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Insulin insulated: barriers to competition and affordability in the United States insulin market

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ABSTRACT

Insulin prices in the United States are skyrocketing. In addition to several challenges common to high-priced prescription drugs, insulin faces several unique legal, regulatory, and practical challenges to increasing access and affordability. Despite the fact that insulin was developed almost 100 years ago, the insulin market is dominated by only three companies and there continue to be no biosimilar competitors in the United States. Unlike many high-priced prescription drugs, insulin has been insulated from competition for years. This article examines the barriers to competition in the insulin market, considering the challenges surrounding regulatory approval, interchangeability, trade secrets, and anticompetitive behavior. Further, this article discusses the potential and limitations of various legislative proposals to address access to insulin. In doing so, this article attempts to explain why there is such limited competition in the insulin market and identifies issues specific to the insulin market for lawmakers to consider in developing proposals to address access to affordable insulin in the United States.

KEYWORDS: biologics, biosimilars, competition, drug pricing, food and drug law, insulin

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I. INTRODUCTION

Insulin prices are skyrocketing in the United States. From 2002 to 2013, the prices of the most popular insulin products tripled,¹ with some costing up to \$900 per patient per month.² The United States comprises only 15 per cent of the global insulin market, yet it accounts for almost 50 per cent of insulin-related revenue.³ These high prices have devastating consequences for patients. One in four people with diabetes in the United States ration their insulin, which can lead to severe complications and even death.⁴

Consequently, insulin has come to the forefront of the drug pricing debate in the United States. In January 2019, Congress held hearings on insulin prices with top executives from insulin companies⁵ and launched a bipartisan probe in February 2019.⁶ Several activist groups have held protests outside the United States headquarters of insulin manufacturers, blaming them for the deaths of several people with diabetes.⁷ The insulin pricing debate has even gained attention in popular culture: in October 2019, Jonathan Van Ness of Netflix's *Queer Eye* discussed insulin pricing challenges with Elizabeth Pfister, founder of T1International, a non-profit organization focused on access to insulin for all.⁸

Several members of Congress have made proposals to address insulin pricing specifically. In late 2018, Senator Elizabeth Warren (D-MA) suggested that the federal government starts its own generic manufacturing plant, with insulin put forth as one

1 William T. Cefalu et al., *Insulin Access and Affordability Working Group: Conclusions and Recommendations*, 41 DIABETES CARE 1299, 1299 (2018).

2 See Katie Thomas, *Drug Makers Accused of Fixing Prices on Insulin*, N.Y. TIMES, Jan. 30, 2017, <https://www.nytimes.com/2017/01/30/health/drugmakers-lawsuit-insulin-drugs.html>.

3 Tracy Tylee & Irl B. Hirsch, *Costs Associated With Different Insulin Preparations*, 314 J. AM. MED. ASS'N 665, 665 (2015).

4 Jing Luo et al., *Strategies to improve the affordability of insulin in the USA*, 5 LANCET DIABETES & ENDOCRINOLOGY 158, 158 (2017); Suvarna Sheth, *Skyrocketing Insulin Prices Prompt New Movement Across The U.S.*, DLIFE, Dec. 28, 2018, <https://dlife.com/sky-rocketing-insulin-prices-prompt-new-movement-a-cross-the-u-s/>. For a recent survey on insulin out-of-pocket costs and findings on insulin rationing, globally and in the United States, see T1INTERNATIONAL, COSTS AND RATIONING OF INSULIN AND DIABETES SUPPLIES: FINDINGS FROM THE 2018 T1INTERNATIONAL PATIENT SURVEY (2019).

5 See Yasmeen Abutaleb, *Congress holds first hearings on insulin, high drug prices*, REUTERS, Jan. 29, 2019, https://www.reuters.com/article/us-usa-healthcare-drugpricing/congress-holds-first-hearings-on-insulin-high-drug-prices-idUSKCN1PN2WJ?fbclid=IwAR1jTzUOzIWSscr2bD7_CJxwRtSR1RcrLlibf_n8tgiBr8dIE9IIDN-yfEiU.

6 Jessie Hellmann, *House Dems launch probe of 'skyrocketing' insulin prices*, THE HILL, Jan. 30, 2019, <https://thehill.com/policy/healthcare/427653-house-democrats-launch-probe-of-skyrocketing-insulin-prices>; Nicholas Florco, *Powerful Senate committee launches bipartisan probe into insulin pricing*, STAT, Feb. 22, 2019, <https://www.statnews.com/2019/02/22/powerful-senate-committee-launches-bipartisan-probe-into-insulin-pricing/>.

7 See, e.g., Sorell Grow, *Groups protest insulin prices outside Lilly headquarters*, INDIANAPOLIS BUS. J., June 20, 2019, <https://www.ijb.com/articles/74295-groups-protest-insulin-prices-outside-lilly-headquarters> (covering protest outside Eli Lilly); Hyacinth Empinado, *Watch: 'I should not have to go beg': A protest over insulin prices is seen as a fight for life*, STAT, Nov. 27, 2018, <https://www.statnews.com/2018/11/27/insulin-prices-protest-sanofi/> (covering protest outside Sanofi).

8 *Getting Curious With Jonathan Van Ness #129: Is There An Insulin Crisis Happening in the U.S.? with Elizabeth Pfister, Founder and Executive Director of T1International*, EARWOLF, Oct. 1, 2019, <https://www.earwolf.com/episode/is-there-an-insulin-crisis-happening-in-the-u-s-with-elizabeth-pfister-founder-and-executive-director-of-t1international/>.

product of focus.⁹ In July 2019, Senators Jeanne Shaheen (R-NH), Tom Carper (D-DE), Kevin Cramer (R-ND), and Susan Collins (R-ME) filed proposed legislation aimed at creating a ‘new insulin pricing model’ predominantly by regulating insulin rebates from pharmacy benefit managers.¹⁰ In February 2019, Representatives Peter Welch (D-VT) and Francis Rooney (R-FL) submitted a bill to allow importation of affordable insulin from Canada and possibly other countries.¹¹

Many states have also taken steps to address access to insulin. For example, Colorado became the first state to legislate a price cap on insulin in 2019,¹² with several other states passing or proposing similar bills.¹³ Nevada, taking a different legislative approach, passed a law to mandate transparency in insulin pricing in 2017.¹⁴

Insulin manufacturers have not completely ignored the calls for action. In response to public pressure surrounding the high insulin prices, Eli Lilly announced in March 2019 that it would provide, through a subsidiary, an authorized generic of its insulin analog Humalog.¹⁵ This insulin product would be identical to Humalog, yet cost half the price of brand name Humalog. Since then, Novo Nordisk announced that it would sell an authorized generic of its insulin analog Novolog at half price,¹⁶ and Sanofi

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- 9 See Alex Thompson & Sarah Karlin-Smith, *Warren bill would get feds into generic drug manufacturing*, POLITICO, Dec. 17, 2018, <https://www.politico.com/story/2018/12/17/elizabeth-warren-bill-drug-manufacturing-prices-1067916>.
 - 10 S.2199—Insulin Price Reduction Act, <https://www.congress.gov/bill/116th-congress/senate-bill/2199/text> (accessed Oct. 17, 2019).
 - 11 H.R. 1478—To amend the Federal Food, Drug, and Cosmetic Act to allow for the importation of affordable and safe insulin by wholesale distributors, pharmacies, and individuals, available at <https://www.congress.gov/bill/116th-congress/house-bill/1478/cosponsors> (accessed Mar. 4, 2019). See also Jessie Hellmann, *Bill would let patients buy cheaper insulin from other countries*, THE HILL, Feb. 20, 2019, <https://thehill.com/policy/healthcare/430784-bill-would-let-patients-buy-cheaper-insulin-from-other-countries> (discussing the most recent proposed bill); Patricia M. Danzon et al., *Commercial Importation of Prescription Drugs in the United States: Short-Run Implications*, 46 J. HEALTH POLITICS, POL’Y & L. 295, 295 (2011) (“To address this apparent disparity, bills have been introduced in Congress to legalize commercial drug importation (also called parallel trade, which is legally permitted in the European Union), permitting wholesalers and other third parties to import on-patent prescription drugs from designated foreign countries into the United States.”).
 - 12 Allison Bailey & Erin Gilmer, *Colorado’s Insulin Price Cap: A Foundation to Build Upon*, T1INTERNATIONAL, July 9, 2019, <https://www.t1international.com/blog/2019/07/09/colorados-insulin-price-cap-foundation-build-upon/>.
 - 13 See, e.g., Jamie Munks, *State lawmakers press case for monthly cap on insulin costs*, CHICAGO TRIBUNE (Sept. 17, 2019), <https://www.chicagotribune.com/politics/ct-illinois-insulin-costs-legislation-20190917-uneqfmsbdv7gb42szxqqgmcm-story.html> (Illinois proposal); Samantha Galvez, *Proposed bill to cap out-of-pocket insulin costs*, FOX 43 (Sept. 4, 2019), <https://fox43.com/2019/09/04/proposed-bill-to-cap-out-of-pocket-insulin-costs/> (Pennsylvania proposal); Lawrence Smith, *Proposal would cap the cost of insulin for some Kentucky diabetics*, WRDB.COM (Sept. 3, 2019), https://www.wdrb.com/news/proposal-would-cap-the-cost-of-insulin-for-some-kentucky/article_099f5e84-ce74-11e9-bb38-ab68af9de638.html (Kentucky proposal); J. Carlisle Larsen, *New Proposal In State Legislature Would Cap The Cost Of Insulin*, WISCONSIN PUBLIC RADIO (July 25, 2019), <https://www.wpr.org/new-proposal-state-legislature-would-cap-cost-insulin> (Wisconsin proposal).
 - 14 See NEV. REV. STAT. § 439B.630, 635, 640 (2017).
 - 15 See *Lilly to Introduce Lower-Priced Insulin*, LILLY, Mar. 4, 2019, <https://investor.lilly.com/news-releases/news-release-details/lilly-introduce-lower-priced-insulin>.
 - 16 See *Novo Nordisk to cut insulin prices in the U.S.*, REUTERS (Sept. 6, 2019), <https://www.reuters.com/article/us-novo-nordisk-usa/novo-nordisk-to-cut-insulin-prices-in-the-us-idUSKCN1VR1JO>.

announced that it would charge patients with no insurance or who pay cash in the United States only \$99 per month for insulin.¹⁷

Even with these discounts and the increased political attention, insulin continues to be out of reach for many people with diabetes. The authorized generics and price decreases by the manufacturers are a good first step, but they do not make insulin affordable to all who need it. More work must be done to make insulin affordable and accessible, particularly taking into account the unique aspects of the insulin market.

