

INSULIN PLAYBOOK

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Supply Chain Incentives: Humalog and NovoLog

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About This Series

This paper is organized to highlight each medication or therapy in this series in three phases: production, commercialization, and access.

Within production, there are critical steps and decisions that manufacturers make regarding research and development, patenting, and manufacturing.

From there, commercialization is intended to look closely at how a product is marketed, labeled, and regulated, and the resultant impact of those decisions on the price of each featured product.

The final step in the process is access, how product acquisition (moving from manufacturer, through wholesalers, and on to pharmacies) and distribution (PBMs, payers, and providers) shapes patient access, which is so often impacted by cost.

Introduction

Diabetes is the seventh leading cause of death and the most prevalent chronic disease in the U.S.¹ In 2022 the CDC estimated that 37.3 million people have diabetes (11.3% of the U.S. population).² The CDC also estimates one in three U.S. adults are prediabetic, which can lead to a Type II diagnosis. The incidence of diabetes continues to rise, with some estimates predicting a 54% increase from 2015 to 2030, along with a 38% increase in diabetes-related deaths.³ Given the prevalence, it is clear that diabetes is a critical health care issue in the U.S.

In addition to being a highly prevalent and deadly disease if not managed effectively, diabetes is very costly. As the prevalence of diabetes and co-existing conditions continues to rise, associated costs are rapidly increasing. In 2017, total direct and indirect costs of diagnosed diabetes was \$327 billion, up from \$261 billion in 2012.⁴ The cost of care for people with diabetes is approximately \$0.25 on every health care dollar or \$16,752 per person with diabetes per year.⁵

Insulin is a biologic drug that has been used to manage diabetes since the early 1920s. While not all people with diabetes use insulin products to manage their condition, it is estimated that about one-quarter of people with diabetes (9.3 million) rely on insulin products.⁶ Today, there are four types of insulin. The types vary based on the insulin's onset, peak time, and duration; fast-acting, shortacting, intermediate-acting, and long-acting, with long- and

Diabetes

In a person with diabetes, the body doesn't make enough insulin or can't use it as effectively. There are three main types of diabetes:

Type I – Thought to be caused by an autoimmune reaction that stops the body from producing insulin. It is usually diagnosed in adolescence. Less than 10% of people with diabetes have Type I.

Type II – The body does not use insulin effectively and can't keep blood sugar levels within normal range. Over 90% of people with diabetes have Type II. It usually develops over time and is diagnosed in adults.

Gestational – A specific type of diabetes that develops during pregnancy and usually goes away after the baby is born.

Insulin Drug Classes

There are four types of insulin based on insulin's onset, peak time, and duration:

Fast-acting

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- Short-acting
- Intermediate-acting
 - Long-acting

¹ CDC. (2020). National Diabetes Statistics Report 2020. In *CDC*. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

² National Diabetes Statistics Report | Diabetes | CDC. (n.d.). https://www.cdc.gov/diabetes/data/statistics-report/index.html#print

³ Rowley, W., Bezold, C., Arikan, Y., Byrne, E., & Krohe, S. (2017). Diabetes 2030: Insights from Yesterday, Today, and Future Trends. *Population Health Management*, 20(1), 6–12. https://doi.org/10.1089/pop.2015.0181

⁴ CDC. (2020). National Diabetes Statistics Report 2020. In CDC. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetesstatistics-report.pdf

⁵ Gerstein, H. C., & Herman, W. H. (2018). The Cost of Diabetes Care—An Elephant in the Room. *Diabetes Care*, 41(5), 929– 932. https://doi.org/10.2337/dci18-0012

⁶ Irving, D. (2021, January 6). The Astronomical Price of Insulin Hurts American Families. *RAND Review*. https://www.rand.org/blog/rand-review/2021/01/the-astronomical-price-of-insulin-hurts-american-families.html

fast-acting being the most commonly used.⁷ Humalog (insulin lispro) and NovoLog (insulin aspart) are both fast-acting insulin products and are among the most commonly prescribed brand-name treatments for people with diabetes.

As a class, insulin products have received substantial media⁸ and congressional⁹ attention, in large part, due to their high prices which restrict access for a substantial population. While insulin is a well-known, successful treatment for managing diabetes, the high and rising costs cause some people with diabetes to ration or skip their prescribed doses, leading to additional adverse health outcomes.¹⁰ In the case of insulin, where there are a number of products available and high demand—two conditions that typically lead to a competitive marketplace—these persistently high costs suggests that the market may not be functioning in expected ways.

This playbook focuses on the regulatory landscape and market incentives that may have contributed to historically high prices for insulin, including new developments in 2022 and 2023 that suggest the market may have reached a tipping point in favor of increased affordability.

