book and corresponding ability to file a paragraph IV certification and force litigation of potentially invalid patents, the BPCIA lays out a private disclosure between the biosimilar and innovator biologic by which to identify potential for patent litigation and undertake the resulting actions. The FDA has implemented a "Purple Book" that simply lists approved biosimilar and interchangeable products. There is no patent information provided, nor is it information required for a BLA applicant to submit. There is a 12-year period of exclusivity provided for innovator biologics and one year of data exclusivity for the first interchangeable biologic product; biosimilars receive no exclusivity on the market.

As means to implement the BPCIA, the FDA has installed a Biosimilar Implementation Committee co-chaired by Directors of CBER and CDER that is responsible for coordination of the implementation activity; the Office of New Drugs (OND) has created Director for Biosimilars, a biosimilar review committee has been created within CDER to advise OND, and the FDA has solicited and responded to public comment across a variety of topics. Reflected in their guidance documents, the FDA has embraced a "totality of the evidence" approach to review of biosimilar and interchangeable products. The FDA has issued guidance documents on eight topics relating to the BPCIA.[132] Three

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[130] Jonathan Stroud, *The Illusion of Interchangeability: The Benefits and Dangers of Guidance -Plus Rulemaking in the FDA's Biosimilar Approval Process*, 63 ADMIN. L. REV. 599, 632 (2011).

[131] *Id.* at 633.

[132] The range of topics include questions and answers on BPCIA implementation, general scientific considerations in demonstrating biosimilarity, quality considerations in demonstrating biosimilarity to a reference protein product, clinical pharmacology data to support biosimilarity, product licensure for fewer than all conditions of use of the reference biologic product, nonproprietary naming standards, considerations in demonstrating interchangeability, and clinical immunogenicity considerations for biosimilar and interchangeable insulin products *See Biosimilars Guidances*, FDA (June 21, 2019), https://www.fda.gov/vaccines-

guidance documents are particularly relevant to insulin products. The guidance document *Nonproprietary Naming of Biological Products* sets forth the FDA's policy on the use of a four-letter suffix following the biologic established name for biosimilar products.[133] For example, the established name for Abrilada, a biosimilar version of Humira (adalimumab) is adalimumab-afzb. The guidance also provides that for interchangeable products, the agency also "intends to designate a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters."[134] However, the agency "does not intend to apply the naming convention described in the Naming Guidance to biological products that are [products originally approved as drugs and being transitioned to biologic status]."[135] This applies to insulin products, which means that any interchangeable insulin will not conform to the suffix requirement but will be subject to some yet-to-be-determined FDA naming regime. The FDA held a public meeting on the topic of the impending switch of insulin to biologics in 2019, which informed the development of the FDA's guidance.[136]

In the guidance *Considerations in Demonstrating Interchangeability*, the agency offers its perspective on the development and review of therapeutic protein interchangeable products.[137] The document offers a generally vague framework, directing industry that the agency will use a "totality of the evidence" approach in tailoring a case-by-case approach as they begin reviewing and approving interchangeable products.[138] In one significant change from the draft document that garnered attention from industry, the final guidance provides that foreign reference products may be used in interchangeability switching studies to support approval where applicants establish a scientific bridge to the reference product that is licensed in the U.S.[139] Finally, in *Clinical Immunogenicity*

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blood-biologics/general-biologics-guidances/biosimilars-guidances [https://perma.cc/68XF-EM7F].

[133] *See Nonproprietary Naming of Biological Products: Update*, FDA (Mar. 2019), https://www.fda.gov/media/121316/download [https://perma.cc/YG9Z-V3ZB].

[134] *Id.* at 1.

[135] *See* Biologics Price Competition and Innovation Act of 2009 (BPCI Act) § 7002(e)(4) (sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Pub. L. 111-148)).

[136] Zachary Brennan, *Interchangeable Insulins: FDA Holds Public Meeting* RAPS (Mar. 13, 2019), https://www.raps.org/news-and-articles/news-articles/2019/5/interchangeable-insulins-fda-holds-public-meeting [https://perma.cc/8CQC-WUP4].

[137] *Considerations in Demonstrating Interchangeability with A Reference Product: Guidance for Industry*, FDA (May 2019), https://www.fda.gov/media/124907/download [https://perma.cc/3XKH-5X6P].

[138] *Id.* at 3.

[139] Sue Sutter, *Biosimilar Interchangeability Switching Studies May Use Foreign Comparators, US FDA Says,* PINK SHEET, May 20, 2019, at 1; *Considerations in Demonstrating Interchangeability, supra* note 137.

Considerations for Biosimilar and Interchangeable Insulin Products the FDA represents its thinking on showing "whether and when comparative clinical immunogenicity studies may be needed to support licensure of proposed biosimilar and interchangeable recombinant human insulins, recombinant human insulin mix products, and recombinant insulin analog products."[140]

The U.S. has been slower to develop the pathways to market for biosimilar products than the European Union yet has taken some direction from the E.U. policy in this realm. The European Medicines Agency (EMA) has issued guidance that requires biosimilar products compare the biosimilar and the authorized reference product based on a quality, non-clinical, and clinical evaluation.[141] In addition to pharmacokinetic and pharmacodynamic studies required to demonstrate equivalence differences, the EMA also requires immunogenicity testing as a part of the approval process.[142] The EMA has issued 12 product-specific guidelines for individual classes of therapeutics[143] rather than general guidance documents that apply across all product types. Notably, both the EMA and the FDA mandate robust post-market pharmacovigilance in the evaluation of the safety and efficacy of biosimilars.[144] Due to the nature of manufacturing biosimilar insulin products, extra caution is necessary to ensure the safety and efficacy of insulin analogs, making post-market pharmacovigilance equally as important as pre-market clinical evaluations.

In general, as a result of FDA guidance, a biosimilar can be licensed once the manufacturer can demonstrate the product's safety and efficacy from chemo-physical studies, animal studies, and clinical studies including immunogenicity assessments.[145] The evaluation of biosimilars is still a case-by-case evaluation in the U.S., and thus, the process lacks standardization.[146] In the case of insulin, clinical studies will focus particularly on immunogenicity as a marker.[147] For insulin analogs, these immunogenicity studies look specifically at the

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[140] Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products: Draft Guidance for Industry, 84 Fed. Reg. 65822 (Nov. 29, 2019).

[141] H. A. Dowlat, M. K. Kuhlmann, H. Khatami & F. J. Amupudia-Blasco, *Interchangeability Among Reference Insulin Analogues and Their Biosimilars: Regulatory Framework, Study Design and Clinical Implications*, 18 DIABETES, OBESITY AND METABOLISM: A J. OF PHARMACOLOGY AND THERAPEUTICS 737, 738 (2016).

[142] *Id.*

[143] *Id.*

[144] *Id.* at 741.

[145] Heinemann & Hompesch, supra note 67, at 11.

[146] *See* Alan W. Carter, *In the Biosimilar Marketplace Will There Be 50 Ways to Leave Your Insulin?*, 10 J. DIABETES, SCI. & TECH. 1188, 1189 (2016); David R. Owens, Wolfgang Landgraf, Andrea Schmidt, Reinhard G. Bretzel & Martin K. Kuhlmann, *The Emergence of Biosimilar Insulin Preparations – A Cause for Concern?*, 14 DIABETES, TECH. & THERAPEUTICS 989, 990 (2012).

[147] Dowlat et al., *supra* note 141, at 742.

formulations of anti-insulin antibodies.[148] The biologic industry has taken issue with some of the FDA's approaches to interchangeable products, as well as with their relevant guidance documents.[149]

C. Toward Interchangeable Insulin

The FDA has not yet approved *any* interchangeable product, nor are there any true biosimilar insulins on the market.[150] Insulin interchangeability, while projected to be imminent, is at least a few years out.[151] There does seem to be some movement for biosimilar insulin thus far with several companies representing that products are in development.[152] For example, Boehringer Ingelheim has publicly disclosed that it is seeking such status for an adalimumab biosimilar product.[153] Clinical trials have begun in several hundred patients.[154] Abbvie's Humira is the biologic reference product, with its key patent set to expire in 2023.[155] By achieving interchangeability status, the product may then be substituted under state laws without prescriber involvement.[156] Each state law sets forth conditions for the substitution and there is marked variability across enacted state laws, discussed infra in Part III.

The FDA has, however, approved competitor products through the "505(b)(2)" NDA process, which is a hybrid mechanism that combines clinical trial aspects with use of publicly available third-party information to support a showing of safety and efficacy.[157] For example, the agency approved a

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[148] *Id.*

[149] Michael Mezher, *Industry Groups Debate FDA's Approach to Interchangeable Insulin Products*, RAPS, (June 5, 2019), https://www.raps.org/news-and-articles/news-articles/2019/6/industry-groups-debate-fdas-approach-to-interchan [https://perma.cc/CF7K-9P88].

[150] John White and Jennifer Goldman, *Biosimilar and Follow-on Insulin: The Ins, Outs, and Interchangeability*, 35 J. PHARMACY & TECH. 25, 25, 31 (2019).

[151] *See generally, id.* at 29, 33.

[152] *Id.*

[153] Brennan, *supra* note 1.

[154] *The VOLTAIRE-X Trial Looks at the Effect of Switching Between Humira and BI 695501 in Patients With Plaque Psoriasis*, CLINICAL TRIALS (Apr. 13, 2020), http://clinicaltrials.gov/ct2/show/NCT03210259 [https://perma.cc/KFT4-Y9MF].

[155] In re Humira (Adalimumab) Antitrust Litig., No. 19-CV-1873, 2020 WL 3051309, at *6 (N.D. Ill. June 8, 2020), *appeal docketed*, No. 20-2402 (7th Cir. July 30, 2020).

[156] *Biosimilar and Interchangeable Biologics: More Treatment Choices*, FDA (Mar. 23, 2020), https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices [https://perma.cc/HY8M-YPTS].

[157] 21 U.S.C. § 355(b)(2); FDA, CLINICAL IMMUNOGENICITY CONSIDERATIONS FOR BIOSIMILAR AND INTERCHANGEABLE INSULIN PRODUCTS: GUIDANCE FOR INDUSTRY, DRAFT GUIDANCE, (2019) https://www.fda.gov/media/133014/download [https://perma.cc/E4NT-AT8W]. The FDA noted the following in the interchangeable insulin guidance document: "FDA has approved many insulin products in NDAs submitted pursuant to section 505(b)(1)

competitor product to the insulin glargine Lantus in June 2020 using the hybrid regulatory pathway for new drugs rather than as either a generic or biosimilar.[158] The resulting product can technically be called a "follow-on product" because it references Lantus in comparative studies within its application, but it is not a biosimilar.[159] Once approved, the NDA status was immediately deemed to be BLA status given the regulatory transition.[160] The FDA also approved several other products, such as the insulin glargine Basaglar (follow-on to Lantus) in 2015 and lispro Admelog (follow-on to Humalog) in 2017, in this manner.[161]

As the FDA transitions insulin from drug to biologic regulation, the agency has made clear that none of the insulins that achieved approval as a new drug either through the full NDA process or the 505(b)(2) process will be eligible for biosimilar status without affirmative approval.[162] Given the time and expense to undertake clinical trials to demonstrate biosimilarity, many anticipate that the transition could mean at least a year delay in any kind of interchangeable product.[163] A delay, but inevitably there will be an interchangeable insulin marketplace.[164] The realized reduction in pricing is not expected to rival the price reductions that accompanied generics.[165] The price reductions for biosimilar insulin products are predicted to be between twenty to forty percent, which is a large decrease from the cost savings of the first market entry of a small-molecule generic.[166] While the market introduction of biosimilar versions of insulin will

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of 79 the FD&C Act. FDA also has approved "follow-on" insulin products in NDAs submitted pursuant to the abbreviated approval pathway described in section 505(b)(2) of the FD&C Act." *Id. See generally What is 502(b)(2)?*, CAMARGO BLOG, https://camargopharma.com/resources/what-is-505b2/ [https://perma.cc/XF2L-G3FB] (last visited Sept. 24, 2020).

[158] Brian Orelli, *Mylan and Biocon Gain FDA Approval for Insulin Equivalent to Sanofi's Lantus*, THE MOTLEY FOOL (June 12, 2020), https://www.fool.com/investing/2020/06/12/mylan-and-biocon-gain-fda-approval-for-insulin-equ.aspx [https://perma.cc/T296-ABUB].