Unlike many of the new high-priced prescription drugs, insulin is almost 100 years old—discovered in 1921 and first used by a patient in 1922.¹⁸ Insulin is also unique in its market structure: a persistent oligopoly both nationally and globally, in particular with respect to the prices of analog insulins. Only three companies—Novo Nordisk, Sanofi, and Eli Lilly—provide insulin in the United States market,¹⁹ despite the existence of several other manufacturers globally.²⁰

The insulin market has been insulated from the traditional expectations and trends of pharmaceutical markets, especially concerning price and competition. This article discusses issues specific to the insulin market that lawmakers must consider in developing legislation to address access to insulin. This article proceeds in four parts. Part I provides background on diabetes and insulin products. Part II introduces the landscape of the insulin market in the United States. Part III analyzes the challenges to increasing competition in the insulin market, focusing on the regulatory, practical, and competitive challenges in the insulin market. Part IV reviews three competition-related proposals that have been raised by legislators and advocates—reciprocal approval, insulin importation, and price capping—and discusses the risks and benefits associated with each proposal as applied to the insulin market.

Ultimately, this article examines the insulin market in hopes of identifying the unique practical, regulatory, and legal barriers that have insulated the insulin market from competition for almost a century. In order to increase competition in the United States insulin market and to improve the affordability and accessibility of insulin, lawmakers must address these barriers.

II. BACKGROUND: DIABETES AND INSULIN TREATMENT

Diabetes is a non-communicable disease, or chronic disease, related to the body's production and use of insulin.²¹ Insulin is a hormone that controls blood sugar by helping the body use and store glucose in the bloodstream.²² While insulin is naturally secreted by the pancreas in healthy individuals, people with diabetes either cannot

17 See Michael Erman, *Sanofi to cut U.S. insulin costs for some patients to \$99 per month*, REUTERS, Apr. 10, 2019, <https://www.reuters.com/article/us-sanofi-fr-insulin/sanofi-to-cut-u-s-insulin-costs-for-some-patients-to-99-per-month-idUSKCN1RM0Y3>.

18 David Beran et al., *A perspective on global access to insulin: a descriptive study of the market, trade flows and prices*, 36 DIABETIC MED. 726, 726 (2019).

19 Cefalu et al., *supra* note 1, at 1300; Luo et al., *supra* note 4, at 158.

20 See Ryan Knox & Veronika Wirtz, *Characterisation of insulin manufacturers*, in INSULIN MARKET PROFILE 14–18 & 92–94 (2016).

21 *Diabetes*, MAYO CLINIC, <https://www.mayoclinic.org/diseases-conditions/diabetes/symptoms-causes/syc-20371444> (last accessed Mar. 12, 2019).

22 *Insulin Basics*, AM. DIABETES ASS'N, (last updated July 16, 2015), <http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/insulin-basics.html>.

produce insulin, produce insufficient insulin, or do not respond to insulin and need other medication to control their blood sugar.²³

There are two types of diabetes, Type 1 and Type 2, which differ based on the body's ability to produce insulin and the requisite treatment. People with Type 1 diabetes cannot produce insulin or produce an insufficient amount of insulin.²⁴ Type 1 diabetes is treated with several daily injections of insulin to control blood sugar.²⁵ In contrast, people with Type 2 diabetes make an insufficient amount of insulin or do not respond to insulin and thus need medication to regulate their blood glucose levels.²⁶ Some people with Type 2 diabetes, approximately 10–25 per cent, also use insulin.²⁷ Estimates indicate that about 7.4 million people in the United States with diabetes use insulin treatment.²⁸ Lack of insulin can lead to diabetic ketoacidosis, coma, and death;²⁹ it is especially life-threatening for people with Type 1 diabetes, who require insulin to survive.³⁰

There are three categories of insulin products: animal insulins, human insulins, and analog insulins. Animal insulins, usually bovine or porcine insulin, are not available or used in the United States.³¹ Human insulins are manufactured using recombinant DNA technology: putting the gene for human insulin in bacteria and then using these bacteria to manufacture the insulin.³² Insulin analogs are synthetically made, modified forms of insulin.³³ The modifications to insulin analogs change the speed at which the body absorbs the insulin.³⁴ For example, rapid acting-insulins have an onset time of about 15 minutes and a peak effectiveness occurring within 1 hour; as such, individuals with diabetes must have a meal immediately after taking rapid-acting insulin or risk hypoglycemia or low blood sugar. Human insulins (also called short-acting

23 *Id.*

24 *Common Questions About Type 1 Diabetes*, JOSLIN DIABETES CTR., https://www.joslin.org/common_questions_about_type_1_diabetes.html (last accessed Mar. 15, 2019).

25 *Id.*; THOMAS E. HUBBARD, BETTER USE OF MEDICINES FOR DIABETES PATIENTS: 5 CRITICAL WAYS TO IMPROVE CARE 9 (Network for Excellence in Health Innovation Sept. 2016), https://www.nehi.net/writable/publication_files/file/better_use_of_medicine_for_patients_with_diabetes_issue_brief_9.7.2016.pdf.

26 *Common Questions About Type 2 Diabetes*, JOSLIN DIABETES CTR., https://www.joslin.org/info/common_questions_about_type_2_diabetes.html (accessed Mar. 15, 2019).

27 David Beran et al., *Insulin in 2016: Challenge and Constraints to Access*, 62 DIABETES VOICE 21, 21 (2016); see also Tylee & Hirsch, *supra* note 3, at 665.

28 Cefalu et al., *supra* note 1, at 1300.

29 For an account of an individual who died because he could not afford his \$1,300.00 insulin bill, see Drew Pendergrass, *How Insulin Became Unaffordable*, HARVARD POLITICAL REV., Jan. 22, 2018, <https://harvardpolitics.com/united-states/how-insulin-became-unaffordable/> (profiling Alec Raeshawn Smith).

30 See Luo et al., *supra* note 4, at 158; Deborah Cohen, *The prickly problem of access to insulin*, 343 BMJ 1, 1 (2011).

31 David Beran et al., *Why Are We Failing to Address the Issue of Access to Insulin? A National and Global Perspective*, 41 DIABETES CARE 1125, 1127 (2018). They are still available in some other countries, but they are not widely used.

32 Erika Gebe, *Making Insulin*, DIABETES FORECAST, July 2013, <http://www.diabetesforecast.org/2013/jul/making-insulin.html>.

33 See *Analogous Insulin*, DIABETES.CO.UK, <https://www.diabetes.co.uk/insulin/analogous-insulin.html> (last accessed Mar. 15, 2019).

34 *Id.*

insulins) typically have an onset time of 30 minutes with a peak of 2–3 hours.³⁵ In comparison, long-acting insulins have an onset time of approximately 1–2 hours but have no significant peak, which makes them more flexible for people with diabetes to plan their day and meals around.³⁶

Insulin analogs are much more commonly used and prescribed than human insulins, in part because of their perceived novelty and superiority.³⁷ They also have more predictable onset and peak times and action profiles, making them easier for individuals with diabetes, in particular Type 1 diabetes, to use and plan their meals.³⁸ However, there are debates about the relative benefits of analog insulins compared with human insulins.³⁹ Some studies have suggested that analog insulins are less cost-effective than human insulins.⁴⁰ Most studies have found some benefits associated with analog insulins. Patients consistently report significant increases in quality of life from the more predictable onset and peaks associated with analog insulins.⁴¹ Some studies have found a decreased risk of hypoglycemia⁴² and a ‘modest’ reduction in nocturnal hypoglycemia⁴³ associated with basal insulin (analog insulins including insulin detemir

35 See Daphne E. Smith-Marsh, *What You Need To Know about Insulin: Get the Basics on the Types of Insulin*, ENDOCRINE WEB (last updated May 16, 2019), <https://www.endocrineweb.com/guides/insulin/what-you-need-know-about-insulin>.

36 *Id.*

37 Beran et al., *supra* note 31, at 1127; Luo et al., *supra* note 4, at 158; Kasia J. Lipska, *Insulin Analogues for Type 2 Diabetes*, 321 J. AM. MED. ASS’N 350, 350 (2019).

38 *Insulin Analogs: Diabetes Education Online*, DIABETES TEACHING CTR. AT THE UNIV. OF CALIFORNIA, SAN FRANCISCO, <https://dtt.ucsf.edu/types-of-diabetes/type2/treatment-of-type-2-diabetes/medications-and-therapies/type-2-insulin-rx/types-of-insulin/insulin-analogs/> (last accessed Aug. 21, 2019).

39 For a literature review of studies comparing the effectiveness of insulin products, see Nathaniel Posner & Veronika J. Wirtz, *Comparison of the efficacy and safety of analogue versus human insulin*, in INSULIN MARKET PROFILE 60 (Health Action International Apr. 2016), http://haiweb.org/wp-content/uploads/2016/04/ACCISS_Insulin-Market-Profile_FINAL.pdf. These debates sometimes consider the possibility of transitioning some patients from more expensive analog insulins to more affordable human insulins as a means to improve affordability of insulin and decrease overall insulin spending. See, e.g., Cefalu et al., *supra* note 1, at 1307 (‘Until there is a systematic plan that addresses a change in benefit design to lower out-of-pocket insulin costs for people with diabetes, human insulin may be a valid alternative to more expensive analog insulins for some patients.’); Warren A. Kaplan & Reed F. Beall, *The global intellectual property ecosystem for insulin and its public health implications: an observational study*, 10 J. PHARMACEUTICAL POL’Y & PRACTICE 1, 7–8 (2017) (‘Off-patent human insulins can effectively manage diabetes. Others have observed the need for older insulins to be manufactured and our findings support and underscore this need. A practical way forward would be to find (potential) generic manufacturers globally and incentivize them toward opportunities to diversify their national insulin markets with acceptable off-patent products for export.’). As human insulins are significantly less expensive than analog insulins, switching physician prescribing patterns and increasing the demand for human insulin over analogs could improve patient access to insulin. Cefalu et al., *supra* note 1, at 1300; Beran et al., *supra* note 27, at 22 (‘analogue insulin is at least 2.4 times more expensive than human insulin.’). This is sometimes called the ‘Walmart Insulin solution,’ oftentimes pejoratively, referring to Walmart providing human insulin products (from either Novo Nordisk or Eli Lilly) for only \$25. See *T1International Statement on Walmart Insulin*, T1INTERNATIONAL (June 1, 2018), <https://www.t1international.com/blog/2018/06/01/t1international-statement-ada-insulin-access-paper/>. While this could be a solution in emergency situations and for some patients with Type 2 diabetes, it will not solve the access to insulin problem and cannot be a long-term solution.