Impact of Incentives

culminating-the-committee

Production

Market Share

Despite the large demand for accessible insulin products, the market is highly concentrated, with 90% of the market controlled by three manufacturers: Eli Lilly and Company (maker of Humalog), Novo Nordisk S/A (maker of NovoLog) and Sanofi S.A. (maker of Lantus).¹¹ Historically, price increases and average rebates have consistently risen for these fast-acting insulins.

⁷ Seery, C. (2022, November 9). *Insulin*. Diabetes. https://www.diabetes.co.uk/about-insulin.html

⁸ González, O. (2022, October 18). High insulin prices lead some adults to ration. Axios. https://www.axios.com/2022/10/18/insulin-rationingprices-study

⁹ Committee on Oversight and Accountability Democrats. (2021, December 10). Chairwoman Maloney Releases Comprehensive Staff Report Culminating the Committee's Sweeping Drug Pricing Investigation [Press release]. https://oversightdemocrats.house.gov/news/press-releases/chairwoman-maloney-releases-comprehensive-staff-report-

¹⁰ Insulin: Examining the Factors Driving the Rising Cost of a Century Old Drug. (n.d.). United States Senate Finance Committee. https://www.finance.senate.gov/imo/media/doc/Grassley-Wyden%20Insulin%20Report%20(FINAL%201).pdf

¹¹ Luo, J., Avorn, J., & Kesselheim, A. S. (2015). Trends in Medicaid Reimbursements for Insulin From 1991 Through 2014. *JAMA Internal Medicine*, *175*(10), 1681. https://doi.org/10.1001/jamainternmed.2015.4338

A recent Congressional probe into drug manufacturers found that Humalog and NovoLog prices have increased 1219% and 627% since their initial launch dates in 1996 and 2000, respectively.¹² As a point of comparison, Humira, which has also received media attention for its high prices and patent protection strategies, has risen 471% over the same period.¹³

Patenting

For decades, the Food and Drug Administration (FDA) classified insulin as a small molecule drug (SMD), as it was on the market long before the Biologics Price Competition and Innovation Act of 2009 (BPCIA) was signed into law in 2010.¹⁴ However, in March 2020, the FDA reclassified insulin as a biologic which allowed for the introduction of biosimilar and interchangeable biosimilar insulins.¹⁵ This designation change has important implications for the introduction of biosimilars, which are analogous to generics for small molecule drugs. By formally classifying insulin as a biologic, new market entrants may be able to move along a streamlined pathway for approval, introducing the potential for more affordable and interchangeable insulins to enter the market.¹⁶

The first interchangeable insulin biosimilar, Semglee, was approved by FDA in July 2021.¹⁷ While this is a first step in improving insulin access, Semglee is a long-acting insulin. People with Type I diabetes typically use both long-acting and fast-acting insulin in combination. Neither Humalog nor NovoLog, which are fast-acting, have FDA-approved biosimilar competitors in the U.S., although they have been approved in Europe. Biosimilars are usually launched at a discount to their reference products and introduce price competition into the market, which can drive significant savings for both individuals and the health care system.¹⁸ However, the introduction of biosimilars (or equivalent generics prior to the reclassification to a biologic) is not always an easy journey. The incumbent manufacturers have strong incentives to maintain their market share and often engage in activities to extend their exclusivity beyond the date of their original patent expiration.

Insulin has been available for just over 100 years, yet the first generic competitors to some of the most

¹³ Ibid.

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¹² Committee on Oversight and Accountability Democrats. (2021, December 10). Chairwoman Maloney Releases Comprehensive Staff Report Culminating the Committee's Sweeping Drug Pricing Investigation [Press release]. https://oversightdemocrats.house.gov/news/press-releases/chairwoman-maloney-releases-comprehensive-staff-reportculminating-the-committee

¹⁴ Implementation of the Biologics Price Competition and Innovation Act of 2009. U.S. Food And Drug Administration. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-pricecompetition-and-innovation-act-2009

¹⁵ Insulin is Now a Biologic–What Does That Mean? | ADA. (2020, March 23). https://diabetes.org/blog/insulin-now-biologic-what-does-mean

¹⁶ FDA. (2020, March 23). Insulin Gains New Pathway to Increased Competition [Press release]. https://www.fda.gov/news-events/pressannouncements/insulin-gains-new-pathway-increased-competition

¹⁷ FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes. (2021, July 28). [Press release]. https://www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-producttreatment-diabetes