[159] *See id.* Some sources mistakenly conflate biosimilar status with follow-on status. They are different. There are no biosimilar or interchangeable insulins listed in the Purple Book. *See generally* Purple Book search for biosimilar and interchangeable insulins., THE PURPLE BOOK, https://purplebooksearch.fda.gov/ [https://perma.cc/S2NF-YHWU] (enter query using the proprietary or nonproprietary name in the search bar to find biosimilar or interchangeable insulins).

[160] *See* DRUGS@FDA: FDA APPROVED DRUGS, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process [https://perma.cc/86F2-XERE] (last visited Sept. 24, 2020).

[161] White, *supra* note 150, at 29-30.

[162] *Id.*

[163] HEAT, *supra* note 86.

[164] White, *supra* note 150, at 29-30.

[165] *See* Heinemann, *supra* note 9, at 459.

[166] *Id.*

induce a reduction in pricing, some point out that those savings may be offset by the need for long-term post-market surveillance and other regulatory costs.[167]

III. RESTRICTING THE INSULIN INDUSTRY THROUGH STATE LEGISLATION

A. Interchangeable Biologic Substitution Laws

Once the FDA does approve an interchangeable biologic—whether insulin or another product—legislation in forty-four states establish mechanisms and requirements for substitution of the interchangeable version for the innovator biologic.[168] These state substitution laws vary in their requirements regarding key provisions such as prescriber and patient notification, record keeping, and information requirements.[169] Additionally, different state laws afford pharmacists different levels of legal immunity.[170] The BPCIA requires the FDA to approve interchangeable status and issue a license prior to allowing substitution of interchangeable products.[171]

Most of the states with interchangeable biologic substitution laws designate a role for the prescriber to determine whether to allow substitution, where the prescriber has the authority to prevent substitution by an indication on the prescription.[172] These provisions address whether and how the prescribing practitioner signals to the pharmacist that the product is not to be substituted for an interchangeable biosimilar product.[173] States vary in the means to accomplish this.[174] For example, both the Illinois and New York laws state that substitution is allowed where the prescriber "does not designate" that a substitution is prohibited;[175] Illinois's law specifically notes that this designation may be achieved "orally, in writing, or electronically."[176] North Carolina, on the other hand,

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[167] *See id.* at 461.

[168] *See generally* Richard Cauchi, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*, NATIONAL CONFERENCE OF STATE LEGISLATORS (May 3, 2019), https://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx [https://perma.cc/ZN9B-USK8]. The National Conference of State Legislators also maintains an overview and tally of these laws. *Id.* *See* Paradise, *supra* note 115, for a comprehensive early analysis of the first eight of these laws.

[169] *See* Cauchi, *supra* note 168.

[170] *See id.*

[171] *See* 42 U.S.C. § 262(i)(3).

[172] Cauchi, *supra* note 168. At least thirty-three states designate such a role for the prescriber within the express text of the law. *Id.*

[173] White, *supra* note 150, at 29-30.

[174] *Id.*

[175] 225 ILL. COMP. STAT. 85 / 19.5(b)(2) (2016); N.Y. EDUC. LAW § 6816-A (McKinney 2012).

[176] 225 ILL. COMP. STAT. 85 / 19.5(b)(2) (2016).

requires a preprinted prescription form containing two signature lines where the prescriber must sign above either "Product Selection Permitted" or "Dispense as Written."[177] Finally, at least four states do not affirmatively allow the prescriber to block substitution with a "brand medically necessary" or "do not substitute" notation.[178]

Notification provisions deal with whether the pharmacist must inform either the patient (or authorized individual presenting the prescription) or the prescribing practitioner in the event of substitution. Forty-four states with interchangeable substitution legislation have an express provision requiring notification or communication to prescribers where a substitution occurs.[179] A practitioner's ability to prohibit substitution is inherent in both the practice of medicine doctrine and the traditional respect for the doctor-patient relationship.[180] Depending on the language contained in the legislation, many argue that this aspect may prove unnecessarily restrictive to substitution and hinder cost savings.[181] The industry is divided about the implications of physician notification requirements.[182] For example, Hospira supported physician notification early on in its own capacity and on behalf of eighteen companies advocating such a position.[183] The Hospira position urges that notification alerts the treating physician to the medication switch in order to provide better subsequent care to the patient.[184] The generic drug association GPhA counters that notification will signal to patients and physicians that interchangeable biosimilar products are not the same as, or even inferior to, the brand product.[185] This position dovetails with the recent FDA-FTC collaborative effort to combat industry activities that have this anticompetitive impact.[186]

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[177] N.C. GEN. STAT. § 90.85.28(b)(2) (2015).

[178] *See* Cauchi, *supra* note 168. Idaho, Montana, Nevada, and North Carolina. *Id.*

[179] *Id.* Maine's legislation is narrow in scope and does not relate to dispensing of interchangeable products; it functions to require brand manufacturers to allow access to their drugs through sale for purposes of developing a generic drug. It's not entirely clear why the Maine statute is listed along with the other state laws here. *See id.*

[180] *See* Brian F. King, *Emerging Market for Biosimilars: State Legislation Should Reconcile Biosimilar Substitution Laws with Existing Laws on Generic Substitution*, 18 DEPAUL J. HEALTH CARE L. 31, 43 (2016).

[181] *See id.*

[182] *See id.* at 39.

[183] Brenda Sandburg, *Waiting for Biosimilars: From Manufacturing to Litigation, Stakeholders Prepare for United States Market*, THE PINK SHEET, June 16, 2014, at 19, 20. The coalition included Actavis, Amgen, Genentech, and Sandoz, among others. *Id.*

[184] *Id.*

[185] *Id.*

[186] HAHN & SIMONS, *supra* note 40.

As to the timing of the notification to the physician, twenty-three states expressly require prescriber notification within five days;[187] seven expressly require notification within three days;[188] two expressly require notification within two days;[189] and one expressly requires notification within 24 hours.[190] The remaining laws do not specify a timeframe, set a "reasonable" timeframe, or do not address prescriber notification at all.[191] States that enacted their automatic substitution provisions in 2015 or later tend to utilize the term "communication" instead of "notification," and most allow for entry of the information into electronic health records, pharmacy benefit manager (PBM) records, or pharmacy records available to the prescriber.[192] Many of the laws also provide that notification by means of telephone, facsimile, or other electronic means is acceptable.[193] These prescriber notification requirements address concerns of maintaining good pharmacovigilance practice, as do the various record-keeping requirements contained in most statutes.[194] These allow for some form of post-market surveillance of interchangeable insulins to monitor potential adverse effects and long-term safety and efficacy concerns for the particular patient, data which can then be aggregated to signal widespread adverse reactions.[195] States without record-retention and prescriber notification requirements may make monitoring adverse events related to prescription of interchangeable insulins more difficult.[196]

Beyond prescriber notification requirements and the ability of a prescriber to block substitution, some states include provisions targeted at informing patients about whether their treatment has been substituted with an interchangeable biologic.[197] Only a few state laws expressly allow the patient the right to refuse substitution after being informed of the availability of an interchangeable.[198] Nine states do not expressly require that the patient be notified of the substitution.[199] Of the states that do require patient notification, the manner of

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[187] Arizona, California, Idaho, Illinois, Iowa, Kansas, Kentucky, Louisiana, Maryland, Michigan, Minnesota, Missouri, Montana, New Jersey, New Mexico, New York, Ohio, Oregon, Rhode Island, Tennessee, Vermont, Virginia, and Washington. Cauchi, *supra* note 168.

[188] Alaska, Connecticut, Nebraska, Nevada, New Hampshire, Oregon, and Texas. *Id.*

[189] Georgia and Hawaii. *Id.*

[190] North Dakota. *Id.*

[191] *Id.*

[192] *Id.*

[193] *See, e.g.*, 225 ILL. COMP. STAT. 85/19.5(c) (2016).

[194] *See* White, *supra* note 150, at 32.

[195] *Id.*

[196] *Id.*

[197] *See, e.g.,* Texas. Cauchi, *supra* note 168.

[198] *See, e.g.,* Virginia. *Id.*

[199] Alaska, Georgia, Hawaii, Idaho, Montana, Nevada, New Jersey, New York, and North Carolina. *Id.*

notification varies: some stipulate that it must be done prior to dispensing,[200] others identify a particular source to make the notification (*e.g.*, within the electronic health record)[201] or include vague language to "inform" the patient.[202] As an offshoot of informing the patient of the substitution, some states have implemented requirements to convey the difference in cost between the originator biologic and the interchangeable or more direct cost-control requirements.[203] For instance, the enacted laws in Colorado, Georgia, Illinois, North Carolina and Texas require that any authorized or allowable substitution have a lower cost than the prescribed biologic.[204] These cost-control requirements were likely implemented to align automatic substitutions with the goal of increasing market competition.[205]

The three most relevant features of these state laws for eventual tort liability are the notification requirements to prescribers, the notification requirement to patients, and whether the prescriber can block substitution with a "brand medically necessary" or similar notation.[206] Figure 4 depicts three representative state laws for comparative purposes.

Figure 4: Select State Interchangeable Biologic Substitution Laws

State	Prescriber Notification	Patient Notification	Prescriber Substitution Block
ID[207]	Yes (5 days)	No	No
IL[208]	Yes (5 days)	Yes	Yes – may "designate that substitution is prohibited"
NC[209]	Yes (reasonable time)	No	Yes – must select "dispense as written" or "product selection permitted" line to sign

[200] *See, e.g.*, Indiana. *Id.*

[201] *See, e.g.*, California. *Id.*

[202] *See, e.g.*, New Mexico. *Id.*

[203] *Id.*

[204] *Id.*

[205] Anne Park Kim & Ross Jason Bindler, *The Future of Biosimilar Insulins*, 29 DIABETES SPECTRUM 161, 164 (2016).

[206] *See* discussion *infra* Part IV.

[207] IDAHO CODE § 54-1769 (2020).

[208] 225 ILL. COMP. STAT. 85/19.5 (2016).

[209] N.C. GEN. STAT. 90-85.28 (1982).

These three features are directly relevant to the liability of manufacturers for negligence, strict liability, and failure to warn claims.[210] Depending on the provisions within the given state law, a patient may be given an interchangeable product without their knowledge, there may be delayed notice to the prescriber of the substitution, or the complete inability of the prescriber to direct the pharmacist not to substitute, all of which could have dangerous consequences for the patient.

Because only follow-on insulins approved through the traditional NDA process have been available in markets up until this point, which are not interchangeable, patient and physician anecdotes relating to switches to biosimilar insulins are not widely available.[211] Without clear information on biosimilar and interchangeable options, patients, physicians, and pharmacists may all face confusion with an increased number of choices designated as biosimilar or interchangeable versions.[212] While most physicians (about 70%) are comfortable with the option of prescribing FDA-approved biosimilars to new patients, there are support and retraining considerations that need to be taken into consideration when switching existing patients from their current therapies to biosimilar or interchangeable insulin.[213] Physicians who have worked with established insulin markets for years may be more reluctant to switch to biosimilar insulins, especially with pending safety concerns.[214] Patients who must pay for insulin themselves support the availability of cheaper insulin.[215] One study of diabetes patient populations revealed that while most patients are open to consideration of biosimilar and interchangeable insulins, manufacturers would need to be proactive to address patient concerns about safety, efficacy, and administration of the biosimilar or interchangeable product as compared to the innovator biologic.[216]

If we return to the hypothetical patient presented at the beginning of the article, we can explore the inconsistency in outcomes depending on the provisions in the state law. As an educated and well-informed diabetic, perhaps our patient is aware that insulin is now a biologic after being transferred from drug status. They may also understand that their pharmacist cannot substitute their doctor's prescription for a generic product because there is no such thing as "generic" insulin products.[217] However, they likely do not realize that because insulin is

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[210] *See* discussion *infra* Part IV.

[211] White & Goldman, *supra* note 150, at 29-30.

[212] *See generally*, Heinemann & Hompesch, *supra* note 67.

[213] White & Goldman, *supra* note 150, at 32.

[214] Heinemann, *supra* note 9, at 461.