40 Cohen, *supra* note 30, at 4.

41 Luo et al., *supra* note 4, at 158.

42 *Id.*

43 Lipska, *supra* note 37, at 350 (‘in clinical trials, insulin analogues modestly reduced the rate of nocturnal hypoglycemia, an important out- come for patients with diabetes. Notably, the clinical trials were open label,

and insulin glargine). Another study found ‘fewer nocturnal and severe hypoglycemic events and better glucose control’ associated with rapid-acting insulins (aspart, glulisine, and lispro) in comparison to regular human insulins.⁴⁴ These benefits of analog insulins are more pronounced in patients with Type 1 diabetes, especially those with a high risk of hypoglycemia.⁴⁵ In contrast, many studies indicate that patients with Type 2 diabetes see little to no benefit from analog insulins.⁴⁶ While both human and analog insulins play a significant role in the treatment of diabetes, the focus of this article is on the more used, more expensive analog insulins.

III. THE UNITED STATES INSULIN MARKET

The insulin market landscape in the United States presents several challenges to increasing competition and lowering prices. The specific context—the players, the prices, and the practical barriers—are thus very important to understanding the problem. This part describes and examines the complexities of the insulin market. Section A introduces the three insulin manufacturers, their respective products, and the pricing trends of these products. Section B discusses the extent to which patents and exclusivities are preventing competition in the insulin market.

A. Insulin Manufacturers, Products, and Prices

The insulin market in the United States is highly concentrated. Only three companies—Novo Nordisk, Sanofi, and Eli Lilly—supply insulin to patients in the United States.⁴⁷ These three companies are commonly called the ‘Big Three’ because they control over 90 per cent of the global insulin market.⁴⁸ The remaining share of the global insulin market is split among approximately seven insulin manufacturers.⁴⁹ Other companies

so they do not have the advantage of blinding, and the nocturnal hypoglycemia outcome was self-reported. Therefore, these trials are subject to risk of bias.”).

44 Karla F.S. Melo et al., *Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis*, 11(2) *DIABETOLOGY & METABOLIC SYNDROME* 1, 12 (2019).

45 Lipska, *supra* note 37, at 351.

46 See, e.g., Jing Luo et al., *The Clinical and Economic Effects of Switching Medicare Beneficiaries with Type 2 Diabetes from Analog to Human Insulin*, 67(1) *DIABETES 4-OR* (2018), http://diabetes.diabetesjournals.org/content/67/Supplement_1/4-OR. (“Switching Medicare beneficiaries with diabetes from analog to human insulin did not change the rates of hospitalization for hypoglycemia or hyperglycemia, slightly increased mean A1c, and reduced the risk of reaching the Part D coverage gap.”); Jing Luo et al., *Implementation of a Health Plan Program for Switching From Analogue to Human Insulin and Glycemic Control Among Medicare Beneficiaries With Type 2 Diabetes*, 321 *J. AM. MED. ASS’N* 374, 382 (2019) (finding that people with Type 2 diabetes with Medicare switching from analog to human insulin was associated with only a small population increase in average HbA1c but was “within the biological within-patient variation of modern HbA1c assays.” and no association between switching from analog to human insulin with risk of serious hypoglycemia or hyperglycemia). See also David Beran et al., *Analogue insulin as an essential medicine: the need for more evidence and lower prices*, *LANCET DIABETES & ENDOCRINOLOGY* 338, 338 (2019) (challenging the inclusion of insulin analogs on the World Health Organization’s List of Essential Medicines as the evidence does not support the superiority of insulin analogs in comparison to recombinant human insulin).

47 Cefalu et al., *supra* note 1, at 1300; Luo et al., *supra* note 4, at 158.

48 Beran et al., *supra* note 19, at 726; Beran et al., *supra* note 31, at 1127.

49 Christophe Perrin et al., *The role of biosimilar manufacturers in improving access to insulin globally*, 5 *LANCET DIABETES & ENDOCRINOLOGY* 578, 578 (2017)

selling insulin have been identified globally, though they are likely distributors of other manufacturers' insulin products.⁵⁰

The Big Three supply a range of insulin products to the United States market, summarized in Table 1. The majority of the insulin products are originator products or the first insulin product of its kind approved for sales and marketing.⁵¹ Both human insulins and insulin analogs are available. The formulations of insulin available in the United States can be categorized into four groups based on their speed of action:⁵² rapid-acting insulins, short-acting insulins, intermediate-acting insulins, and long-acting insulins. While the insulin products can be grouped generally based on their speed of action, the level of interchangeability among the groups varies. For example, there has been little difference observed between NovoLog (insulin aspart) and Humalog (insulin lispro).⁵³ Some studies have indicated there are no differences between the outcomes in patients taking Levemir (insulin detemir) and Lantus (insulin glargine),⁵⁴ while others have shown significant improvements in patients switching from Levemir to Lantus.⁵⁵

The prices of all insulin products—human and analog—are increasing in the United States. From 2002 to 2013, the prices of the most popular insulin products tripled,⁵⁶ and from 2012 to 2016, the average price paid for insulin by patients with type 1 diabetes nearly doubled.⁵⁷ Payers are also experiencing drastic increases. Medicaid reimbursements for insulin products increased at near exponential rates from 1991 to 2014, and in 2015, the second largest expenditure of Medicare Part D was for insulin glargine (Lantus), Sanofi's top insulin product.⁵⁸ The increases in the list prices of

50 Beran et al., *supra* note 18, at 728.

51 See WORLD HEALTH ORGANIZATION & HEALTH ACTION INTERNATIONAL, MEASURING MEDICINE PRICES, AVAILABILITY, AFFORDABILITY AND PRICE COMPONENTS 234 (2d ed. 2008) (defining “Originator pharmaceutical product/originator brand”).

52 For additional information on these types of insulin, see *Insulin Basics*, AM. DIABETES ASS'N (last updated July 16, 2015), <http://www.diabetes.org/living-with-diabetes/treatment-and-care/medication/insulin/insulin-basics.html>. There are other types of insulin products (such as include Sanofi's Afrezza, an inhaled insulin), but this article will focus only on injectable insulins. There are also mixture products available, not indicated in Table 1. Many of these mixtures are, however, described in Table 2 when discussing their associated patents.

53 Patrick N. Rasca et al., *Comparative Effectiveness of Rapid-Acting Insulins in Adults with Diabetes*, 23(3) J. MANAGED CARE & SPECIALTY PHARMACY, 291, 295 (2017). See also Carol Homko et al., *Comparison of Insulin Aspart and Lispro: Pharmacokinetic and metabolic effects*, 26(7) DIABETES CARE 2027, 2030 (2003) (describing the actions of both insulin aspart and insulin lispro as “indistinguishable”).

54 Thomas Danne & Jan Bolinder, *New Insulins and Insulin Therapy*, 15 DIABETES TECH. & THERAPEUTICS S-40, S42 (2013) (citing Sanne G. Swinnen et al., *Insulin detemir versus insulin glargine for type 2 diabetes mellitus*, 7 COCHRANE DATABASE SYST. REV. (2011), CD006383). Both of these studies looked specifically at Type 2 Diabetes.

55 P. Levin et al., *Therapeutically interchangeable? A study of real-world outcomes associated with switching basal insulin analogues among US patients with type 2 diabetes mellitus using electronic medical records data*, 17 DIABETES, OBESITY, & METABOLISM 245, 245, 247, & 251 (2015).

56 Cefalu et al., *supra* note 1, at 1299.

57 Kevin Truong, *Can changing rebate rules stop the 'carousel' of insulin price hikes*, MEDCITY NEWS (June 9, 2019), <https://medcitynews.com/2019/06/can-changing-rebate-rules-stop-the-carousel-of-insulin-pricing-hikes/?rf=1> (“Between 2012 and 2016, average insulin spending for patients with Type 1 diabetes nearly doubled from \$2,864 to \$5,705 and a recent clinical study published in JAMA Internal Medicine found that 30 percent of patients ration their insulin.”) (citing Darby Herkert et al., *Cost-Related Insulin Underuse Among Patients With Diabetes*, 179 J. AM. MED. ASS'N INTERNAL MED. 112 (2019)).

58 Luo et al., *supra* note 4, at 158.

Table 1. Insulin Manufacturers: Market Share and Products.¹⁵³

Company	Global Market Share (by Volume)	Global Market Share (by Revenue)	Insulin Products			
			Rapid-acting insulins	Short-acting insulins (Human recombinant insulins)	Intermediate-acting insulins	Long-acting insulins
Novo Nordisk	52%	41%	NovoLog (insulin aspart)	Novolin R	Novolin N (insulin NPH)	Levemir (insulin detemir)
Sanofi	17%	32%	Apidra (insulin glulisine); Admelog (follow-on of Humalog)	—	—	Lantus (insulin glargine)
Eli Lilly	23%	23%	Humalog (insulin lispro); authorized generic Humalog	Humulin R	Humulin N (insulin NPH)	Basaglar (follow-on of Lantus)

individual products are also shocking. The list price of a NovoLog vial increased 353 per cent from 2001 to 2016, while the list price of a NovoLog FlexPen increased 270 per cent from 2003 to 2016,⁵⁹ and the price of Humalog increased 585 per cent (from \$35 to \$234 per vial) from 2001 to 2015.⁶⁰

There is also a ‘widening gap between the net and list price of insulin.’⁶¹ Insulin manufacturers purport that their list prices have fallen and that the increasing prices patients pay for insulin are related to the rebates negotiated by pharmacy benefit managers.⁶² Pharmacy benefit managers negotiate rebates with manufacturers, with higher rebates incentivizing pharmacy benefit managers to prioritize that manufacturer’s product on the health plan’s formulary.⁶³ In the case of insulin, the rebates paid to pharmacy benefit managers have reportedly increased to approximately half the list price of insulin.⁶⁴ This model results in pharmacy benefit managers negotiating rebates that benefit themselves and not the patients. In fact, several advocates worry that the half-priced authorized generics will not make insulin any more affordable to consumers, as pharmacy benefit managers will be incentivized to negotiate a higher rebate for the more expensive originator product instead of taking a decreased profit on the new authorized generic.⁶⁵ There have been several legislative proposals to address the incentives of pharmacy benefit managers,⁶⁶ but with the extreme

59 *Id.*

60 AGATA DABROWSKA, CONG. RESEARCH SERV., R44620, BIOLOGICS AND BIOSIMILARS: BACKGROUND AND KEY ISSUES 6 (2019). Note that one vial of insulin may only last a patient two weeks. *Id.*

61 Cefalu et al., *supra* note 1, at 1303.

62 Eric Sagonowsky, *Fed up with the blame game on insulin prices, lawmakers say enough is enough*, FIERCEPHARMA, Apr. 10, 2019, <https://www.fiercepharma.com/pharma/fed-up-blame-game-insulin-pri-ces-lawmakers-say-enough-enough> (“The drugmakers said their net prices have fallen as the rebates they pay PBMs have mushroomed, while the PBMs argued their negotiations save health systems money.”); Truong, *supra* note 58 (“Deflecting blame over the pharma industry’s rising list prices for insulin, Reilly said in most cases the net prices seen by drugmakers have decreased over the past 10 years and called out PBMs for refusing to put lower-priced insulin alternatives onto their formularies. She stated the theory that PBMs may be disinclined to offer lower cost drugs due to what she termed as the ‘addictive nature of rebates.’ In most cases discounts and rebates negotiated between PBMs and manufacturers are kept secret and higher rebates are often used as leverage for better formulary placement.”).