¹⁸ Mulcahy, A. W. (2022, January 26). Projected US Savings From Biosimilars, 2021–2025. RAND. https://www.rand.org/pubs/external_publications/EP68829.html

common insulin products didn't make it to market until recently. The reasons behind this are complex but one driver is the practice known as "patent thicketing," where manufacturers make incremental changes to their products and seek additional patents, thereby extending the overall patent exclusivity for reformulated drugs. While some of the reformulations have measurable impact on the safety and efficacy of the drug, others may have less meaningful impacts and operate mainly to extend patent exclusivity. Additionally, for products that are delivered by a medical device, such as an injectable pen common among insulin products, the combination of the medication and the device patents allows for extended patent protection. For example, while patents have expired on certain formulations of Humalog and NovoLog, the injectable pens used to deliver those medications are still covered by active patents.¹⁹

Commercialization and Access

Regulation

The Inflation Reduction Act (IRA), signed into law in August 2022 includes several provisions aimed at lowering prescription drug costs and improving access for Medicare beneficiaries.²⁰ One of the prescription drug provisions specifically impacts long and fast-acting insulins, which includes Humalog and NovoLog.

The IRA will limit monthly cost-sharing for insulin products to no more than \$35 per month, which represents substantial savings for individuals with diabetes covered by Medicare. In 2020, Medicare spending on Humalog and NovoLog alone was \$5 billion and of that total, \$273 million was spent out-of-pocket by beneficiaries.²¹ This legislation would reduce out-of-pocket spending by beneficiaries to no more than \$420 per beneficiary per year for all insulin products. This provision went into effect for Part D on January 1, 2023 and for Part B on July 1, 2023. The IRA also enables the Secretary of Health and Human Services (HHS) to negotiate drug prices for Medicare. The provision has various safeguards that will prevent the Secretary from negotiating Medicare prices on drugs, including those prescription drugs which: (1) have been FDA-approved for less than nine years (small-molecule drugs) or 13 years (biologics), (2) made up less than \$200 million of Medicare spending in 2021, (3) have a generic or biosimilar, or (4) have orphan designation. In August 2023, NovoLog was selected by HHS as

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¹⁹ Knox, R. G. (2020). Insulin insulated: barriers to competition and affordability in the United States insulin market. Journal of Law and the Biosciences, 7(1). https://doi.org/10.1093/jlb/lsaa061

²⁰ Inflation Reduction Act, H.R.5376, 117th Cong. (2022). https://www.congress.gov/bill/117th-congress/house-bill/5376/text

²¹ Drug Spending metrics calculated from all 2020 Part D Events data, accessed via NORC's CMS Research DUA, with Humalog and NovoLog NDC codes respectively. Total Cost and Total Patient Amount come directly from the Gross Drug Cost (total spending for the prescription claim, including Medicare, plan, and beneficiary payments) and Amount Paid by Patient fields. Total Medicare Amount is the difference of those two calculated amounts.

one of the ten drugs selected for negotiation, though it is important to note that negotiated prices will not be applicable until 2026.²²

While provisions within the IRA, specifically the cap, are expected to have a significant impact on Medicare beneficiaries' access to insulin, it leaves millions of Americans who are not on Medicare without such protections. In fact, there are some who speculated that prices would go up in the commercial market as manufacturers and other actors along the supply chain look to offset losses related to decreased Medicare-related revenue.²³ However, some insulin manufacturers have taken a different approach. Within a single month, the three major insulin manufacturers in the United States – Eli Lilly, Novo Nordisk, and Sanofi—all announced price cuts for at least some of their insulins.²⁴ First, Eli Lilly, the maker of Humalog, announced a slate of insulin price reductions and a new out-pocket-cap for their insulin products that mirrors the IRA provisions. Patients with commercial insurance, regardless of carrier, and those who are uninsured, would have a \$35 cap on out-of-pocket costs for all Eli Lilly insulin products distributed through participating retail pharmacies.²⁵ Additionally, Novo Nordisk announced a \$35 monthly cap on Lantus for people with private insurance beginning January 1, 2024.²⁷

These announcements largely preempt a proposal in President Biden's FY 2024 budget to expand the \$35 monthly insulin cap in the IRA to commercially insured populations.²⁸ While the exact reasons for these proactive price decreases are not clear, there are a number of possibilities. One reason could be an effort to maintain market share ahead of the introduction of biosimilars. In March 2022, CivicaRX, a non-profit generic drug and pharmaceutical company, announced their intent to bring to market generic

²² HHS. (2023, August 29). HHS Selects the First Drugs for Medicare Drug Price Negotiation [Press Release]. https://www.hhs.gov/about/news/2023/08/29/hhs-selects-the-first-drugs-for-medicare-drug-price-negotiation.html

²³ Health Payer Intelligence. (2022, August 18). How the Inflation Reduction Act Will Impact Employers, Health Plans. *HealthPayerIntelligence*. https://healthpayerintelligence.com/features/how-the-inflation-reduction-act-will-impact-employershealth-plans