[215] *Id.* at 460.

[216] Alasdair R. Wilkins et al., *Patient Perspectives on Biosimilar Insulin*, 8 J. DIABETES SCI. & TECH. 23, 25 (2014).

[217] Generic drug status is demonstrated using measures of bioequivalence to the innovator reference product. For biologics, a biosimilar is measured as "highly similar" to the reference innovator biologic product. For interchangeable status, the FDA must determine that in

now a biologic, there are potentially 50 different substitution laws in place at the state level that will apply once an insulin product achieves interchangeable status.[218] Using the three state laws depicted in Figure 4 as models, the variations among them result in strikingly different outcomes for the patient.

In Illinois, the process of interchangeable substitution contains all three core requirements depicted in Figure 4: prescriber notification within a specified time period, patient notification, and the ability of the prescriber to block substitution.[219] Notably, the Illinois law also requires that for the law to apply, the product must have been licensed and met interchangeable status or the FDA must "[have] determined [the product] is therapeutically equivalent as set forth in the latest edition of or supplement to the United States Food and Drug Administration's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)."[220] The law provides that if the prescribing physician "does not designate orally, in writing, or electronically" that substitution is not allowed, the substitution may proceed.[221] The law also requires that the pharmacy "informs the patient of the substitution" yet provides no specific mechanism of communication to the patient.[222] The prescriber must be notified within five days of the substitution, including specific product and manufacturer information, through either interoperable electronic medical record system, electronic prescribing technology, a pharmacy benefit manager system, or a pharmacy record.[223] The law also allows communication through fax, phone, electronic submission, "or other prevailing means."[224]

Idaho's law provides many of the same provisions and language for notification to the prescriber, timing of notification as within five days, and alternate means of communication to the prescriber.[225] Unlike Illinois's law, however, the Idaho law provides that the prescriber cannot block substitution with a notation on the script, at least by the provisions included in the statute.[226] Also noticeably absent is any mention of notification to the patient when the pharmacist substitutes an interchangeable product.[227]

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addition to satisfying the highly similar status, the product must also be able to be substituted in the case of a patient without concern about harm. *Biosimilar and Interchangeable Products*, FDA (Oct. 23, 2017), https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#interchange [https://perma.cc/67BL-GFDT].

[218] *See* Cauchi, *supra* note 168.

[219] 225 ILL. COMP. STAT. 85/19.5 (2016).

[220] 225 ILL. COMP. STAT. 85/19.5(a)(2) (2016).

[221] 225 ILL. COMP. STAT. 85/19.5(b)(2) (2016).

[222] 225 ILL. COMP. STAT. 85/19.5(b)(3) (2016).

[223] 225 ILL. COMP. STAT. 85/19.5(c)(1)-(4) (2016).

[224] 225 ILL. COMP. STAT. 85/19.5(c) (2016).

[225] IDAHO CODE § 54-1769(1) (2020).

[226] *See* IDAHO CODE § 54-1769 (2020).

[227] *See Id.*

In North Carolina, the prescriber must be notified within a "reasonable time" of the substitution rather than a specific time frame, leaving the judgment on reasonableness up for interpretation.[228] Like both Illinois's and Idaho's laws, North Carolina's law requires the product be "determined by the United States Food and Drug Administration to meet the standards set forth in 42 U.S.C. § 262(k)(4) or deemed therapeutically equivalent by the United States Food and Drug Administration."[229] As mentioned earlier, North Carolina's law offers two choices for the prescriber regarding substitution that the prescriber must select in writing the patient script by attaching a signature over either "Product Selection Permitted" or "Dispense as Written."[230] This either-or selection requirement on the prescription paperwork prompts the physician to consider the substitution issue, whereas the Illinois law is written that the prescriber may "designate...that substitution is prohibited."[231] North Carolina's law contains no express provision for notification to the patient of the substitution. North Carolina's law also provides an example of pharmacist liability, where substitution pursuant to the law "shall impose no greater liability upon the pharmacists for selecting the dispensed drug or biologic product or upon the prescriber of the same than would be incurred by either for dispensing the drug or biological product specified in the prescription."[232]

Thus, for our hypothetical insulin patient described in Part I, the following outcomes are possible, depending on the state. In Illinois, the physician may refuse substitution and is fully informed of any substitution within a five-day timeframe, and the patient has the most complete information with which to decide upon a course of treatment.[233] The patient may affirmatively refuse the substitution and opt for the originally scripted insulin product. Coupled with the recently enacted insulin price cap law in Illinois, this is the best outcome with respect to transparency and ultimate cost. Where the patient does opt instead for the insulin prescribed, the costs will be limited to $100 per month where the patient has an individual health insurance plan.[234] See Part II.B., below, for discussion of these insulin price laws.

In Idaho, it is not expressly provided that the prescriber may prevent substitution and it is unclear whether the pharmacist will consider any notation on the script when substituting under the law.[235] Where there is substitution, the

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[228] N.C. GEN. STAT. § 90-85.28(b2) (2020).

[229] N.C. GEN. STAT. § 90-85.27(3a) (2020).

[230] N.C. GEN. STAT. § 90-85.28(b)(1) (2020).

[231] 225 ILL. COMP. STAT. 85 / 19.5 (2020).

[232] N.C. GEN. STAT. § 90-85.31 (2020).

[233] *See* 225 ILL. COMP. STAT. 85 / 19.5 (b)(2) (2020); 225 ILL. COMP. STAT. 85 / 19.5 (c) (2020).

[234] Pricing Prescription Insulin Act, Pub. Act 101-0625, 2019 Ill. Legis. Serv. 6. (West) (codified at 5 ILL. COMP. STAT. 375 / 6.11 (2020)).

[235] *See* IDAHO CODE § 54-1769(1) (2020).

prescriber must be informed of the substitution within five days.[236] However, the pharmacist is not expressly obligated to inform the patient of the substitution and thus it is also unclear what will happen if the patient attempts to opt out if and when he or she becomes aware of the interchangeable substitution.[237]

In North Carolina, the prescriber must select for one of two substitution options in writing the script, which affirmatively requires that the prescriber consider the issue of substitution.[238] If the prescriber does not indicate "dispense as written" but rather "product selection permitted", the pharmacist must notify the physician of that substitution within a vague "reasonable time."[239] It is unclear what may be deemed "reasonable" and what factors may be involved in that determination. Like Idaho, there is no express requirement that the patient be notified of the substitution.

B. Insulin Price Cap Laws

Another resulting variation in patient outcomes will be due to state insulin price cap laws, a recent addition to state legislative efforts to counter escalating costs. As of July 2020, eleven states had passed legislation capping copayments for insulin prescriptions to at or under $100/month.[240] Colorado,[241]

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[236] *Id.*

[237] *See Id.*

[238] N.C. GEN. STAT. § 90-85.28(b) (2020).

[239] *Id.;* N.C. GEN. STAT. § 90-85.28(b2) (2020).

[240] Karena Yan, *Eight States Pass Legislation to Place Caps on Insulin Price; Five More Await Ruling*, THE DIATRIBE FOUNDATION (Apr. 20, 2020), https://diatribe.org/foundation/about-us/dialogue/eight-states-pass-legislation-place-caps-insulin-price-five-more-await-ruling [https://perma.cc/9767-3FHW]; Sheryl Huggins Salmon, *Minnesota Becomes Latest U.S. State to Pass Insulin Pricing Cap,* EVERYDAY HEALTH (Apr. 20, 2020), https://www.everydayhealth.com/type-1-diabetes/new-mexico-becomes-third-us-state-to-pass-insulin-pricing-cap/ [https://perma.cc/B4YX-2UC4]; Brook Seipel, *Virginia Lawmakers Pass One of the Lowest Insulin Price Cap in Nation at $50 a Month,* THE HILL, https://thehill.com/policy/healthcare/486419-virginia-lawmakers-pass-lowest-insulin-price-cap-in-nation-at-50-a-month [https://perma.cc/PY87-4885]; Press Release, American Diabetes Association, Co-Pays For Insulin and Diabetes Medication Capped at $25 in Connecticut (Aug. 6, 2020), https://www.diabetes.org/newsroom/press-releases/2020/co-pays-for-insulin-and-diabetes-medications-capped-at-25-in-CT [https://perma.cc/HT3W-Z658].

[241] COLO. REV. STAT. § 10-16-151(2) (2020).

Connecticut,[242] Illinois,[243] Maine,[244] Minnesota,[245] New Mexico,[246] New York,[247] Utah,[248] Virginia,[249] Washington,[250] and West Virginia[251] all have policies capping prices, while Florida,[252] Kentucky,[253] and Tennessee[254] have introduced legislation to do the same. Many of these states not only elected to place a cap on cost-sharing for insulin, but also extended the coverage to other necessities for patients with diabetes, such as glucose monitors and test strips. Additionally, a few have directed that studies be conducted on the effect of the legislation on prescription drug pricing. Figure 5, below, provides a short summary of the state legislation.

Figure 5: Insulin Price Caps by State

State	Prescription limits	Applicability	Enforcement & Penalties	Effective
CO[255]	$100 for a 30-day supply and $300 for a 90-day supply (per prescription)	All carriers marketing and issuing health coverage plans with insulin coverage and	- Civil penalties - cease and desist orders	Apr. 15, 2020

[242] Act Concerning Diabetes and High Deductible Health Plans, Pub. Act 20-4, 2020 Conn. Acts 32 [Spec. Sess] (to be codified at CONN. GEN. STAT. § 38a-492d (2022)).

[243] Pricing Prescription Insulin Act, Pub. Act 101-0625, 2019 Ill. Legis. Serv. 6. (West) (codified at 5 ILL. COMP. STAT. 375 / 6.11 (2020)).

[244] Act of Mar. 18, 2020, ch. 666, 2020 Me. Laws 1812 (codified at ME. STAT. tit. 24-9 § 4317-C (2020)).

[245] Alec Smith Insulin Affordability Act, ch. 73, sec. 4, 2020 Minn. Sess. Laws Serv. 4 (West) (codified at MINN. STAT. § 151.74 (2020)).

[246] Act of Mar. 4, 2020, ch. 36, 2020 N.M. Legis. Serv. 36 (West) (to be codified at N. M. STAT. §59A-22-41 (2020)).

[247] Act of Jan. 22, 2020, ch. 56, 2020 N.Y. Laws 34 (to be codified at N.Y. INS. Law § 3216 (McKinney 2021)).

[248] Insulin Access Act, ch. 67, 2020 Utah Laws 310 (to be codified at UTAH CODE ANN. § 31A-22-626 (LexisNexis 2021)).

[249] Act of Apr. 8, 2020, ch. 881, 2020 Va. Legis. Serv. 1 (West) (codified at VA. CODE ANN. § 38.2-3407.15:5 (2020)).

[250] Act of Mar. 31, 2020, ch. 245, 2020 Wash. Sess. Laws 1774 (to be codified at WASH. REV. CODE § 48.43.0003 (2021)).

[251] Act of Mar. 7, 2020, ch. 2020, W. Va. Acts 2 (codified as W. VA. CODE § 5-16-7g (2020)).

[252] S.B. 116, 2020 Leg., Reg. Sess. (Fla. 2020).

[253] H.B. 12, 2020 Leg., Reg. Sess. (Ky. 2020).

[254] S.B. 1718, 2020 Leg., Reg. Sess. (Tenn. 2020).

[255] 3 COLO. CODE REGS. § 702-4:4-2-68 (LexisNexis 2020).

State	Prescription limits	Applicability	Enforcement & Penalties	Effective
		HSA plans (not including catastrophic or grandfathered)	- suspension/revocation of license	
IL[256]	$100 for a 30-day supply of insulin, test strips, and oral agents to control blood sugar	Plans that apply to a group or individual policy of accident and health insurance	Enforced by the department of insurance	Jan. 1, 2021
ME[257]	$35 cap for a 30-day supply of insulin	Any plan that provides coverage of insulin drugs after January 1, 2021.	None specified	Jan. 1, 2021
MN[258]	$35 for a 30-day supply, manufacturer programs limiting co-pays to $75 for a 30-day supply for families making below 400% of the Federal Poverty Line	Requires insulin makers to provide emergency insulin free of charge	$200,000/month for manufacturers who do not comply	July 1, 2020
NM[259]	$25 cap for 30-day supply	"Each individual and group health plan, certificate of health insurance, and	Enforcement by superintendent	Jan. 1, 2021

[256] Pricing Prescription Insulin Act, Pub. Act 101-0625, 2019 Ill. Legis. Serv. 6. (West) (codified at 5 ILL. COMP. STAT. 375 / 6.11 (2020)).