63 See Pendergrass, *supra* note 29 (“The United States does not negotiate prices with drug manufacturers. The for-profit companies who are supposed to negotiate, PBMs, do so in their own interests and not the interests of patients. Patients are left powerless, and are shamed publicly for their weakness.”).

64 Cefalu et al., *supra* note 1, at 1303.

65 Joshua Cohen, *Rising Out-Of-Pocket Costs For Insulin Indicates Market Failure*, FORBES, Mar. 22, 2019, <https://www.forbes.com/sites/joshuacohen/2019/03/22/rising-out-of-pocket-costs-for-insulin-i-ndicates-market-failure/#707b8edb5075> (“In the case of Lilly’s authorized generic pharmacy benefit managers (PBMs) now have two options: Negotiate a higher rebate for the higher-priced branded Humalog, or pay the lower price for the authorized generic and receive a smaller rebate. In the current rebate system, for some PBMs, the incentive may be to favor branded Humalog.”).

66 See, e.g., Paige Minemyer, *Senator introduces bill to end PBM drug rebates in commercial plans*, FIERCEHEALTHCARE, Mar. 7, 2019, <https://www.fiercehealthcare.com/payer/senator-introduces-bill-to-end-pbm-drug-rebates-commercial-plans>; Susannah Luthi, *Senators to boost Trump’s proposed ban on PBM rebates*, MODERN HEALTHCARE, Mar. 6, 2019, <https://www.modernhealthcare.com/payment/senators-boost-trumps-proposed-ban-pbm-rebates>; Michael Olive, *Drug-Price Debate Targets Pharmacy Benefit Managers*, PEW CHARITABLE TRUSTS, Feb. 12, 2019, <https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2019/02/12/drug-price-debate-targets-pharmacy-benefit-managers>.

concentration of the insulin market, these may not ultimately be effective in making insulin affordable.⁶⁷

B. Insulin Patent Protection

Unlike many pharmaceutical markets, which see the entry of generic competitors, no generic or biosimilar insulins have been approved in the United States.⁶⁸ This is not due to patent protection of the existing products.⁶⁹ The patents for the majority of human and analog insulin products have expired or are about to expire.⁷⁰ At the end of 2015, 11 insulin products had no associated patents or exclusivities.⁷¹ This number has since risen to approximately 17 by July 2019 (including those products where only the insulin pen device is protected), shown in Table 2.

Even though there are very few insulin products that have patent protection on the compound itself, the vast majority of insulin products still have patent protection on the pens and other devices that deliver the dose of insulin. Novo Nordisk has patents for Novolog, Novolin, and FIASP products; Sanofi has patents on the devices for all of its products; and Eli Lilly still has patents on some devices that deliver Humulin and Humalog.

The patent protection on the devices is significant. Because the pens and other insulin delivery devices can only be used on with one brand of insulin, competition on those products is effectively delayed. While a prospective competitor could develop a follow-on biologic or biosimilar of the insulin, it would have to develop its own delivery device. This may only be a partial barrier, but with the popularity of pens and pumps and the inability for interoperable devices, the device patent protection serves as a notable obstacle to competitor entry—the focus of the next part.

IV. CHALLENGES TO INCREASING COMPETITION AND AFFORDABILITY IN THE INSULIN MARKET

The reasons for the limited competition in the insulin market are unclear. This part examines the challenges to increasing competition and affordability in the insulin market, focusing on the issues specific to insulin and the interaction between the manufacturers and other players in the insulin market. Section A examines the legal and regulatory barriers to the approval of new insulin products, especially biosimilars. Section B discusses the challenges to obtain interchangeability approval for biosimilar and follow-on biologic insulin products and the impact on affordability. Section C highlights the barriers to entry in the insulin market, particularly for new companies, and the risks of, and anticipation of, anticompetitive conduct that prevent successful market entry.

67 Therefore, the remainder of this article will focus on barriers to insulin affordability and pricing by focusing on the manufacturers, and not the impact of pharmacy benefit managers, payers, or other actors in the healthcare industry.

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

69 See Beran et al., *supra* note 31, at 1127; Beran et al., *supra* note 27, at 21; Kaplan & Beall, *supra* note 29, at 6.

70 Cefalu et al., *supra* note 1, at 1300.

71 Jing Luo & Aaron S. Kesselheim, *Evolution of insulin patents and market exclusivities in the USA*, 3 LANCET DIABETES & ENDOCRINOLOGY 835, 837 (2015).

Table 2. Insulin Products With and Without Patent Protection.¹⁵⁴

Company	Patent on Insulin Product	Patent on Insulin Device	No Patent Protection
Novo	<ul style="list-style-type: none"> • FIASP 	<ul style="list-style-type: none"> • Novolin 70/30 Pen 	<ul style="list-style-type: none"> • Levemir Flextouch
Nordisk	<ul style="list-style-type: none"> • NovoLog Mix • NovoLog • Ryzodeg 70/30 • Tresiba 	<ul style="list-style-type: none"> • FIASP Flextouch • NovoLog Mix Flexpen • NovoLog Mix Flexpen 70/30 • Novolog Penfill • NovoLog Flexpen 	<ul style="list-style-type: none"> • NovoLog Mix 70/30 Injectable • NovoLog Injectable • Novolin R Injectable • Novolin N
Sanofi	<ul style="list-style-type: none"> • Toujeo • Apidra 	<ul style="list-style-type: none"> • Lantus Solostar • Lantus Injectable • Toujeo Max Solostar • Toujeo Solostar • Apidra Solostar • Admelog Solostar 	<ul style="list-style-type: none"> • Admelog
Eli Lilly		<ul style="list-style-type: none"> • Humulin 70/30 Pen • Humulin N Injectable • Humulin R • Humalog Mix 50/50 Kwikpen • Humalog Mix 75/25 Kwikpen • Humalog Kwikpen 	<ul style="list-style-type: none"> • Basaglar • Humulin R Kwikpen • Humalog Mix 50/50 Injectable • Humalog Mix 75/25 Injectable • Humalog • Humulin N

A. FDA Approval of Biosimilar Insulins

Introducing competitor insulin products in the United States—including biosimilar insulins—could improve affordability and accessibility of insulin. The current regulatory environment, however, is in a state of transition and does not promote the approval of biosimilar insulins.

Insulin is a biologic, which is a drug ‘derived from living materials, including viruses, therapeutic serums, toxins and antitoxins, vaccines, blood and blood products, and cells, tissues, and gene therapy products.’⁷² Most drugs are small molecule drugs, which are regulated under the Federal Food Drug and Cosmetic Act (FDCA) and approved under a New Drug Application (NDA) or associated accelerated pathway.⁷³ Most biologics are approved through a Biologics License Application (BLA) under the Public Health Service Act (PHS Act).⁷⁴ However, insulin was approved before the Food and Drug Administration (FDA) created the biologics approval process and was regulated as a small molecule drug under the FDCA until March 23, 2020.⁷⁵

This regulatory inconsistency served as a practical barrier for introducing competition into the insulin market, particularly biosimilar competition. Biosimilars are drugs that are ‘highly similar to the [biologic] reference product notwithstanding minor differences in clinically inactive components’ and has ‘no clinically meaningful differences . . . in terms of the safety, purity, and potency of the product’ with the reference biologic.⁷⁶ Under the PHS Act, biosimilars must be based on an approved

72 Jordan Paradise, *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, 63–64 (2015) (citing Public Health Service Act § 351(i), 42 U.S.C. § 262(i) (2012)). See also DABROWSKA, *supra* note 61, at 1 (“A biologic or biological product is a preparation, such as a therapeutic drug or a vaccine, made from living organisms, either human, animal, yeast, or microorganisms. Biologics are composed of proteins (and/or their constituent amino acids), carbohydrates (such as sugars), nucleic acids (such as DNA), or combinations of these substances. Biologics may also be cells or tissues used in transplantation.”); W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1032 (2016) (“Biologics are complex macromolecular therapeutics produced by living sources rather than through chemical synthesis. Biologics as a class include therapeutic proteins, toxins and antitoxins, viruses, blood and blood products, gene therapy products, and whole cells, among others. As a general matter, they are much more complex than traditional small-molecule drugs.”).

73 See 21 U.S.C. § 355(b)(1) (2012 & Supp. I 2013) (NDA process).

74 42 U.S.C. § 262 (2012); Richard Dolinar et al., *A Guide to Follow-On Biologics and Biosimilars with a Focus on Insulin*, 24(2) ENDOCRINE PRACTICE 195, 197 (2018).

75 Zachary Brennan, *Updated: The 505(b)(2) Pathway and Why Some Follow-on Insulins Are not Yet Biosimilars in the US*, REGULATORY FOCUS: REGULATORY AFFAIRS PROFESSIONALS SOCIETY, Dec. 11, 2017, [https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/12/updated-the-505\(b\)\(2\)-pathway-and-why-some-follow-on-insulins-aren%E2%80%99t-yet-biosimilars-in-the-us](https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/12/updated-the-505(b)(2)-pathway-and-why-some-follow-on-insulins-aren%E2%80%99t-yet-biosimilars-in-the-us); Maria Lapteva et al., *Comparison of Regulatory Guidelines for Insulins/Biosimilars*, in BIOSIMILAR INSULIN REGULATORY PROFILE 14 (Health Action International April 2017).

76 42 U.S.C. § 262(i)(2). See also Joanna Shepherd, *The Prescription For Rising Drug Prices: Competition Or Price Controls?*, 27 HEALTH MATRIX 315, 343 (2017) (“Under BPCIA, a proposed biologic substitute does not have to demonstrate bioequivalence, but merely biosimilarity, to a reference product.”); DABROWSKA, *supra* note 1, at 1 (A biosimilar, sometimes referred to as a follow-on biologic, is a therapeutic drug that is highly similar but not structurally identical to a brand-name biologic”).

reference biologic product.⁷⁷ Because insulin had been regulated as a small drug, there was no reference biologic insulin product for which a biosimilar could be developed.⁷⁸

As a result of this regulatory inconsistency, while there have not yet been any biosimilar insulins approved, there have been two ‘follow-on’ biologic insulins approved.⁷⁹ Follow-on biologics are products based on existing biologic—like a biosimilar—but are not approved under the biosimilar approval pathway.⁸⁰ Instead, follow-on insulins have been approved under the FDCA 505(b)(2) regulatory pathway, which is a New Drug Approval pathway distinct from the abbreviated pathways for generics or biosimilars.⁸¹ The 505(b)(2) pathway allows the applicant to use studies from the originator product to support its application because of chemical similarities, but does not result in a generic or interchangeable drug.⁸²

Insulin is now in a point of transition:⁸³ effective March 23, 2020, insulins are now regulated as biologics under the PHS Act, as amended by the Patient Protection and Affordable Care Act.⁸⁴ Whereas before no biosimilar insulins could be approved before with no insulin reference products recognized under the PHS Act, insulins will now be regulated as biologics, making way for biosimilar applications and competitors.⁸⁵ The FDA is optimistic that this will increase competition in the insulin market significantly, and there are several products globally that now have the potential to enter the United

77 See generally 42 U.S.C. § 262 (defining biosimilars and interchangeable biosimilars in the context of a licensed reference product under the PHS Act).

78 *Is Biosimilar Insulin Available*, BIOSIMILARS RESOURCE CTR., <https://www.biosimilarsresourcecenter.org/faq/biosimilar-insulin-available/> (accessed Aug. 21, 2019).

79 Basaglar, Eli Lilly’s follow-on insulin glargine (Lantus), was approved by the FDA in late 2015. *FDA Approves Basaglar® (insulin glargine injection), a Long-Acting Insulin Treatment*, LILLY, Dec. 16, 2015, <https://investor.lilly.com/news-releases/news-release-details/fda-approves-basaglar-insulin-glargine-injection-long-acting>. Admelog, Sanofi’s follow-on insulin lispro (Humalog), was approved by the FDA in December 2017. Mary Caffrey, *Sanofi’s Insulin Lispro Follow-On, Admelog, Wins FDA Approval*, AM. J. MANAGED CARE MANAGED MARKETS NETWORK, Dec. 11, 2017, <https://www.ajmc.com/newsroom/sanofis-insulin-lispro-followon-admelog-wins-fda-approval>; *FDA approves Admelog, the first short-acting “follow-on” insulin product to treat diabetes*, U.S. FOOD & DRUG ADMIN., Dec. 11, 2017, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm588466.htm>. Other insulin follow-on products and biosimilars are in the pipeline. John White & Jennifer Goldman, *Biosimilar and Follow-On Insulin: The Ins, Outs, and Interchangeability*, 25 J. PHARMACY TECH. 25, 31 (2019). Biocon (in cooperation with Mylan) Gan and Lee, and Wockhardt have all begun Phase 3 clinical trials for follow-on Lantus products. See *id.* Gan and Lee, Wockhardt, and Julphar Pharmaceuticals have also begun or completed Phase 1 clinical trials for their products: Gan & Lee and Wockhardt for their Lantus follow-on products and Julphar for a follow on Humulin product. See *id.*

80 While some articles use follow-on biologic and biosimilar interchangeably, see, e.g., DABROWSKA, *supra* note 61, this article differentiates follow-on biologics and biosimilars by their approval pathway. Biosimilars are approved under the BLA pathway while follow-on biologics, for the purposes of this article, are those insulins approved through the FDCA 505(b)(2) pathway.

81 Jack T. Rasmussen & Heather J. Ipema, *Formulary Considerations for Insulins Approved Through the 505(b)(2) ‘Follow-on’ Pathway*, 53(2) ANNALS OF PHARMACOTHERAPY 204, 204 (2019).

82 See 21 U.S.C. § 355(b)(2) (detailing requirements for a 505(b)(2) application).

83 WARREN KAPLAN & REED BEALL, *INSULIN PATENT PROFILE 10* (Health Action International April 2016), <http://haiweb.org/wp-content/uploads/2016/04/ACCISS-PatentReport-FINAL.pdf>.

84 See *Insulin Gains New Pathway to Increased Competition*, U.S. FOOD & DRUG ADMIN., March 23, 2020, <https://www.fda.gov/news-events/press-announcements/insulin-gains-new-pathway-increase-d-competition>.

85 *Id.*

States market. While this is a major step in promoting insulin competition, there remain several more barriers.

B. Interchangeability of Biosimilar and Follow-On Biologic Insulins

A further regulatory barrier to biosimilar insulin competition is interchangeability. Unlike generics, biosimilars are not automatically substitutable with the biologic. To be interchangeable, a manufacturer must demonstrate that the product (1) is ‘biosimilar’ to the reference product, (2) ‘can be expected to produce the same clinical result as the reference product’, and (3) does not pose a greater risk ‘in terms of safety or diminished efficacy’ compared to the reference product if a patient were to switch or alternate use.⁸⁶ The FDA to date has only approved 19 biosimilar products of any kind,⁸⁷ and no biosimilar has yet received interchangeability status.⁸⁸ This outlook is not supportive of seeking approval of an interchangeable biologic, which may be necessary for effective market entry and competition.

Interchangeability of the biosimilar and originator biologic is especially important for the competition to bring a price decrease.⁸⁹ Without interchangeability, biosimilars are only associated with a limited price decrease. Biosimilars and the current follow-on insulin products are typically only 15 per cent cheaper than the originators.⁹⁰ In comparison, generics are typically at least 50 per cent, and as high as 80 per cent, cheaper than the originator product.⁹¹ The difference in price decrease associated with generics and biosimilars is largely due to the lack of automatic substitution;⁹² because biosimilars are not automatically substitutable with the originator biologic (without

86 21 U.S.C. § 262(k)(4). See also Cefalu et al., *supra* note 1, at 1307 (interchangeable product approval requires “show[ing] that the biosimilar is ‘expected to produce the same clinical result’ as the original biologic medication and that ‘switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching.’”); Shepherd, *supra* note 78, at 343 (“A product approved as biosimilar may further be deemed interchangeable with another biologic if its manufacturer can demonstrate that switching between the reference biologic and the proposed substitute presents no additional risk in safety or efficacy for consumers. Importantly, under federal law, interchangeable products may be substituted for reference biologics without a prescribing doctor’s intervention.”).

87 See DABROWSKA, *supra* note 671, at 10–11 (May 19, 2019); White & Goldman, *supra* note 81, at 25 (eleven); Michael A. Carrier & Carl J. Minniti III, *Biologics: The New Antitrust Frontier*, 2018 UNIVERSITY OF ILLINOIS L. REV. 1, 16 (2018); KRISTA MAIER & MEGHAN RILEY, IMPROVING INSULIN ACCESS AND AFFORDABILITY 5 (Am. Diabetes Ass’n May 2018).

88 See Carrier & Minniti, *supra* note 99, at 16; MAIER & RILEY, *supra* note 89, at 5.

89 Jing Luo et al., *Trends in Medicaid Reimbursement for Insulin From 1991 Through 2014*, 175 J. AM. MED. ASS’N INTERNAL MED. 1681, 1686 (2015); Kaplan & Beall, *supra* note 39, at 7.

90 Cefalu et al., *supra* note 1, at 1308; MAIER & RILEY, I *supra* note 89, at 5; Maria Lapteva et al., *Profile Summary*, in BIOSIMILAR INSULIN REGULATORY PROFILE 3–4 (Health Action International Apr. 2017).

91 Carrier & Minniti, *supra* note 89, at 10; MAIER & RILEY, *supra* note 89, at 5.

92 Automatic substitution is largely governed by state law. See Yaniv Heled, *Follow-On Biologics Are Set Up To Fail*, 2018 ILLINOIS L. REV. 113, 126 (2018) (“While BPCIA authorizes the FDA to make substitutability determinations, actual substitution of original products with their follow-on versions is governed by state laws (regulating the practice of medicine and dispensation of biomedical products).”). Some states already have laws allowing prescriptions for a biologic to be filled with biosimilars deemed interchangeable, just like generics. Cefalu et al., *supra* note 1, at 1307–08. See also Gary M. Fox, Note, *Suggestions for State Laws on Biosimilar Substitution*, 24 MICH. TELECOMM. & TECH. L. REV. 253, 259–69 (2018) (describing federal laws governing biosimilar interchangeability and making recommendations for state laws governing biosimilar interchangeability and substitution); Shepherd, *supra* note 78, at 337 (“Moreover, many states require biosimilars to be deemed interchangeable before they can be automatically substituted for their biologic

interchangeability approvals), a patient will not receive a biosimilar unless a physician specifically prescribes it.⁹³ Some studies suggest that clinicians in the United States and Europe are often cautious or unaware of biosimilars as an option in treatment.⁹⁴ Other studies have also indicated similar concern regarding biosimilar insulins among patients.⁹⁵ If biosimilar insulins enter the market and interchangeability cannot be achieved, research would need to strongly support the safety and equivalence in order to support physician and patient buy-in. However, with approved interchangeable biosimilar insulins and trust from the community, significantly larger price drops could occur.

Compounding the challenge to interchangeability of biosimilar insulins is the secrecy surrounding the manufacturing processes.⁹⁶ The manufacturing process of pharmaceuticals, including biologics, is generally regulated by trade secrets law.⁹⁷ Unlike patents, which expire, trade secrets have no expiration date and only lose

counterpart at pharmacies. A high hurdle for what constitutes interchangeability will limit automatic substitution of affordable.”).

93 Erika Lietzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 FLORIDA STATE UNIV. L. REV. 883, 907 (2017) (“because biosimilar biologics will not be deemed interchangeable by FDA or substitutable under state pharmacy laws, they must achieve market penetration differently. If a biosimilar is to be dispensed to a patient, it must be prescribed-selected by a treating physician for that patient. State law will not make the choice automatically.”).