[257] H. P. 1493, 129 Leg., 2nd Reg. Sess. (Me. 2020), 2020 Me. Laws 1812 (codified at ME. REV. STAT. ANN. tit. 24-a § 4317-C (West 2020)).

[258] Alec Smith Insulin Affordability Act, ch. 73, sec. 4, 2020 Minn. Sess. Laws Serv. 4 (West) (codified at MINN. STAT. § 151.74 (2020)).

[259] Prescription Drug Cost Sharing Act, ch. 36, 2020 N.M. Legis. Serv. 1 (West) (to be codified at N. M. STAT. ANN. §59A-22-41 (2021)).

State	Prescription limits	Applicability	Enforcement & Penalties	Effective
		managed health care plan."		
NY[260]	$100 cap for 30-day supply	State-regulated commercial plans	Enforcement by superintendent	Jan. 1, 2021
UT[261]	$30 per prescription of a 30-day supply	State-regulated health and accident plans	None specified	Jan. 1, 2021
WA[262]	$100 cap for 30-day supply	All health benefit plans that cover insulin, and other necessary devices	None specified	Jan. 1, 2021
WV[263]	$100 cap for 30-day supply	Policy, plan, or contract issued or renewed on or after July 1, 2020	None specified	Jan. 1, 2021

Colorado's statute requires carriers to limit copayments for prescription insulin drugs to $100 for a 30-day supply and $300 for a 90-day supply.[264] Effective April 1, 2020, this regulation applies to: "all carriers marketing and issuing health coverage plans that provide coverage for prescription insulin drugs in the State of Colorado issued or renewed on or after January 1, 2020"; and to Health Saving Account-qualified (HSA-qualified) high deductible health plans, not

[260] Act of Jan. 22, 2020, ch. 56, 2020 N.Y. Laws 34 (codified at N.Y. INS. LAW § 3216 (McKinney 2021)).

[261] Insulin Access Act, ch. 67, 2020 Utah Laws 310 (codified at UTAH CODE ANN. § 31A-22-626 (LexisNexis 2021)).

[262] Act of Mar. 31, 2020, ch. 245, 2020 Wash. Sess. Laws 1774 (to be codified at WASH. REV. CODE § 48.43.0003 (2021)).

[263] Act of Mar. 7, 2020, ch. 2020, W. Va. Acts 2 (codified as W. VA. CODE § 5-16-7g (2020)).

[264] COLO. CODE REGS. § 702-4:4-2-68 (2020) (allowing insurers to charge $100 per prescription, not per month).

including catastrophic plans or grandfathered health benefit plans.[265] The statute also identifies enforcement mechanisms, including civil penalties, cease and desist orders, and suspension or revocation of license.[266]

The Minnesota statute, the Alec Smith Insulin Affordability Act, is significantly more specific. The bill sets an eligibility standard for patients requiring that individuals are not enrolled in medical assistance or in prescription drug coverage that limits the total amount of cost sharing that the enrollee is required to pay for a 30-day supply to $75 dollars or less.[267] The bill caps insulin copayments for eligible patients at $35 for a 30-day supply.[268] The law also places restrictions on manufacturers, requiring manufacturers to make their patient assistance programs available to any individual who has a family income of less than 400% of the federal poverty guidelines and is not enrolled in prescription drug coverage that limits insulin copayments to $75 or less.[269] There is a $200,000 penalty on manufacturers making over $2 million in profits for noncompliance.[270] This bill, which went into effect on July 1, 2020, is currently the subject of a lawsuit filed by PhRMA.[271] Manufacturers allege that the law allows the state to "commandeer private property for its public policy goals" without just compensation.[272]

The remaining eight laws effective January 1, 2021 share similar features, as noted in Figure 5. The Illinois statute requires an insurer that provides coverage for prescription insulin to limit the total amount that an insured is required to pay for a 30-day supply of covered prescription insulin drugs, test strips, and oral agents to control blood at an amount not to exceed $100, regardless of the quantity or type of covered prescription insulin drug used to fill the insured's prescription.[273] Plans that apply to a group or individual policy of accident and health insurance amended, delivered, issued, or renewed on or after January 2021 must adhere to this act.[274] The law also requires states to monitor and create a report of findings to gauge what works and what does not.[275]

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[265] *Id.*

[266] *Id.*

[267] Alec Smith Insulin Affordability Act, ch. 73, sec. 4, 2020 Minn. Sess. Law Serv. 3 (West) (codified at MINN. STAT. §151.74 (2020)).

[268] *Id.*

[269] *Id.*

[270] *Id.*

[271] Alicia Ault, *Big Pharma Sues to Block Minnesota Insulin Affordability Law*, RXLIST (July 3, 2020), https://www.rxlist.com/script/main/art.asp?articlekey=239205 [https://perma.cc/7PKH-K7D2].

[272] *Id.*

[273] Pricing Prescription Insulin Act, Pub. Act 101-0625, 2019 Ill. Legis. Serv. 6. (West) (codified at 5 ILL. COMP. STAT. 375 / 6.11 (2020)).

[274] *Id.*

[275] *Id.*

Maine's law bars carriers that provide coverage for prescription insulin drugs from imposing any deductible, copayment, coinsurance or other cost-sharing requirement on an enrollee that results in an out-of-pocket cost to the enrollee that exceeds $35 per prescription for a 30-day supply of covered prescription insulin drugs, regardless of the amount of insulin needed to fill the enrollee's insulin prescriptions.[276] The enacted statute was deemed effective on March 31, 2020 and covers all policies, contracts and certificates executed, delivered, issued for delivery, continued or renewed in this State on or after January 1, 2021.[277]

The New Mexico statute requires each individual and group health plan, certificate of health insurance, and managed health care plan in the state of Mexico to provide coverage for individuals with insulin and non-insulin-using diabetes and patients with elevated blood glucose levels induced by pregnancy.[278] The statute caps the amount an individual with diabetes is required to pay for a preferred formulary prescription insulin drug or a medically necessary alternative at $25 for a thirty-day supply.[279] The scope of the coverage, like that in Maine, extends beyond insulin to other equipment like blood glucose test strips for monitors, injection aids, and even oral agents for controlling blood sugar levels.[280] In addition, the statute lists basic health benefits that the patient covered by a qualifying insurance plan is required to receive.[281] These include group health plans, forms of self-insurance, and plans renewed under the Health Care Purchasing Act.[282] The Act also requires the superintendent to convene an advisory committee for the creation of a report entailing an update on the benefits and potential costs of cost-sharing provisions for New Mexico residents to be submitted to the legislature.[283]

The New York law tackles caps cost-sharing for prescription insulin at $100 for a 30-day period[284] and applies cap regardless of the amount of insulin necessary to fill the prescription.[285] The statute also allows the Superintendent of Insurance to investigate certain prescription drug price increases of more than 50% over a 12-month period that results in an increase greater than $5 per unit and

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[276] Act of Mar. 18, 2020, ch. 666, 2020 Me. Laws 1812 (to be codified at ME. STAT. tit. 24-A, § 4317-C (2021)).

[277] *Id.*

[278] Prescription Drug Cost Sharing Act, ch. 36, 2020 N.M. Legis. Serv. 1 (West) (to be codified at N.M. STAT. § 59A-22-41 (2020)).

[279] *Id.*

[280] *Id.*

[281] *Id.*

[282] *Id.*

[283] *Id.*

[284] Act of Apr. 3, 2020, ch. 56, 2020 N.Y. Laws 343 (to be codified at N.Y. INS. LAW § 3216 (McKinney 2021)).

[285] *Id.*

communicate the results to the newly created drug accountability board.[286] This board, like the advisory committee in New Mexico, will evaluate and report to the Superintendent on a drug's impact on premium costs, affordability, and price compared to therapeutic benefit.[287] This statute amended the insurance law, and thus covers state-regulated commercial plans.[288]

Utah's law provides incentives for health benefit plans to reduce insulin co-pays by directing the Public Employees' Benefit and Insurance Program to purchase insulin at discounted prices and to create a program that allows individuals covered under a Utah health plan to purchase the discounted insulin.[289] Additionally, the statute caps the co-pays for insulin at $30 per prescription.[290] The statute also specifies that the cap is to be in effect regardless of whether the insured has met the deductible – a notable difference from other plans.[291] Like other states, Utah also provides coverage for diabetes self-management and commissions the Insurance Department to conduct a study on insulin pricing.[292] The scope of this program does not expressly require cost-sharing other than a co-payment of an insured before the plan will cover insulin at the lowest tier, and also excludes state-sponsored plans.[293]

The Washington law caps the total amount that an enrollee is required to pay for a covered insulin drug at an amount not to exceed $100 per thirty-day supply of the drug.[294] This subsection of the bill covers all health benefit plans that cover insulin, and other necessary devices.[295] The statute commissions a work group to discern strategies to reduce the cost of and total expenditures on insulin for patients, health carriers, payers, and the state before the statute goes into effect.[296] The West Virginia law caps the total amount that an insurer can require a covered patient with diabetes to pay for a 30-day supply of insulin at $100, regardless of the quantity or type of insulin needed to fill the person's needs.[297]

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[286] *Id.*

[287] *Id.*

[288] *Id.*

[289] Insulin Access Act, ch. 67, 2020 Utah Laws 310 (to be codified at UTAH CODE ANN. § 49-20-420 (LexisNexis 2020)).

[290] *Id.*

[291] *Id.*

[292] *Id.*

[293] *Id.*

[294] Act of Mar. 31, 2020, ch. 245, 2020 Wash. Sess. Laws 1774 (to be codified at WASH. REV. CODE § 48.43.0003 (2021)).

[295] Act of Mar. 31, 2020, ch. 245, 2020 Wash. Laws 1775 (to be codified at WASH. REV. CODE § 48.20.391 (2021)).

[296] Act of Mar. 31, 2020, ch. 346, 2020 Wash. Laws 2609 (to be codified at WASH. REV. CODE § 70.14.002 (2021)).

[297] Act of Mar. 7, 2020, ch. 2020, W. Va. Acts 2 (codified as W. VA. CODE § 5-16-7g (2020)).

The law also prohibits a manufacturer, wholesaler, or PBM from passing on the costs of prescribed insulin to the pharmacist or pharmacy.[298] This law only specifies that a policy, plan, or contract that is issued or renewed on or after July 1, 2020 must provide coverage for prescription insulin drugs, however, does not specify specifically what health plans will be governed by the law.[299] Finally, the Virginia legislation simply limits costs sharing for Virginians to $50 for a 30-day supply for patients with state-regulated commercial insurance.[300]

IV. FRAMING LIABILITY: STATE TORT LAW AND FEDERAL PREEMPTION

Drugs, biologics, and medical devices raise confounding liability issues for several reasons, the most obvious one being that most of these products may not be sold without prior government approval.[301] Congress has given the FDA the authority to weigh the risks against the benefits of new drugs and biologics, or of certain types of devices, before approving them for the market.[302] This raises the question of when, if ever, a manufacturer should be liable for harms caused by properly manufactured FDA-approved products. Another characteristic of drugs and biologics is that they can be inherently dangerous, even when properly used, but they can also provide significant, even lifesaving, medical benefits.

Several core questions have framed the case law in the realm of state tort liability for harm caused by drugs, biologics, and medical devices. Should a drug manufacturer be liable at all for harm from a product approved by the FDA if the potential harm was identified on the FDA's approved labeling? What if the physician did not advise the patient of the potential risk during the informational counseling process? What if the harm to the patient is one that was not discovered during a clinical trial because it arose only after several years of product use? What if the company failed to analyze its post-market adverse events reports and as a result did not realize the drug was causing problems after long-term usage?