94 Preston Atteberry et al., *Biologics Are Natural Monopolies (Part 1): Why Biosimilars Do Not Create Effective Competition*, HEALTH AFF. BLOG, Apr. 15, 2019, <https://www.healthaffairs.org/doi/10.1377/hblog20190405.396631/full/> (“Another barrier to entry for biosimilars that lowers the expected returns for potentially competing manufacturers is that physicians perceive them as less safe and less effective. This impression has been reinforced by case reports regarding novel side effects, reducing the proclivity of physicians to prescribe biosimilars. Unlike small-molecule generics, biosimilars cannot “bypass” the physician via automatic pharmacy-level substitution without first earning an “interchangeable” FDA designation”) (citing Hillel Cohen et al., *Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians*, 33(12) ADVANCES IN THERAPY 2160 (2016); *Switching may not be suitable for patients with immunogenicity*, GENERICS AND BIOSIMILARS INITIATIVE (Sept. 30, 2019), <http://www.gabionline.net/Biosimilars/Research/Switching-may-not-be-suitable-for-patients-with-immunogenicity>); See generally Emily Leonard et al., *Factors Affecting Health Care Provider Knowledge and Acceptance of Biosimilar Medicines: A Systematic Review*, 25 J. MANAGED CARE & SPECIALTY PHARMACY 102 (2019).

95 One study suggested that brand loyalty may factor into insulin competition. Luo & Kesselheim, *supra* note 72, at 837 (“Additionally, patients and providers might have strong brand loyalty or preferences for existing products.”). Another patient perspective study agreed that brand loyalty was a factor (in comparison to company loyalty), but those patients surveyed indicated that they would be willing to try insulins made by other smaller companies. MOLLY LEPESKA, *INSULIN USERS’ PERSPECTIVE PROFILE 19* (Health Action International June 2017) (“In terms of willingness to change insulins, brand loyalty seemed more important than company loyalty. Of the 20 who answered the question, 17 respondents indicated they would be willing to use insulins from “smaller, lesser known companies.” Only three said they had ‘no preference.’ Most indicated that they were open to trying other insulins, but would need assurances, for example, ‘that it was the type they needed,’ or they would be willing to try, but “with reservations”. Of those willing, the largest reason given for considering new insulin was a recommendation from their doctors or other assurances that the insulin was ‘good.’”).

96 White & Goldman, *supra* note 81, at 26; Brendan McArdle, *Rumble in the BPCIA: Biologics vs. Biosimilars*, 17 HOUS. J. HEALTH L. & POL’Y 381, 385 (2017).

97 See, e.g., W. Nicholson Price II, *Expired Patents, Trade Secrets, and Stymied Competition*, 92 NOTRE DAME L. REV. 1611, 1618 (2017) (hereinafter Price, *Expired Patents*) (“For instance, a drug may be patented, but the methods of manufacturing that drug may be protected by trade secret.”); See W. Nicholson Price II, *Making Do In Making Drugs: Innovation Policy And Pharmaceutical Manufacturing*, 55 BOSTON COLLEGE L. REV. 491, 527 (2014) (hereinafter Price, *Making Do*) (“For biological manufacturing processes, patent protection strategies may differ because manufacturing methods are unusually central for biologics. Even

protection by the independent invention of the trade secret by another.⁹⁸ This is particularly important in understanding the limited competition in biologics markets. The final three-dimensional structure of biologics and biosimilars is highly dependent on the manufacturing process used⁹⁹ and as such similar manufacturing is key to manufacturing similar molecules. While the general process of insulin manufacturing is known, the details are highly confidential trade secrets.¹⁰⁰ “[T]he manufacturing protocols for existing biologic products, including insulins, are the proprietary information of the originator pharmaceutical company, and therefore other manufacturers may not duplicate the production process¹⁰¹ unless the biosimilar companies independently develop the same process, which is extremely difficult.¹⁰² As a result, it is exceedingly challenging, complex, and expensive for biosimilar manufacturers to generate products identical or nearly identical to the originator eligible for interchangeability.

While the FDA has released some guidance on interchangeability approval,¹⁰³ additional disclosures and support could help fast-track such approvals, such as limited disclosure of manufacturing techniques. Professors Price and Rai, for example, have suggested various potential disclosure mechanisms, including through the patent and FDA approval systems.¹⁰⁴ These would likely be strongly opposed by the industry, as the trade secret protection is extremely advantageous for them.¹⁰⁵ But given the continued unaffordability of insulin and limited competition, exploring such regulatory reforms may be warranted.

C. Entry Barriers and Anticompetitive Practices

Even if reforms can be instituted to increase competition in the United States insulin market, the current market control of the Novo Nordisk, Sanofi, and Eli Lilly—the ‘Big Three’—may prevent successful entry of new products and their ability to compete.

The massive market control of the Big Three serves as a practical barrier to entry, and the potential for anticompetitive conduct magnifies this risk. The Big Three have

more so than for small-molecule drugs, the manufacturing complexity and development costs for biologics can serve as a potent barrier to entry, keeping competitors off the market.”).

98 Price, *Expired Patents*, *supra* note 99, at 1614.

99 White & Goldman, *supra* note 81, at 26; Price & Rai, *supra* note 74, at 1034.

100 Dzintars Gotham et al., *Production costs and potential price for biosimilars of human insulin and insulin analogues*, 3 *BMJ GLOBAL HEALTH* 1, 5 (2018). See also Price, *Making Do*, *supra* note 99, at 527 (explaining the value of trade secret protection for manufacturing over patent protection) (“the public disclosure required by a patent can lower that entry barrier by providing information about both the biologic-specific manufacturing process and general manufacturing processes for biologics, making patents particularly unattractive.”).

101 White & Goldman, *supra* note 81, at 26. See also Martin K. Kuhlmann & Andrea Schmidt, *Production and manufacturing of biosimilar insulins: implications for patients, physicians, and health care systems*, 4 *BIOSIMILARS* 45, 48–49 (2014).

102 Price, *Expired Patents*, *supra* note 99, at 1612.

103 See, e.g., *Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed Guidance for Industry*, U.S. FOOD & DRUG ADMIN., Feb. 2020, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biosimilars-and-interchangeable-biosimilars-licensure-fewer-all-conditions-use-which-reference>.

104 Price & Rai, *supra* note 74, at 1052–1062 (exploring potential policy solutions).

105 *Id.* at [1046–48].

been accused of anticompetitive conduct in the past,¹⁰⁶ and a new competitor could elicit anticompetitive tactics in response. In other countries, the Big Three have already taken advantage of their dominant market position to price out other competitors. Novo Nordisk, for example, has priced out competitors in India.¹⁰⁷ In the event of a new market entrant in the United States, the Big Three could offer substantially cheaper prices for their insulin products, pricing competitors out of the market and protecting the existing oligopoly.¹⁰⁸ At that point, it may not be financially possible for the competitors to re-enter the market. Some companies, including Merck and Samsung Bioepis, have already abandoned their prospective entrance in the United States insulin market because of these perceived pricing barriers.¹⁰⁹ The hold of the Big Three on the global insulin market makes it questionable whether it is ‘financially viable’ for new biosimilar manufacturers to enter the market.¹¹⁰ Even though insulin could be sold at much lower prices and still yield profits,¹¹¹ the market control of the Big Three makes it hard for a company to enter and gain any market hold in the first place.

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- 106 See Thomas, *supra* note 1; Press Release, Attorney General Lori Swanson Files Lawsuit Against Pharmaceutical Companies Over Deceptive Price Spikes For Insulin, Oct. 16, 2018, https://www.ag.state.mn.us/Office/PressRelease/20181016_InsulinPriceHikes.asp; Eric Sagonowsky, *Amid insulin market scrutiny, Novo faces class action alleging ‘collusive price fixing’*, FIERCE PHARMA, Jan. 12, 2017, <https://www.fiercepharma.com/pharma/novo-faces-new-shareholder-suit-for-alleged-collusive-price-fixing>. See also Michael S. Sinha et al., *Antitrust, Market Exclusivity, and Transparency in the Pharmaceutical Industry*, J. AM. MED. ASS’N E1, E2 (May 7, 2018) (“a group of patients sued insulin manufacturers Sanofi, Novo Nordisk, and Eli Lilly, alleging simultaneous price hikes that increased the price of insulin products by 150% over 5 years.”).
- 107 Cohen, *supra* note 30, at 3. Similar conduct by other manufacturers has been seen in other countries; for example, “larger manufacturers offered substantially cheaper products—at least 3–15% of their U.S. price” in developing countries like India, Brazil, and Indonesia. Aaron S. Kesselheim, *Think Globally, Prescribe Locally: How Rational Pharmaceutical Policy in the U.S. Can Improve Global Access to Essential Medicines*, 34 AM. J.L. & MED. 125, 131 (2008).
- 108 These price drops would likely be followed by continued escalating prices after their competitors exit the market, potentially leaving patients worse off than before. This tactic, often called predatory pricing, could be an antitrust violation under the Robinson-Patman Act, 15 U.S.C. § 13(a) (2012), or the Clayton Antitrust Act, 15 U.S.C. § 2 (2012). The Supreme Court, however, has not generally been receptive to predatory pricing cases, especially when the low price is above cost. See generally *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.* 509 U.S. 209 (1993); C. Scott Hemphill & Philip J. Weiser, *Beyond Brooke Group: Bringing Reality to the Law of Predatory Pricing*, 127 YALE L.J. 2048 (2018); Aaron S. Edlin, *Predatory Pricing: Limiting Brooke Group to Monopolies and Sound Implementation of Price–Cost Comparisons*, 127 YALE L.J. F. 996 (2018). If the insulin manufacturers were to drop their prices below cost, which would be difficult and unlikely, there could be a successful claim. Even if the conduct did not constitute an antitrust violation, it would have significant anticompetitive consequences in the insulin market and would have devastating consequences for patients in the short term. For a detailed discussion of the potential antitrust issues surrounding biologics and biosimilars, see Carrier & Minniti, *supra* note 89.
- 109 Avik S. A. Roy, Testimony Before the United States Congress House Committee on Oversight and Reform, Prescription Drug Prices: A Key Driver of High Health Care Costs 9, Jan. 29, 2019, <https://docs.house.gov/meetings/GO/GO00/20190129/108817/HHRG-116-GO00-Wstate-RoyA-20190129.pdf>; Arlene Weintraub, *Merck ditches biosimilar Lantus, but will that ease the path for Mylan’s rival insulin product?*, FIERCEPHARMA, Oct. 12, 2018, <https://www.fiercepharma.com/pharma/merck-ditches-biosimilar-lantus-but-will-ease-path-for-mylan-s-rival-insulin-product>.
- 110 Heinemann, *supra* note 69, at 461.
- 111 The study by Gotham et al. indicated that “it may be possible to profitably manufacture biosimilar insulins at prices of US\$72 per year or less for human insulin and US\$133 per year or less for insulin analogues.” Gotham et al., *supra* note 102, at 5.