All three product areas (drug, biologic, device) are implicated with insulin, as it is being transitioned from a drug to a biologic, and products will often be "combination products" under FDA regulations including a medical device delivery component.[303] The Supreme Court has squarely addressed federal preemption in the context of both drugs and medical devices, though not

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[298] *Id.*

[299] *Id.*

[300] Act of Apr. 8, 2020, ch. 881, 2020 Va. Legis. Serv. 1 (West) (codified at VA. CODE ANN. § 38.2-3407.15:5 (2020)); *see also* Alex Day, *Virginia Caps Insulin Co-Pays at $50 for Virginians with Diabetes*, AM. DIABETES ASS'N (Apr. 24, 2020), https://www.diabetes.org/newsroom/press-releases/2020/insulin-co-pays-virginia [https://perma.cc/AX2H-MVNY].

[301] 21 U.S.C. § 355(a).

[302] 21 U.S.C. § 355(d).

[303] 21 U.S.C. § 353(g)

biologics. There is lower court variation on both the question of federal preemption for biologics and how the preemption analysis is undertaken when dealing with a combination product (*e.g.*, a drug-device, drug-biologic, biologic-device, or all three). Also unclear is what the transition from drug to biologic status means for preemption purposes.

Products liability claims against manufacturers of FDA-regulated products can be divided into three general categories: claims alleging that a product was produced with a manufacturing defect, claims alleging that the product was defectively designed, and claims alleging that the product was accompanied by inadequate warnings. Manufacturing defect claims are possible when a specific product comes out of the factory with an unintended flaw—for example, pills that were inadvertently mixed with poisonous adulterants. In these cases, the manufacturer will be strictly liable for any resulting injuries, regardless of how much care it took to ensure the product's safety.[304]

Design defect claims challenge the way the manufacturer chose to develop the entire product line. In general, products can be considered defectively designed when an alternative, cost-effective design exists that would have prevented the injury. However, design defect claims involving drugs and biologics are rarely successful. Some courts have ruled that design defect liability is never appropriate because these products are "unavoidably unsafe"; in other words, that there is simply no way to make them safer without compromising their utility. The Third Restatement of Torts recognizes only one circumstance in which design defect liability would be appropriate for drugs: when "reasonable healthcare providers, knowing of [the product's] foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients."[305] It is hard to imagine this standard being satisfied for any drug or biologic that has received FDA approval. Even drugs with serious safety warnings, such as the diabetes drug Avandia, continue to be prescribed for limited groups of patients who have not benefited from alternative treatments.[306]

The final theory of liability, inadequate warnings or failure to warn, accounts for most products' liability cases against drug, biologic, and medical device manufacturers. In an inadequate warning claim, the plaintiff alleges that her injuries were due to a risk in the product that the manufacturer should have disclosed in its labeling. The assumption behind these claims is that if the risk had been disclosed, the plaintiff would have decided not to take the drug or use the device, thereby avoiding the injury. Most courts agree that the manufacturer will

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[304] RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 2(A) (CMT. A) (AM. L. INST. 1998).

[305] *Id.*

[306] *See* Lisa Rappaport, *Heart Risks from Diabetes Drug Avandia Confirmed in New Study*, EVERYDAY HEALTH (Feb. 10, 2020), https://www.everydayhealth.com/type-2-diabetes/heart-risks-from-diabetes-drug-avandia-confirmed-in-new-study/ [https://perma.cc/AHJ8-MDZG].

not be liable for failure to warn of unknowable risks or failing to anticipate scientific advances. Manufacturers do have a duty to track new scientific developments or new information about risks attendant to the use of their products, and to so advise prescribers.[307] The developing ability of manufacturers to mine medical records for post-market information about products will likely greatly affect this duty, and manufacturers' ability to fulfill it. While manufacturers are not required by tort law to advise prescribers of risks compared to other products, this may change if comparative effectiveness gains traction in the United States.

Manufacturers may not actively market their products for any uses other than those listed on the FDA-approved labeling, but physicians are free to prescribe them for non-approved purposes, a practice known as "off-label" prescribing.[308] In some cases, off-label uses may represent the standard of care and may be reimbursed by both governmental and private third-party payers.[309] Courts are split on the question of whether manufacturers have a duty to warn with respect to the risks of common off-label uses.[310] Liability for failure to warn is most likely where the manufacturer encouraged or knew about the off-label use.[311] Promotional activities can undermine an otherwise adequate warning if they downplay risks, over-emphasize benefits, or otherwise encourage physicians to discount risks discussed in product warnings.[312] This can also occur when a company representative is present during the physician's conversation with a patient.[313] Case law regarding off-label promotion practices and the authority of the FDA to prohibit them is in flux,[314] with the FDA increasingly entering into settlement agreements with industry rather than proceeding through litigation.[315]

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[307] 21 U.S.C. § 355(o)(4).

[308] CONG. RSCH. SERV., R45792, OFF-LABEL USE OF PRESCRIPTION DRUGS, 2 (2019).

[309] *Id.* at 11.

[310] James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 300, 315-316 (2003).

[311] *Id.*

[312] *Id.*

[313] *Id.*

[314] *See* United States v. Caronia, 703 F.3d 149, 168-169 (2d Cir. 2012); United States v. Vascular Solutions, Inc. 181 F. Supp. 3d 342, 346 (W.D. Tex. 2016).

[315] *See* Amarin Pharma, Inc. v. U.S. Food & Drug Admin., 119 F. Supp. 3d 196 (S.D.N.Y. 2015); Press Release, Department of Justice, Par Pharm. Pleads Guilty and Agrees to Pay $45 Million (March 5, 2013), https://www.justice.gov/opa/pr/par-pharmaceuticals-pleads-guilty-and-agrees-pay-45-million-resolve-civil-and-criminal [https://perma.cc/775W-7PWP]. The Par settlement and corporate integrity agreement, dated March 5, 2013, involved $22.5 million (civil) and $22.5 million (criminal) fines. *Id. See also* Press Release, Pacira Biosciences, Inc., Pacira Pharm. Announces Favorable Resolution (Dec. 15, 2015), https://investor.pacira.com/news-releases/news-release-details/pacira-pharmaceuticals-announces-favorable-resolution-us-food [https://perma.cc/8K4K-8UW5]. The *Pacira* settlement involved a

A. Medical Devices

An exhaustive analysis of the case law regarding the application of federal preemption concepts in the drug and medical device context is unnecessary here. Countless scholars have explored the matrix of Supreme Court decisions that frame the bounds of preemption. It is a complex web of express and implied preemption and the role of FDA regulations. This section provides a summative discussion of the relevant cases in order to explore the challenges in the biologic realm.

For medical devices, Congress included an express preemption provision in the Medical Device Amendments to the FDCA, providing that a state cannot have a law regarding medical devices:

> (1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter.[316]

Because so many states had laws that applied to the safety of medical devices at the time of enactment of the 1976 Medical Device Amendments to the federal FDCA, Congress wanted to ensure that federal law prevailed over these state laws. Two Supreme Court cases establish that medical devices that undergo extensive FDA review and approval via the premarket approval (PMA) process involving rigorous clinical trials are subject to federal preemption of state tort laws; on the other hand, medical devices that enter the market through FDA's "clearance" process based on substantial equivalence (a comparative assessment) rather than approval are not subject to federal preemption of state tort liability.[317]

The foundation 1996 Supreme Court case of *Medtronic v. Lohr* held that the statute did not preempt state law where the device at issue entered the market through the 510(k) clearance process, which simply determines whether the device is substantially equivalent to one already on the market.[318] The Court grounded this decision in the statutory language, in that the 510(k) process does not "relate[]" to "the safety or effectiveness" of a medical device because it relates specifically to substantial equivalence rather than the safety and efficacy as

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rare FDA "recession letter" dated December 15, 2015 to rescind language contained within an issued Warning Letter from the agency. *Id.*

[316] Federal Food, Drug, & Cosmetic Act (FDCA) § 521, 21 U.S.C. § 360k(a) (2014).

[317] Riegel v. Medtronic, Inc., 552 U.S. 312, (2008); Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996).

[318] Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996). The "510(k)" refers to the section of the Food, Drug & Cosmetic Act that sets forth the clearance process, requiring certain manufacturers to submit a premarket notification to the FDA prior to introducing their products into the market. Federal Food, Drug, & Cosmetic Act (FDCA) §510(k), 21 U.S.C. §§ 360(k), 360(n), 360c(f)(1), 360c(i) (2014).

measured through clinical trials.[319] Twelve years later, the Court decided another device case which involved a device that had undergone the FDA's premarket approval (PMA) process, including an evaluation of safety and effectiveness based on clinical trials.[320] In *Riegel v. Medtronic*, the Court concluded that the FDCA preempted state tort law claims when a PMA device was at issue.[321] The differences between these two cases lie in the statutory language of the express preemption clause. Simply stated: if the device entered the market after FDA approval through the PMA process, the express preemption clause applies because any state law relating to "requirements" of "safety or efficacy" would be "different from" the federal requirements; if the device entered the market through after being declared substantially equivalent to an existing product, the express preemption clause does not apply because the clearance process does not assess safety or efficacy or mandate product-specific requirements but only general, standardized controls over manufacturing and labeling.

There is developing litigation in the lower courts regarding medical devices with multiple component parts that add an additional layer to the preemption analysis. One recent case in the U.S. District Court for the District of Columbia is instructive on this point in the insulin context.[322] Plaintiffs brought a variety of claims against the manufacturer of an insulin infusion pump.[323] The court dismissed many of the claims, but the negligence, strict liability, breach of express warranties, and failure to warn claims survived dismissal.[324] The insulin infusion pump was approved as a product to continuously or intermittently administer insulin to the user based on the product's monitoring and feedback system.[325] The product consisted of a small syringe in the pump connected to the patient via cannula; accompanying electronics and algorithms calculate the dosages necessary over the course of the day.[326] Plaintiff alleged a product malfunction left her unresponsive in a coma due to a hypoglycemic episode and resulted in severe and persistent brain injury requiring constant care.[327] The court offered no conclusion on the issue of preemption in the process of declining to dismiss the claims, but did note that the infusion pump had entered the market as a Class III PMA device, thus raising the question of whether the express preemption

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[319] *Lohr*, 518 U.S. at 500.

[320] *Riegel*, 552 U.S. 312 (2008).

[321] *Id.* at 312.

[322] Kubicki *ex rel.* Kubicki v. Medtronic, No. 12-00734 CKK, 2013 WL 1739580 at *9-10 (D. D.C., March 21, 2013).

[323] *Id.*

[324] *Id.*

[325] *Id.* at *1.

[326] *Id.*

[327] *Id.*

provision applies in this situation.[328] The opinion also emphasized that "the FDA granted premarket approval to the *entire* device."[329]

A 2018 Third Circuit case explored a medical device product described as a "hybrid" implanted hip replacement system, comprised of medical device components that were assessed independently from each other by the FDA either as a Class II cleared component or Class III PMA components.[330] When the separately reviewed and approved or cleared products were implanted together, they made up the entirely of the patient's hip replacement system.[331] The court stated "[t]he question of first impression we confront today arises at the intersection of these different classes of devices with their different approval schemes: How do we apply the Medical Device Amendments' express preemption provision to a 'hybrid system,' i.e., a system that is itself a 'device' but that is comprised of Class II components in addition to one or more Class III components?"[332] There, the court held that the malfunctioning part (the metal liner mediating the connection between the hip socket and thighbone) was to be assessed based on its route to market, *i.e.* the PMA pathway.[333] Thus, the express preemption provision applied to preempt state tort liability claims.[334]

On the other hand, an earlier Massachusetts district court case arose from injuries resulting from an insulin pump and continuous glucose monitoring system manufactured by Medtronic.[335] The Plaintiffs claimed the pump was defective and that its malfunction caused a hypoglycemic reaction resulting in injury.[336] There, the court found that because the entire product was granted FDA approval with specific requirements regarding safety and efficacy applicable to that device, rather than individual components evaluated on differing statutory and regulatory bases, the state tort claims were preempted.[337] There was no need to focus on which component was at fault because the product had been assessed and approved as a whole.[338] The court made this determination both on the express preemption provision in the statute and a letter received by Medtronic from the

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[328] *Id.* at *8.

[329] *Id.* at *5.

[330] Shuker v. Smith & Nephew, PLC, 885 F.3d 760, 772 (3d Cir. 2018).

[331] *Id.* at 768.