It is also extremely expensive to develop a biosimilar: the estimated investment is 7 to 8 years and between \$100 million and \$250 million,¹¹² in comparison to 1 year and \$1 million to \$4 million for small molecule generic drugs.¹¹³ This may cost less for companies already manufacturing insulin for the United States market and for other countries, given their existing experience and technology, but there would still likely be a delay in entry until the company can provide studies to demonstrate similarity or interchangeability.

Policies to prevent these anticompetitive pricing strategies and lower the entry barriers should be contemplated alongside these competition-promoting strategies. Further antitrust enforcement in the insulin market could deter anticompetitive conduct on the part of the Big Three. Even so, the barriers to entry are so significant and the market control of the Big Three so complete that they deter competition in the first place. Without substantial reforms, the insulin market will likely remain insulated from competition.

V. CONSIDERING THREE POLICY PROPOSALS

The previous part raised the challenges specific to the insulin market that have prevented competition thus far. Reforms in biologic approval, biosimilar approval, and interchangeability would go a long way in supporting the entry of new insulin products. Antitrust oversight and enforcement in the insulin industry would also promote and protect new market entrants that may help insulin accessibility and affordability.

These barriers are crucial to understanding why the insulin market has been insulated from competition and to developing effective reforms, but addressing these barriers only goes so far to increasing competition in the insulin market. While addressing these challenges would make the insulin market environment more welcoming for new market entrants, they would not promote entry itself or decrease the price of insulin.

This part considers three reforms that have been discussed to increase affordability and access and raises the benefits and challenges associated with each as a solution to insulin accessibility and affordability. Section A discusses implementing a reciprocal approval policy. Section B considers legalizing importation of insulin. Section C reviews price capping and price regulation of insulin. The goal of this part is not to advocate for one solution to access to insulin, but to discuss proposals that have already been put forth by lawmakers and policy experts and to analyze the benefits of challenges of each in the context of the insulin market specifically.

A. Reciprocal Approval of Existing Insulins

Taking advantage of existing companies with the capacity to increase their supply and enter the United States insulin market could be a fast and effective way to increase access, affordability, and competition. This could be done with reciprocal approval of products already approved in other countries. Such a reciprocal approval policy

112 Erwin A. Blackstone & Joseph P. Fuhr, Jr., *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS 469, 470 (2013). Not only are the fixed costs of manufacturing insulin (and other biologic) high, but the variable, marginal, and fractional costs are also high in comparison to small molecule drugs. See Price, *Making Do*, *supra* note 99, at 499–500.

113 Blackstone & Fuhr, *supra* note 112, at 469–470.

would allow the FDA to approve drugs based on approvals by certain other comparable medicines regulatory authorities.¹¹⁴

While there are only three manufacturers supplying insulin in the United States, there are an estimated 34 insulin manufacturers globally.¹¹⁵ These manufacturers only make up about 10 per cent of the global market and none supply the United States market.¹¹⁶ An early review identified over 40 companies providing insulin in other countries and additional investigation and meetings with manufacturers suggest that approximately 10 of these companies are independent of the other companies (not licensors or distributors).¹¹⁷

Outside of the United States, there are a few biosimilar human insulin and analog insulin products available. For example, in addition to the Big Three products discussed above, there are several other insulin products manufactured for the Indian market by other large manufacturers, including Biocon and Wockhardt.¹¹⁸ Wockhardt, an Indian manufacturer, launched the first insulin analog in Asia in 2003.¹¹⁹ Biocon, an Indian manufacturer, received approval for an insulin glargine biosimilar in Japan in 2016¹²⁰ and in Mexico in 2015, in cooperation with its local partner Pisa Pharmaceuticals.¹²¹

Studies have demonstrated that reciprocal approval policies would greatly increase the number of generic products available in the United States, reaching four or more approved manufacturers for 39 per cent of the products studied if reciprocal approval applied to seven non-United States regulators.¹²² This would have a lesser impact on

114 Ravi Gupta et al., *Affordability and availability of off-patent drugs in the United States- the case for importing from abroad: observational study*, 360 *BMJ* 1, 7 (2018) (“One way in which such a system may increase competition is by providing incentives for international suppliers to enter US drug markets by lowering the cost of FDA approval. Reciprocal approval could also facilitate regulatory responses to mitigate bad public health outcomes when drugs face shortages or dramatic price increases. Thus, international sources could lead to increased US competition for a meaningful number of drugs and might be worth pursuing in concert with other strategies. These strategies would include continuing the increased resources and capacity at FDA; prioritizing approvals and waiving application fees for drugs with few generic versions; and where medically appropriate, permitting automatic substitution of drugs within treatment 49 classes at the pharmacy level.”); Lietzan, *supra* note 95, at 899 (“regulators in the developed world—not only the EMA, Health Canada, and FDA, but also Japan’s Ministry of Health, Labor, and Welfare (MHLW), and the Australian Therapeutic Goods Administration (TGA), among others—are taking similar approaches to biosimilar approval, much as they do with innovative drug and biologic approval.”).

115 Beran et al., *supra* note 18, at 728.

116 Beran et al., *supra* note 18, at 728; Beran et al., *supra* note 27, at 21; Knox & Wirtz, *supra* note 20, at 14.

117 Perrin et al., *supra* note 49, at 578.

118 Kaplan & Beall, *supra* note 39, at 6. Bovine insulin is manufactured by USV (product Longact). Human insulins are manufactured by Wockhardt (product Wosulin) and Biocon (product Insugen). Insulin glargine is manufactured by Wockhardt (product Glaritus) and Biocon (product Basalog). Other insulin combination products are available manufactured by Cadila.

119 Wockhardt launches Asia’s first recombinant human insulin, REDIFF BUSINESS, 2003, <http://www.rediff.com/money/2003/aug/04wockhardt.htm>.

120 Beran et al., *supra* note 31, at 1127 (citing *Biocon’s insulin glargine launched in Japan*, BIOCON, July 15, 2016, http://www.biocon.com/biocon_press_releases_150716.asp); *Biocon receives regulatory approval for insulin glargine in Japan*, BUSINESS STANDARD (2016), http://www.business-standard.com/content/b2b-pharma/biocon-receives-regulatory-approval-for-insulin-glargine-in-japan-116033000194_1.html).

121 Kaplan & Beall, *supra* note 39, at 6.

122 Gupta et al., *supra* note 116, at 4 (“Furthermore, 66 (39%) could reach the threshold of four or more approved manufacturers if the FDA permitted reciprocal approval of drugs approved by any of the seven non-US regulators.”).

complex drugs like biologics, although the study did not single out insulin.¹²³ Due to the complexity of biologics, the study suggested first permitting reciprocal generic drug approval for small molecule drugs and excluding complex drugs (like insulins).¹²⁴

If interchangeability could be achieved and the system were effective and trusted, this could eventually be a means to increase competition in the insulin market. Even so, other local reforms would need to be instituted to increase supply and affordability as well as address the failures in the biosimilar market and approval process.¹²⁵

B. Insulin Importation

Prescription drug importation,¹²⁶ including insulin importation, has been proposed as one method to reduce generic entry barriers and decrease drug prices.¹²⁷ With the high costs of insulin and the significantly lower prices abroad,¹²⁸ some people are already travelling from the United States to Mexico to purchase insulin at a cheaper price.¹²⁹ There, some patients find that they can buy their insulin at one tenth of the cost in the United States.¹³⁰ Other people are going to Canada to purchase insulin or having insulin shipped from Canada.¹³¹

It is currently illegal to import medicines from abroad if the same medicines have not been approved by the FDA, though the FDA has exercised significant enforcement discretion on the issue.¹³² Several bills have been proposed to change this,¹³³ with some

123 *Id.* at 7 (“Among FDA approved drugs with few generic competitors, only 22 drugs (13%) were complex products, of which only 12 had at least one manufacturer with approval from a non-US regulator.”).

124 *Id.* (“If US legislators designed a system to facilitate reciprocal generic drug approval, it could initially exclude this small number of complex drugs to build trust while studying the interchangeability of complex products approved outside the US to determine whether the system could eventually be extended to this class of products.”).

125 *Id.* (“Reciprocal approval of prescription drugs in the USA from international sources could help with rising prices and shortages of off-patent drugs, but only along with other strategies dealing with the domestic causes of generic drug market failures.”).

126 Importation is distinct from purchasing insulin manufactured abroad: Novo Nordisk and Sanofi largely manufacture their insulin products abroad. Beran et al., *supra* note 18, at 728. Importation is purchasing medicines abroad supplied to a foreign country for treating patients in that country and priced according to that country’s system.

127 Fiona Scott Morton & Lysle T. Boller, *Enabling Competition in Pharmaceutical Markets* 41 (Hutchins Center Working Paper No. May 30, 2017).

128 Danzon et al., *supra* note 11, at 295 (“The issue of prescription drug prices in the United States, especially relative to other countries, remains of keen interest; some observers note, ‘the same drugs, manufactured in the same factory, routinely sell for nearly two times as much in the US as they do in other countries’”).

129 See, e.g., Robin Cressman, *Crossing Borders to Afford Insulin*, TINTERNATIONAL, Aug. 16, 2018, <https://www.tinternational.com/blog/2018/08/16/crossing-borders-afford-insulin/>.

130 *Id.*

131 Some cities, counties, and schools even have policies of importing drugs from Canada, despite the fact it is illegal and discouraged by the FDA. See Phill Galewitz, *Cities, Counties, and Schools Sidestep FDA Canadian Drug Crackdown, Saving Millions*, KAISER HEALTH NEWS, Dec. 8, 2017, <https://khn.org/news/cities-counties-and-schools-sidestep-fda-canadian-drug-crackdown-saving-millions/>.

132 Gupta et al., *supra* note 116, at 6. However, “The 2003 Medicare Modernization Act allowed for drug importation with the certification of the Secretary of Health and Human Services, but it has never been implemented.” *Id.*

133 Danzon et al., *supra* note 11, at 295 (“To address this apparent disparity, bills have been introduced in Congress to legalize commercial drug importation (also called parallel trade, which is legally permitted in the European Union), permitting wholesalers and other third parties to import on-patent prescription drugs from designated foreign countries into the United States.”).

specifically geared at increasing the affordability of insulin. Some states have also taken action to allow this, but these laws have been struck down on preemption grounds.¹³⁴ Regardless, to make insulin importation a possible solution, importation would need to be legalized.