[332] *Id.* Class II medical devices are subject to the 510(k) clearance process, while Class III products may be subject to the premarket approval (PMA) process. *Id.* at 764.

[333] *Id.*

[334] *Id.* at 775.

[335] Duggan v. Medtronic, Inc., 840 F. Supp. 2d 466, 468 (D. Mass. 2012).

[336] *Id.* The plaintiffs' claims included negligence, breach of implied warranty of merchantability, breach of implied warranty of fitness for a particular purpose, unfair and deceptive acts or practices in violation of Massachusetts law, and loss of consortium. *Id.*

[337] *Id.*

[338] *Id.* at 471.

FDA which indicated that the approval was given to the entire product.[339] In response to a citizen's petition by the plaintiff to the FDA, the agency had made it clear that the PMA was granted for the entire system, not just the pump and monitor components.[340] In deciding the case, the District Court walked through the analysis set forth in *Riegel v. Medtronic*.[341]

B. Drugs

Congress did not include an express preemption provision in the FDCA for drugs. The original 1906 federal law and subsequent amendments set forth robust requirements for assuring the safety and efficacy of drug products, predating the federal medical device provisions by decades. The Supreme Court has instead applied implied preemption precedent,[342] coupled with application of the FDA's own regulations about label changes to approved drugs, to address liability for failure to strengthen a label's warning in this realm.[343] The FDA regulation provides that the holder of an approved drug can implement certain changes following submission of a supplement to the agency, typically called a "Changes-Being-Effected 0" or CBE-0 supplement. The "0" denotes the immediacy with which the change can be made, as there is a zero day wait for implementing the change.[344] The FDA may disapprove the supplemental application containing the label change and will then order the manufacturer to cease distribution of the drug products that display the change.[345] Changes amendable to the CBE-0 process include:

> (i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have

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[339] *Id.*

[340] *Id.*

[341] *Id.* at 469; Riegel v. Medtronic, Inc., 552 U.S. 312 (2008).

[342] Implied preemption occurs in the absence of an applicable express preemption clause, where the federal and state laws are nonetheless incompatible. There are several different forms of implied preemption. Implied field preemption arises when the scope of a federal statute is so broad as to indicate a Congressional intent to occupy the whole field, or exclusively regulate the subject matter at issue. Implied conflict preemption arises in a couple of circumstances. One circumstance of conflict preemption occurs when it is impossible to comply with both state and federal law. That is, they demand contradictory actions that cannot be simultaneously achieved. The second situation of implied conflict preemption arises when adherence to state law will disrupt policy goals underlying federal law. This form of preemption is sometimes referred to as implied obstacle preemption. *See generally*, CONG. RSCH. SERV., R45825 FEDERAL PREEMPTION: A LEGAL PRIMER (2019).

[343] 21 CFR §314.70 (2019).

[344] The FDA also has a "CBE-30" designation for changes that require 30-day lead time. 21 CFR §314.70(c)(3) (2019).

[345] 21 CFR §314.70(c)(7) (2019).

> the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;
>
> (ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;
>
> (iii) Changes in the labeling to reflect newly acquired information, except for changes to the information required in 201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:
>
> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under 201.57(c) of this chapter;
>
> (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;
>
> (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
>
> (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or
>
> (E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.[346]

The outcome of Supreme Court preemption cases for drug products is deeply unsatisfying and problematic from a public health standpoint. Essentially, the ability of a patient to bring a state tort claim against a drug manufacturer based on theories of failure to warn, breach of implied warranty, negligence, and design defect turns on whether that drug entered the market as a new, innovator drug or as a generic version based on measures of bioequivalence to the innovator drug.[347] In *Wyeth v. Levine*, the Supreme Court held that state failure to warn claims were not preempted for innovator drugs, meaning that there was no implied conflict preemption, because innovator drugs approved through the new drug approval process had the power to make changes to the product label to strengthen a warning without FDA approval under the regulation.[348] In both *PLIVA v. Mensing*, involving the failure of a generic manufacturer to change its label to reflect a new side effect,[349] and *Mutual Pharmaceutical v. Bartlett*, involving a design defect claim for a generic drug, the Supreme Court found implied conflict preemption existed.[350]

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[346] 21 CFR §314.70(c)(6) (2019).

[347] *See* 21 U.S.C. §355(j)(2)(A)(iv).

[348] Wyeth v. Levine, 555 U.S. 555, 555 (2009).

[349] PLIVA, Inc. v. Mensing, 564 U.S. 604, 625-626 (2011).

[350] Mutual Pharmaceutical Co. v. Bartlett, 570 U.S. 472, 472 (2013).

In *PLIVA*, specifically, the Court determined that a private party could not comply with the state law without first obtaining the approval of a federal regulatory agency and, therefore, it was preempted.[351] The conflict was grounded in the fact that generic drug labels are required by both federal statute and regulations to be identical in form to the brand drug label under the statute.[352] Thus, the regulation as written did not apply to generic drugs. The Supreme Court expressly calls out this problem in *PLIVA*, and nudges either the FDA or Congress to address it. The decision states "[f]ollowing [the] argument to its logical conclusion, it is also possible that, by asking, the Manufacturers could have persuaded the FDA to rewrite its generic drug regulations entirely or talked Congress into amending the Hatch-Waxman Amendments."[353] Subsequent to the case, several legislative bills were introduced but were never enacted.[354]

The FDA also issued a notice of proposed rulemaking in November of 2013 to amend the regulation to also apply to generic drugs.[355] The FDA acknowledged that the proposed rule would alter the long-standing policy that the labeling of generics must be identical to the reference drug product but noted a change in circumstances necessitating the revision to the regulation.[356] The comment period closed March 13, 2014[357] and the FDA has since rescinded the proposal rule as a result of backlash from the generic drug industry and Congress. Twenty-eight members of Congress signed a letter to the FDA, offering "grave

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[351] *PLIVA*, 564 U.S. at 624.

[352] 21 U.S.C. §355(j)(2)(A). The statute requires the generic drug to have labeling "the same as the labeling approved for the listed drug." §355(j)(2)(A)(v). In addition to labeling having to be the same, so also does the active ingredient, route of administration, dosage form, and strength of the product. §355(j)(2)(A)(ii) & (iii).

[353] *PLIVA*, 564 U.S. at 621.

[354] *See., e.g.,* Patient Safety and Generic Labeling Improvement Act, S. 2295, 112th Cong. (2012).

[355] Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67985 (proposed Nov. 13, 2013). The FDA took five years to finally abandon the effort by withdrawing the proposed rule in December 2018. Withdrawal of Proposed Rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 83 Fed. Reg. 64299 (Dec. 14, 2018). The FDA's effort included a Regulatory Impact Analysis. FDA, SUPPLEMENTAL APPLICATIONS PROPOSING LABELING CHANGES FOR APPROVED DRUGS AND BIOLOGICAL PRODUCTS: PRELIMINARY REGULATORY IMPACT ANALYSIS, FOOD AND DRUG ADMINISTRATION, https://www.fda.gov/media/87380/download [https://perma.cc/L3PV-HZZ7].

[356] Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67,988-67,989 (proposed Nov. 13, 2013).

[357] Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products: Correction and Extension of Comment Period, 78 Fed. Reg. 78,796 (Dec. 27, 2013).

concerns" about the proposed regulation.[358] The letter questioned the authority to promulgate such a rule given the statutory language and urges that it would lead to inconsistency in drug messages to consumers and physicians alike.[359] The letter states that the proposed rule would "conflict directly with the statute, thwart the law's purposes and objectives, and impose significant costs on the drug industry and healthcare consumers."[360]

In the most recent 2019 case of *Merck Sharp & Dohme v. Albrecht*, the Court revisited language from *Wyeth v. Levine* and held that where there is "clear evidence" of impossibility to comport with both the federal and state requirement, impossibility preemption exists. Specifically, there must be clear evidence that the FDA would not have approved a change to a label.[361] The case defines clear evidence as evidence showing that the manufacture fully informed the FDA of the justifications for the warning required by state law and the FDA informed them that they would not approve the changes to include that warning. The Court also determined the issue as one for a judge, not a jury, to decide.[362] The Court remanded the issue to the Court of Appeals to determine whether there was clear evidence in the case.[363]

C. Biologics

The Supreme Court has not yet addressed biologic preemption as a general matter. As with drugs, Congress did not provide an express preemption provision for biologics within the Public Health Service Act[364] or the precursor Biologics Control Act of 1902.[365] Given harmonization in the regulatory processes for drugs and biologics, many of the regulations applicable to drugs are also applicable to biologics, either through express statement in the regulations, by statute, or through FDA policy expressed in guidance documents or other

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[358] Kurt R. Karst, *Lawmakers Express "Grave Concerns" with Generic Drug Labeling Proposal; Demand Answers from FDA,* FDA LAW BLOG (January 22, 2014), https://www.fdalawblog.net/2014/01/lawmakers-express-grave-concerns-with-generic-drug-labeling-proposal-demand-answers-from-fda/ [https://perma.cc/G4M2-LW92].

[359] *Id.*

[360] *Id.*

[361] Merck Sharpe & Dohme Corp. v. Albrecht, 139 S.Ct. 1668, 1668 (2019). The *Wyeth* decision stated that "absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it as impossible for Wyeth to comply with both federal and state requirements." Wyeth v. Levine, 555 U.S. 555, at 571 (2009).

[362] *Albrecht*, 139 S.Ct at 1672.

[363] *Id.* at 1680-1681. Subsequent lower court cases are now wrestling with this task now, with the fullness of the FDA record as one issue. *See, e.g., In re* Zofran (Ondansetron) Prods. Liab. Litig., 368 F. Supp. 3d 94, 95 (D. Mass. 2019).

[364] Pub. L. No. 78-410, §351(a), 58 Stat. 702 (1944).

[365] Pub. L. No. 57-244 ch. 1378, 32 Stat.728 (1902).

informal means.[366] For example, allowing enhancement of drug label warnings without affirmative FDA approval of the changes in advance of the change's implementation is one process that applies to both biologics approved via BLA and drugs approved via NDA.[367] A biologic-specific provision in the regulations, 21 C.F.R. §601.12, addresses changes to an approved BLA label; the language is nearly identical to the regulations pertaining to NDA drugs.[368]

Several state courts have issued decisions addressing the question of whether and how biologic preemption analysis differs from drug and device preemption. The case *In re Genentech, Inc., Herceptin (Trastuzumab) Marketing & Sales Practices Litigation* arose from a claim, based in California state tort law, alleging that Herceptin, a biologic drug (approved via the BLA process) used to treat breast cancer, was not sold in vials that contained 440 or more mg/mL of the drug.[369] The plaintiffs alleged that this was a breach of expressed and implied warranties and unjust enrichment under California state law.[370] The BLA for Herceptin was approved for a range of 440±35 mg/mL per vial, which meant that the FDA had determined that the manufacturing process used in production of the drug was safe so long as the concentration of the vial was within that specific range.[371] In order to comply with California state law, Genentech would have had to alter the manufacturing or labeling procedures for Herceptin. Because an approved BLA must be in conformance with federal law both for its labeling and manufacturing procedures, this change would have required that Herceptin go through an FDA approval process again.[372]

The court applied *PLIVA*, determining that, while the product that was being approved and the congressional statute outlining its approval mechanism may have been different, the same concept applied: a state law could be preempted by implied preemption if it served as an obstacle to the execution of an agency's congressionally-specified goal.[373] In this case, California state law was preempted because the FDA acknowledges that reasonable variation between the product and its label must be tolerated, and Genentech's compliance with the state law claims would conflict with that FDA principle.[374] Thus, the Plaintiff's

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[366] *See* Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act 2009*, 65 FOOD & DRUG L.J. 671, 687 (2010).

[367] 21 C.F.R. §601.12(f)(2)(i) (2019) (applying the general NDA drug labeling requirements to BLA biologics).

[368] *Compare* 21 C.F.R. §601.12(f)(2)(i) (2019) *with* 21 CFR §314.70(c)(6)(iii)(2019).

[369] *In re* Genentech, Inc., Herceptin (Trastuzumab) Mktg. & Sales Pracs. Litig., 367 F. Supp. 3d 1274, 1277 (N.D. Okla. 2019).

[370] *Id.*

[371] *Id.*at 1278-79.

[372] *Id.* at 1278, 1288-89.

[373] *Id.* at 1282.

[374] *Id.* at 1284-86, 1288.

state-law claims conflict with federal legislation and were deemed preempted as they were in *PLIVA*.[375]

The issue of federal preemption of state unfair competition law in the biologic context was addressed by the Supreme Court in *Sandoz Inc. v. Amgen Inc.*, a case relating to the complex patent information exchange and disclosure processes in the BPCIA rather than the invocation of state tort liability for harm to a consumer.[376] The preemption issue was remanded back to the Federal District Court, which held that the BPCIA preempts state law remedies under both conflict preemption and field preemption theories.[377] The court pointed out that requiring biosimilar applicants to comply with the BPCIA's "detailed regulatory regime" in addition to 50, potentially different, state-law regimes would place an unreasonable burden that Congress did not intend to impose with the passage of the BPCIA.[378]

Despite the sense that courts are treating biologic preemption relating to innovator biologics as they do preemption relating to innovator drugs, there is a lack of clarity about preemption's application to biosimilar or interchangeable biologic products. Largely because of the relative recency of the BPCIA, introducing two abbreviated routes to market for biologic products, the legal scholarship lacks a focused assessment of any existing case law. The BPCIA requires biosimilars to be "highly similar" to the innovator biologic, rather than bioequivalent, and the statute does not require the label to be "the same as" or identical to the innovator, as generic drugs must be in order to enter the market.[379] Arguably, this suggests that there is thus no conflict or obstacle preemption issue within the biosimilar or interchangeable realm and that biosimilar and interchangeable products will not benefit from the protection of implied preemption, at least with respect to challenges relating to the product's label. In addition, the FDA guidance regarding labeling of biosimilar products states that

> [w]hen new information becomes available that causes information in labeling to be inaccurate, the application holder must take steps to change the content of its product labeling, in accordance with 21 C.F.R. 601.12. All holders of marketing applications for biological products have an ongoing obligation to ensure their labeling is accurate and up to date.[380]

The referenced section 601.12 mimics the CBE-0 drug regulation in the sense that it provides for addition without prior approval by the FDA of heightened

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[375] *Id.* at 1289-90.

[376] Sandoz Inc. v. Amgen Inc., 137 S.Ct. 1664, 1669 (2017).

[377] Amgen Inc. v. Sandoz Inc., 877 F.3d 1315, 1320, 1330 (Fed. Cir. 2017).

[378] *Id* at 1329.

[379] 42 U.S.C §262(k)(2)(A)(i).

[380] U.S. FOOD & DRUG ADMIN., LABELING FOR BIOSIMILAR PRODUCTS: GUIDANCE FOR INDUSTRY (2018), https://www.fda.gov/media/96894/download [https://perma.cc/NMV2-9ZX4].

warnings on the label.[381] The guidance linking these requirements is worded as applicable to *all* biologic products, which includes biosimilars and interchangeable biologics. Future litigation will undoubtedly test this language, as well as the ability of the FDA to issue such a directive with significant implications for legal liability through guidance document.

D. Combination Products

Where a product is a combination of two or three of drug, biologic and medical device, the preemption analysis could turn on how the product or component that caused the harm got to market. As Professor George Horvath notes, combination products have two identities: their identity imparted by their statutory definition as a combination product and their regulatory identity which leads them to be reviewed as either a drug, device, or biological product.[382] Combination products also have multiple mechanisms of action and their regulatory identity is chosen based on the primary mode of action, defined as the one that contributes the most significant therapeutic effect.[383] A chemical primary mode of action will be regulated as a drug,[384] a mechanical or physical mode of action will be regulated as a medical device, and a biological mode of action will be regulated as a biologic.[385] With a faulty combination product, it is often straightforward to determine which component of that product caused the harm, though sometimes it is not. For example, the insulin pen Lantus (a recombinant insulin glargine), which is a combination biologic-medical device, is a biologic by regulatory identity. The approval of Lantus was through the drug approval process, but the product has now been deemed a biologic by the FDA. [386] The biologic mode of action (as a therapeutic to treat diabetes) is distinct from its device mode of action (delivering the biologic into the body); however, the two modes of action are combined into a single product. While the FDA can incorporate basic

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[381] 21 C.F.R. §601.12(f)(2) (2011).

[382] George Horvath, *Emergent Regulatory Systems and Their Challenges: The Case of Combination Medical Products*, 94 WASH. L. REV. 1697, 1749 (2019).

[383] 21 C.F.R. §3.2(k), (m) (2019).

[384] FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: INTERPRETATION OF THE TERM "CHEMICAL ACTION" IN THE DEFINITION OF DEVICE UNDER SECTION 201(H) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2011), http://www.fdalawblog.net/wp-content/uploads/archives/docs/ChemicalAction%20Guidance.pdf [https://perma.cc/U6XX-EPM6] (FDA defines a chemical mode of action as one that "[t]hrough either chemical reaction or intermolecular forces or both, the product: (1) Mediates a bodily response at the cellular or molecular level, or (2) combines with or modifies an entity so as to alter that entity's interaction with the body of man or other animals."). *Id.*

[385] 21 C.F.R. §3.4(a) (2019).

[386] *Lantus Approval Information*, DRUGS@FDA: FDA-APPROVED DRUGS, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021081 [https://perma.cc/86F2-XERE] (last visited Sep. 24, 2020) ("This Former NDA Was Deemed To Be a BLA on March 23, 2020.").

safeguards for development of the medical device aspects of the product, the overall product entered the market through the drug (and later transitioned to biologic) approval process.

The Supreme Court has not addressed combination product preemption and the state of the case law in the lower courts is inconsistent. For example, the New Jersey case of *R.F. v. Abbott Laboratories* involved an HIV blood screening test classified as a combination product – both a biologic and a medical device.[387] The product's development, manufacture and field testing was overseen by the Office of Biologics and Research and Review (OBRR) and largely regulated by as a biologic; however, the OBRR required that the test be listed as a medical device and its package insert drafted pursuant to the regulations for labeling medical devices.[388] The FDA was closely involved in determining the labeling and post-marketing considerations of the product as well.[389] The plaintiff was infected with HIV following a blood transfusion for which the donor tested negative using the HIV test in question.[390] Plaintiffs argued that Abbott was aware that the product was producing false-negative results and was required under New Jersey law to warn of the incidence and the inherent dangerousness of borderline samples in a supplemental package insert or instruct blood banks to retest such borderline samples.[391]

The Supreme Court of New Jersey held that the FDA's exercise of control and initiative over the product's "development, packaging, and field performance monitoring" along with "the unique circumstances under which the Test arose (a national health crisis. . .)," give rise to implied obstacle preemption.[392] The court reasoned that the FDA was responsible for meeting the goals set out by Congress, and it was the agency's determination that calling for repeated tests in the event of borderline-negative results would not be worth the risk of diminishing the nation's blood supply.[393] In a fact-specific determination largely independent from any analysis of the scope of the FDA's product approval pathway, the Court decided that it was best not to second-guess the FDA's methods in achieving its express goals.[394]

Overall, there is jurisdictional inconsistency about whether a combination product preemption analysis should focus on the regulatory identity (how it got to market) or the specific mode of action or component part that allegedly caused

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[387] R.F. v. Abbott Lab'ys., 745 A.2d 1174, 1178 (2000).

[388] *Id.*

[389] *Id.* at 1180-83.

[390] *Id.* at 1184.

[391] *Id.* at 1185.

[392] *Id.* at 1188.

[393] *Id.* at 1194.

[394] *Id.*

the harm.[395] This inconsistency and uncertainty as to preemption outcome adds to the challenges that will face litigants regarding biosimilar and interchangeable insulin products because many products that are utilized by patients as an insulin system are approved or cleared as separate or integrated products. And, as insulin is moved from drug status to biologic status, it is unclear what the present "deemed biologic" status as transitioned from the original new drug approval pathway as an NDA, 505(b)(2), or ANDA (generic) drug will mean for what case law to apply.

V. PROTECTING PATIENTS AND THE PUBLIC HEALTH

The legal and regulatory landscape for insulin is complex; its currently a mix of state law directives and procedures as positioned against uncertain federal preemption law. There is a certain futility in attempting to identify nearly limitless outcomes for patients depending on the patchwork of state and federal statutory and common law. However, moving forward as the U.S. anticipates that interchangeable insulin products will inevitably enter the market, there are several broad issues to be addressed that can serve to infuse uniformity and predictability into the process for patients and prescribers. The purpose of this article is to present the range of complex legal questions facing interchangeable insulins and the patients that will use them. This Part suggests five modest means to begin to address the legal uncertainties and the level of understandings of prescribers, patients, and the general public.

A. Raise Awareness about Biologics

There is a foundational need to educate prescribers and patients about the scientific and regulatory distinctions between traditional chemical drugs and complex biological products. This can be addressed through various means, including broad public awareness campaigns, professional training requirements, and continuing medical education content and venues. At the state level, in addition to prescriber-pharmacist communication requirements, states should implement provisions that require pharmacists to inform and educate patients as well. Supplementing patient consent requirements with required education requirements may help quell patient confusion but may work against the goals of introducing biosimilars into the market by highlighting the differences in products rather than the similarities. Ultimately, while states with stricter automatic substitution requirements regarding informational exchange may discourage use of biosimilar insulins, stringent post-market requirements allow for more robust surveillance of such therapies to feed into the regulatory process.

There may also be a role for the FDA's utilization of risk evaluation and mitigation strategies (REMS) authorized by statute. The Food and Drug

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[395] *See generally,* Horvath, *supra* note 382 (providing a careful assessment of the scope of this case law).

Administration Amendments Act of 2007 (FDAAA) introduced REMS as a means to enhance the post-approval authority over drugs and biologics by the FDA.[396] The scope and format of REMS include enhanced communications to prescribers, patient medication guides targeted to more general information presented in comprehensible language, and mechanisms to ensure product vigilance and reporting.[397] The FDA can require REMS as either a condition of approval[398] or, in the case of already approved products, as a subsequent condition for continued marketing.[399] REMS may require a medication guide for patients; physician prescribing information; communications to health care providers and pharmacies; limitations on labeling, promotion, and prescribing in order to assure safe use by patients; and a plan for implementation.[400] FDAAA also contains related post-market provisions that allow the FDA to require further studies for safety and efficacy of an approved product, along with increased authority for the FDA to review these commitments on a continuing basis.[401] Violations subject manufacturers to litigation under misbranding provisions and trigger civil money penalties.[402] The FDA currently requires 60 active REMS for drugs and biologics, the majority of which include elements to assure safe use (ETASU) that take the form of distribution restrictions, training and recordkeeping requirements for prescribers and pharmacists, and prescribing limitations.[403]

As the FDA works to transition insulin from drug products to biologics, and eventually approves an interchangeable product, REMS could be implemented for individual products or as a shared system of requirements in the post-market realm. The REMS could address aspects of prescriber and patient understandings about interchangeable products (as compared to generic drugs), the basics of the operation of interchangeable biologic substitution laws (as opposed to generic drug substitution laws), and the importance of diligence in tracking patient prescriptions and related adverse outcomes. The FDA may resist a role in conveying legal information about state laws, yet the newness of the interchangeable pathway to market and the connection between the product status assigned by the FDA and triggering of state-by-state variation in substitution mechanisms bears consideration of taking on that role.

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[396] Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified in scattered sections of 21 U.S.C.).

[397] *Id.*

[398] Federal Food, Drug, & Cosmetic Act (FDCA) § 505-1(a)(1), 21 U.S.C. § 355-1(a)(1).

[399] Federal Food, Drug, & Cosmetic Act (FDCA) § 505-1(a)(2), 21 U.S.C. § 355-1(a)(2).

[400] Federal Food, Drug, & Cosmetic Act (FDCA) § 505-1(c)-(f), 21 U.S.C. § 355-1(c)-(f).

[401] Federal Food, Drug, & Cosmetic Act (FDCA) §§ 505(p), 505-1, 21 U.S.C. §§ 355(p), 355-1(g)(2).

[402] Federal Food, Drug, & Cosmetic Act (FDCA) § 502(y), 21 U.S.C. § 352(y).

[403] *See* FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS),* http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm [https://perma.cc/ZZ57-B9UQ].