Supporters of prescription drug importation assert that Americans would save \$50 billion over 10 years¹³⁵ or somewhere in the range of 0.2–2.5 per cent of current spending.¹³⁶ While this could be a short-term solution in the United States, such a policy could have devastating effects on the global market. By expanding the United States insulin market to include other countries, companies could be incentivized to raise the prices at a global scale, aggravating the global problem of access to medicines. Legalized importation would likely also influence the trade routes, which could negatively impact the global supply. Other countries could suffer decreased sales, disruptions to supply, higher prices, and delayed access to new prescription drugs.¹³⁷ This risk is especially salient in Canada, where some pharmacies in border towns have seen limited supplies of insulin following mass-purchases from Americans crossing the border.¹³⁸ As Canada is facing its own challenges with increasing insulin prices, a legalized importation policy could divert supply to the United States and exacerbate the problem of access to insulin in Canada and beyond.¹³⁹

Limitations on importation would be needed to make it a safe, viable option. First, there would likely need to be guidelines on where individuals can import insulin from. The FDA is considered the gold standard for drug approval, and removing limitations on which regulatory approvals are adequate could incentivize a ‘race to the bottom.’¹⁴⁰ A study by Gupta et al. recommends only allowing importation of prescriptions from ‘manufacturers approved by non-[United States] peer regulators with strong safety records under a baseline set of requirements for approval.’¹⁴¹

134 Gupta et al., *supra* note 116, at 6 (“For example, the Maine Pharmacy Act was passed in 2013 to allow direct importation of prescription drugs for personal use from pharmacies in Canada, the United Kingdom, New Zealand, and Australia, but was later ruled unconstitutional under the premise that importation is a federal issue.”).

135 Danzon et al., *supra* note 11, at 295.

136 *Id.* at 314–15. These figures are an estimate and would be dependent on several decisions of exporting countries. *See id.* (“Under plausible assumptions, savings to U.S. payers/consumers would likely be in the range of 0.2 to 2.5 percent of current drug spending, which implies a minimal impact on aggregate U.S. health care spending. These figures may underestimate savings: if potential exporting countries are willing to provide unlimited supply for export to the United States and forced-sale provisions can be fully enforced, savings may be higher. These estimates may also overestimate savings: if major export sources permit higher launch prices or experience launch delays, and if the supply of new drugs shifts toward products that are exempt from importation, savings may be lower.”).

137 *Id.*

138 See Jan Hux, *Canada Has Its Own Diabetes Crisis*, POL’Y MAGAZINE, Aug. 27, 2019, <https://www.google.com/search?client=safari&rls=en&q=Canada+Has+Its+Own+Diabetes+CrisisJan+Hux&ie=UTF-8&oe=UTF-8>.

139 *Id.*; Colleen Fuller, *Animal Insulin Withdrawal: Lessons for Patient Advocates Today*, T1INTERNATIONAL, Aug. 19, 2019, <https://www.t1international.com/blog/2019/08/19/animal-insulin-withdrawal-lessons-patient-advocates-today/>.

140 Gupta et al., *supra* note 116, at 6 (“Importation should occur only from manufacturers approved by non-US peer regulators with strong safety records under a baseline set of requirements for approval, precluding a “regulatory race to the bottom.””).

141 *Id.*

Even if successfully implemented, this would not be a sustainable, long-term solution to access and affordability in the United States—or globally. Other avenues should be explored to truly achieve affordable access to insulin for all.

C. Price Capping Insulin

Another proposal to increase insulin affordability is price capping or price control. Price controls are laws which mandate ‘limits on prices or government-required discounts on prices.’¹⁴² Such a law has already been passed in Colorado¹⁴³ and has been proposed in several other states.¹⁴⁴

Distinct from the proposals previously discussed that would increase competition in the insulin market, price capping would not aim to increase competition in the market but only to increase affordability. An article published in *Health Affairs* not only advocates for price control of biologics and biosimilars but also asserts that biologics are a natural monopoly, and therefore, competition-based proposals will not work to improve the affordability of biologics.¹⁴⁵ The study rightly identified several of the regulatory failures in the biosimilar market discussed in Part III: the lack of biosimilars approved, the limited price reductions associated with biosimilar competition, the lack of interchangeability, the high barriers to entry, and the regulatory confusion leading to follow-on biologics.¹⁴⁶ These factors lead the authors to conclude that biologics are a ‘natural monopoly’: markets where there is a ‘a legacy supplier’ and numerous or sizable barriers to entry ‘relative to the profits available to a new entrant.’¹⁴⁷ The legacy supplier—or in the case of the insulin market, legacy suppliers—therefore have such an advantage in comparison to new entrants that it is not financially feasible for new companies to enter the market.¹⁴⁸ While recognizing that regulatory reforms may have some positive influence on biosimilar competition and biologic affordability, the authors conclude that these reforms will not be enough to make biologics affordable and therefore recommend price controls.

Price control policies may mandate drugs to a lower, more affordable price. The *Health Affairs* authors project massive cost savings if biologics were subject to price

142 Shepherd, *supra* note 78, at 317.

143 See Bailey & Gilmer, *supra* note 12.

144 See, e.g., Munks, *supra* note 13 (Illinois proposal); Galvez, *supra* note 13 (Pennsylvania proposal); Smith, *supra* note 13 (Kentucky proposal); Larsen, *supra* note 13 (Wisconsin proposal).

145 See Atteberry et al., *supra* note 96; Mark Trusheim et al., *Biologics Are Natural Monopolies (Part 2): A Proposal For Post- Exclusivity Price Regulation Of Biologics*, HEALTH AFF. BLOG, Apr. 15, 2019, <https://www.healthaffairs.org/doi/10.1377/hblog20190405.839549/full/>. See also Alex Brill & Benedic Ippolito, *Biologics Are Not Natural Monopolies*, HEALTH AFF. BLOG, July 2, 2019, <https://www.healthaffairs.org/doi/10.1377/hblog20190701.349559/full/> (challenging the arguments of Atteberry et al. and Trusheim et al.); Peter B. Bach et al., *Biologics Are Still Natural Monopolies*, HEALTH AFF. BLOG, July 31, 2019, <https://www.healthaffairs.org/doi/10.1377/hblog20190729.128229/full/> (responding to Brill & Ippolito).

146 See Atteberry et al., *supra* note 96.

147 See Trusheim et al., *supra* note 147.

148 *Id.* (“One such advantage comes from the legacy supplier’s ability to lower its price at any time to a level that is still marginally profitable but that would not justify a new entrant undertaking the investment to challenge for market share.”).

caps.¹⁴⁹ A price control on insulin could have the same immediate effect—massive cost savings for consumers.¹⁵⁰

However, manufacturers will look to recoup these costs in other ways. The mandated discounts—a form of price control—under Medicaid Medicare have been linked to increased prices for other consumers.¹⁵¹ If the price control applied to all consumers in the United States, it may incentivize manufacturers to withdraw (if the mandated price is too low) or to raise prices in other less regulated markets. If price controls are applied only to government programs (including Medicare and Medicaid but also the 340B Program, Veterans Health Administration, and the Department of Defense), this may exacerbate the existing affordability issues, lowering the cost for individuals with government-funded health insurance but increasing the cost of insulin for people with private insurance. Whether or not the insulin market is a natural monopoly, these potential price effects are concerning and could leave patients worse off than they started.

Price controls could also have a negative impact on access to insulin globally. Like importation, where the supply could shift to the United States, increasing prices and decreasing access in other countries, insulin price controls could result in higher prices and drug shortages abroad.¹⁵² This effect is more likely if the price caps were applied to all buyers in the United States, not just those with government insurance.

While federal legislation to cap insulin prices may seem attractive and would avoid the regulatory and practical barriers to increasing competition in the insulin market, it may cause more problems than it solves. Some price regulation may be the solution, but the greater effects on the insulin market both in the United States and beyond must be considered. Legislation should take into account not only the unique aspects of the insulin market in the United States but also the greater impact on insulin access and affordability globally.

VI. CONCLUSION

The United States insulin market has been insulated from competition since insulin was discovered almost 100 years ago. As insulin prices continue to skyrocket and people

149 *Id.*

150 For a more detailed analysis of price capping and pharmaceutical price regulation more generally, see generally Michelle M. Mello & Rebecca E. Woltz, *Legal Strategies for Reining in “Unconscionable”- Prices for Prescription Drugs*, __ NORTHWESTERN L. REV. __ (forthcoming 2020).

151 Shepherd, *supra* note 78, at 337 (citing Mark Duggan & Fiona M. Scott Morton, *The Distortionary Effects of Government Procurement: Evidence from Medicaid Prescription Drug Purchasing*, 121 Q.J. ECON. 1, 1 (2006); David H. Howard et al., *Pricing in the Market for Anticancer Drugs*, 29 J. ECON. PERSPECTIVES 139, 140 (2015); CONG. BUDGET OFFICE, *HOW THE MEDICAID REBATE ON PRESCRIPTION DRUGS AFFECTS PRICING IN THE PHARMACEUTICAL INDUSTRY 2* (1996); GOV’T ACCOUNTABILITY OFFICE, GAO/ HEHS-94-194 FS, *CHANGES IN BEST PRICE FOR OUTPATIENT DRUGS PURCHASED BY HMOs AND HOSPITALS 2* (1994); Jim Hahn, *Federal Drug Price Negotiation: Implications for Medicare Part D*, CONG. RES. SERV., Apr. 19, 2007, <http://congressionalresearch.com/RL33782/document.php?study=Federal+Drug+Price+Negotiation+Implications+for+Medicare+Part+D>).

152 Shepherd, *supra* note 78, at 317, 337–40.

153 The information on the company global market share (by volume and revenue) was collected from Knox & Wirtz, *supra* note 20, at 14.

154 Products with patents and exclusivities based searches of the Orange Book and USPTO Patent Database.

with diabetes remain too often unable to afford their insulin, lawmakers must consider reforms to improve access to and affordability of insulin in the United States.

Given the unique challenges presented by the insulin market—its limited competition, regulatory challenges for approval and interchangeability, and practical challenges with trade secrets, anticompetitive behavior, and pricing of biologics—lawmakers need to understand why insulin has been insulated from competition and take these factors into account in developing legislation to improve access to insulin. Some of these issues can be addressed with regulatory reform, but comprehensive action must be taken to achieve universal access to affordable insulin. Several proposals have been made to increase insulin competition and affordability, each with their own benefits and risks to consumers. Going forward, lawmakers must work to develop solutions to the skyrocketing prices of insulin in the United States. Reforms must consider the unique aspects of the insulin market and take steps to provide access to affordable insulin to all.

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