B. Adopt Uniform Interchangeable Substitution Laws

Prior literature traces the development of state initiatives supporting the drafting and enactment of interchangeable biologic substitution laws. Some state laws were enacted as the result of early intensive lobbying efforts on behalf of industry, trade associations, and patient advocacy groups. Ultimately some common ground was reached among different segments of industry and stakeholders advising the development of later legislation.[404] Early legislation tended to skew toward the efforts of brand-name industry.[405] For example, the North Dakota law contains specific language formulated by Amgen and Genentech;[406] the Massachusetts law, passed in June 2014, was promoted by both BIO and the Massachusetts Biotechnology Council;[407] and reporting by the California's Secretary of State note that lobbying entities included AbbVie, Amgen, BIO, Genentech, and PhRMA.[408] Some sources report that the FDA, among others, was initially very concerned about these state efforts with one spokesperson stating that the state laws were "efforts to undermine trust in these products."[409] Concerns over widespread confusion among legislators about biosimilars were feeding misunderstanding and misperceptions.[410]

The self-interested drivers of the legislation aside, in comparison to well-established generic substitution laws, the interchangeable biologic substitution laws are lacking in specificity, are untested in application, and are variable across jurisdictions in troubling ways for patients given the nature of biologic products. These aspects were discussed in Part III.A. Coupled with the FDA and FTC scrutiny over potential antitrust behaviors in the biologic realm, the time is ripe for a reassessment of the purpose and function of these state laws. One avenue to accomplish this is through a Model State Law committee and process that reviews the laws and compares to generic substitution laws in a rigorous

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[404] Robert Weissman & Hannah Brennan, *Competition Inhibitors: How Biologics Makers are Leveraging Political power to Maintain Monopolies and Keep Prices Sky High*, PUBLIC CITIZEN 26-28 (Dec. 18, 2014), https://www.citizen.org/wp-content/uploads/report-biologics-industry-leverages-political-power-to-maintain-monopolies-and-inflate-prices.pdf [https://perma.cc/7WJT-DE5Q].

[405] Paradise, *supra* note 115, at 79.

[406] Dan Stanton, *Cali Gov Vetoes Biosimilar Bill, Thwarting Amgen and Genentech*, BIOPHARMA REP. (Oct. 16, 2013), https://www.biopharma-reporter.com/Article/2013/10/16/Biosimilars-restricting-bill-vetoed-by-California-Governor [https://perma.cc/Y27L-6R9D].

[407] Adrianne Appel, *Massachusetts Governor Signs Biosimilars Bill with Patient Notification*, 12 PHARM. L. & INDUSTRY REP. (BNA) 916, 916 (2014).

[408] Weissman & Brennan, *supra* note 404, at 27. *See also* Sandburg, *supra* note 183, at 20.

[409] Alaric DeArment, *Reports: FDA Says Carve-out Bills 'Undermine Trust' in Biosimilars*, DRUG STORE NEWS (Aug. 29, 2013), https://drugstorenews.com/news/reports-fda-says-carve-out-bills-undermine-trust-biosimilars [https://perma.cc/LR9M-TWKL].

[410] *See* Sandburg, *supra* note 183, at 20.

and meaningful way without conflicts of interest at play. The National Consumer Law Center may be ideally situated to lead this effort at initial stages.

C. Cap Prices at the Federal Level

Many states are taking aggressive action with laws that set caps on insulin costs through a variety of methods.[411] However, this legislation likewise suffers from jurisdictional inconsistency and will ultimately lead to inconsistent interpretation in the courts. The Minnesota legal challenge is one example of how this may play out in the court system as more states pass legislation.[412] Patients in one state with such a law, like Colorado, will have a much different cost profile for their insulins (whether the innovator biologic or an interchangeable product) than a patient without such a law. Variation in the actualization of the "cap" will also be an issue, where some states cap the total across all necessary insulin costs per month, including combinations of products and supporting devices, and others cap per prescription, which may add up to hundreds of dollars for multiple products on a monthly basis.[413]

Given that insulin is a life-saving treatment for a tremendous proportion of the U.S, and global, population, it seems an appropriate and equitable public health action to cap insulin costs at the federal level. Mechanisms to accomplish this rely chiefly on Congress; prior bills seeking to establish federal caps on pricing through various means have failed.[414] There may be a role for building in pricing caps into the efforts to harmonize state laws through model legislation as well.

D. Provide Clarity and Parity on Preemption

The complicated matrix of federal preemption case law speaks for itself across the FDA-regulated product areas. In the past, both Congress and the FDA have attempted to revise the CBE-0 requirements to also apply to generic drugs.[415] Both of those efforts have resulted in no change to the stark difference

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[411] *See* Amy Martyn, *States are Trying to Cap the Price of Insulin. Pharmaceutical Companies are Pushing Back*, NBC NEWS (Aug. 15, 2020), https://www.nbcnews.com/news/us-news/states-are-trying-cap-price-insulin-pharmaceutical-companies-are-pushing-n1236766 [https://perma.cc/YH25-ZEZU].

[412] *See Pharmaceutical Industry Sues to Block Minnesota Insulin Law*, MOD. HEALTHCARE (Jul. 1, 2020), https://www.modernhealthcare.com/legal/pharmaceutical-industry-sues-block-minnesota-insulin-law [https://perma.cc/59TK-7LLF].

[413] *See* discussion *supra* Part III.B.

[414] *See* Peter Sullivan, *Chances for Drug Pricing, Surprise Billing Action Fade until November*, THE HILL (Mar. 24, 2020), https://thehill.com/policy/healthcare/489334-chances-for-drug-pricing-surprise-billing-action-fade-until-november [https://perma.cc/A6TC-GZ4P].

[415] *See* Amrita Singh, Nicole M. Maisch & Maha Saad, *Update on Generic-Drug Labeling Requirements*, U.S. PHARMACIST (June 23, 2015), https://www.uspharmacist.com/article/update-on-generic-drug-labeling-requirements [https://perma.cc/Y6KG-JRSC]; Withdrawal of

in outcome on preemption for new drugs approved through the NDA process and generic drugs requiring "sameness" to the NDA drug, including all labeling. These initiatives could be revived to provide parity in this realm and confer an affirmative obligation on the drug manufacturer to enhance warnings when appropriate.

The regulation, as currently written, applies only to drugs. Amending it to sync outcomes for drugs would not solve the problem for biologics. However, the FDA has a separate regulation pertaining to changes to a biologic label, as discussed in Part IV.C. That regulation, 21 C.F.R. §601.12, establishes requirements similar to the CBE-0 drug regulation by allowing addition of heightening warnings on the label without prior approval by the FDA.[416] In addition, FDA guidance seems to require that both biologic innovators and any biosimilar or interchangeable products are held to the same standard to change the product labeling in the face of risk information.[417] If this reading is accurate, no conflict or obstacle preemption would apply regarding changes to the label to enhance safety warnings of biosimilar or interchangeable products. But this reading is subject to interpretation and has not been subject to judicial scrutiny through a state tort liability lens. Congress, or the FDA, could address this issue through legislation, or rulemaking. However, there is a final issue of FDA authority to act through guidance document with the binding effect of law, which is discussed in E, below.

E. Examine the FDA's Authority to Act by Guidance Document

Finally, an exploration of the FDA's use of guidance documents in the biosimilar and interchangeable biologic arena to issue policy with legally binding impact is warranted. While Congress clearly instructs the agency within the BPCIA to act through guidance along with public comment, it remains to be seen whether that process is appropriate in developing product review and approval requirements to implement the statute. Perhaps more importantly from a judicial perspective, it is unclear whether FDA guidance documents regarding biosimilars and interchangeable biologics, will be subject to judicial deference – *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, *Skidmore*, or otherwise. This includes guidance that sets forth general evidentiary requirements and considerations, and those specifically that address changes to a product label as discussed above.

Proposed Rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 83 Fed. Reg. 64,223, 64,299 (Dec. 14, 2018).

[416] 21 C.F.R. § 601.12(f)(2)(A) (2019).

[417] FDA, LABELING FOR BIOSIMILAR PRODUCTS (2018) at 9-10, https://www.fda.gov/media/96894/download [https://perma.cc/NA8F-NQNV]. Again, the statute requires biosimilars to be "highly similar" to the innovator biologic, rather than bioequivalent, and the statute does not require the label to be "the same as" or identical to the innovator, as generic drugs must be in order to enter the market.

The Supreme Court has not opined on the deference question with respect to FDA guidance documents. There is a 1986 Supreme Court Case, *Young v. Community Nutrition Institute*, where the Court gave *Chevron* deference to an FDA "action level", a threshold numerical limit on the presence of a contaminant in food without rendering it adulterated under the statute.[418] The action level did not go through notice and comment rulemaking but was published in the Federal Register.[419] The court applied the two prong inquiry identified in *Chevron* two years prior – that where a statute that the agency administers is silent or ambiguous with regard to a particular issue, the courts should defer to an agency's reasonable interpretation of that statute.[420] The case involved a regulation defining and applying the bubble concept to measuring and capping industrial emissions.[421] In 1997, FDA made guidance documents non-binding on the agency through notice and comment rulemaking, which was codified by Congress that same year and required FDA to develop good guidance practices, which the FDA subsequently did through notice and comment rulemaking.[422] Among other things contained in the good guidance practices, the guidance document must state that the guidance "does not legally bind the public or FDA."[423]

Christensen v. Harris County then reinvigorated the concept of "lesser" *Skidmore* deference in 2000, looking at an agency's "power to persuade" through means other than rulemaking.[424] One year later, the Supreme Court held in *U.S. v. Mead Corp.* that where an agency operates through interpretation that is not derived from statutory authority in particular, deference will depend on "the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position."[425] Notably, *Wyeth v. Levine* tangentially involved an issue of deference, where the Court did not give any level of deference to an FDA statement in the preamble to a regulation.[426] But there it was a change to long-standing FDA policy without notice and comment rulemaking and this was a preemption case ultimately scrutinizing Congressional intent. The lower courts are inconsistent in applying deference to different types of FDA

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[418] Young v. Cmty. Nutrition Inst., 476 U.S. 974, 977, 980 (1986).

[419] *Id.* at 978.

[420] Chevron U.S.A. Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837, 842-43 (1984).

[421] *Id.* at 837, 862, 866.

[422] 21 C.F.R. § 10.115 (2019); The Food and Drug Administration's Development, Issuance, and Use of Guidance Documents, 62 Fed. Reg. 8867, 8961 (Feb. 27, 1997).

[423] 21 C.F.R. § 10.115 (2019).

[424] Christensen v. Harris County, 529 U.S. 576, 587 (2000). *Skidmore v. Swift & Co.* ruled that an administrative agency's interpretive rules were to be given deference according to their "power to persuade." The case precedes the 1984 *Chevron* decision. 323 U.S. 134, 140 (1944).

[425] U.S. v. Mead Corp., 533 U.S. 218, 228 (2001).

[426] Wyeth v. Levine, 555 U.S. 555, 577 (2009).

actions, and the FDA will sometimes concede that certain informal policy is subject to the lesser *Skidmore* deference.[427]

Although the FDA has followed Congressional directive by acting through guidance document plus public notice and comment, challenges will arise as to the legal effect of guidance documents pertaining to biosimilars and interchangeable products. Where Congress approves of FDA's actions already taken, they may confirm the legality through legislation. It is extremely likely given the momentum to bring an interchangeable insulin product to market that the FDA's policy effectuated through guidance document will be tested in the context of an insulin product.

CONCLUSION

The FDA and the biopharmaceutical industry have signaled through various means that interchangeable insulins are on the horizon. Once an interchangeable product is approved by the FDA, a cascade of legal questions will follow regarding the scope of the statute introducing the abbreviated routes to market for biologic products, agency actions in issuing guidance documents to implement the statute, state legislation governing product substitution and insulin price caps, and the complex judicial landscape for federal preemption of state tort liability. There is room to move across all these fronts proactively to anticipate problems and alter the legal frameworks at both the federal and state level. This article identifies the scope of these challenges and offers five modest suggestions to address them prior to the realization of interchangeable insulin.

[427] *See, e.g.*, Fellner v. Tri-Union Seafoods, L.L.C., 539 F.3d 237, 250 (3d Cir. 2008).