²⁴ Sanofi answers the call, joining Eli Lilly, Novo Nordisk in cutting insulin prices. (2023, March 17). *Fierce*

Pharma. https://www.fiercepharma.com/pharma/sanofi-answers-call-joining-eli-lilly-novo-nordisk-cutting-price-insulin ²⁵ Lilly Cuts Insulin Prices by 70% and Caps Patient Insulin Out-of-Pocket Costs at \$35 Per Month. (2023, March 1). [Press

release]. https://investor.lilly.com/news-releases/news-release-details/lilly-cuts-insulin-prices-70-and-caps-patient-insulin-outpocket

²⁶ Novo Nordisk to lower U.S. prices of several pre-filled insulin pens and vials up to 75% for people living with diabetes in January 2024. (2023, March 14). [Press release]. https://www.novonordisk.com/news-and-media/latest-news/lowering-us-list-prices-of-several-products-.html

²⁷ Press Release: Sanofi cuts U.S. list price of Lantus®, its most-prescribed insulin, by 78% and caps out-of-pocket Lantus costs at \$35 for all patients with commercial insurance. (2023, March 16). [Press release]. https://www.sanofi.com/en/media-room/press-releases/2023/2023-03-16-20-06-43-2629188

²⁸ Fiscal Year 2024: Budget in Brief. (2023). U.S. Department of Health & Human Services. https://www.hhs.gov/sites/default/files/fy-2024budget-in-brief.pdf

insulin products that would be interchangeable with Lantus, Humalog, and NovoLog at a price of no more than \$30 per vial.²⁹

Another reason could be the significant activity at the state level to control insulin costs. In 2019, Colorado became the first state to implement a price cap on out-of-pocket costs at \$100. Since then, nearly two dozen more states have passed similar measures, including Louisiana and Maryland as recently as last year (2022). These protections, however, are typically limited to insurance products over which the state has explicit control including those sold on the Affordable Care Act Health Insurance Marketplace and those covering state employees; employer-sponsored plans that are governed by the Federal Employee Retirement Income Security Act of 1974 (ERISA) are exempt.³⁰ Another reason, which is detailed below, could be the complex nature of negotiations with pharmacy benefit managers (PBMs).

Distribution

While there has been significant attention from the administration on manufacturers' role in lowering prices for insulin, the ultimate price encountered by the consumer is also impacted by other actors in the health care system, notably health plans, PBMs, pharmacies, and wholesalers. A 2021 study of 32 insulin products found that while list prices increased by 40.1% between 2014 and 2018, the net price received by the manufacturer decreased by 30.8%, on average.³¹ Health plans have seen a slightly smaller reduction in insulin related expenditures, down 24.7% from 2014 to 2018. Conversely, the share of expenditures retained by PBMs increased by 154.6%, the share retained by pharmacies increased by 228.8%, and share retained by wholesalers increased by 74.7%, all over the same time.³²

A key function of any PBM is the creation and maintenance of its drug formulary, and this function is often influenced by rebates that have been negotiated with manufacturers. An exclusionary rebate is a specific type of rebate that may have contributed to the consistently high prices of insulin. Exclusionary rebates occur when a manufacturing company incentivizes the PBM to exclude certain medications from their formularies, often to maintain market share for their brand-name products over available generics. Over the last ten years, the number of formulary exclusions has grown significantly, from nearly zero up to approximately 600 excluded drugs per formulary across the three biggest PBMs: Caremark (CVS Health), Express Scripts (Cigna), and OptumRx (United Health Group).³³ The U.S.

³² Ibid.

²⁹ Civica Rx. (2022). Civica to Manufacture and Distribute Affordable Insulin. Civica Rx. https://civicarx.org/civica-to-manufacture-anddistribute-affordable-insulin/

³⁰ Ollove, M. (2023, January 13). More States Are Doing What They Can to Cap Insulin Costs. The Pew Charitable Trusts. https://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2023/01/12/more-states-are-doing-what-they-can-tocap-insulin-costs

³¹ Herman, W. H., Ribero, R., Ryan, M., & Sood, N. (2021). Estimation of the Share of Net Expenditures on Insulin Captured by US Manufacturers, Wholesalers, Pharmacy Benefit Managers, Pharmacies, and Health Plans From 2014 to 2018. JAMA Health Forum, 2(11), e213409. https://doi.org/10.1001/jamahealthforum.2021.3409

³³ Fein, A. J., PhD. (2023, January 10). The Big Three PBMs' 2023 Formulary Exclusions: Observations on Insulin, Humira, and Biosimilars. https://www.drugchannels.net/2023/01/the-big-three-pbms-2023-formulary.html

The recent announcements³⁵ from Eli Lilly and Novo Nordisk of their intentions to lower the list prices of their insulins is likely to have a significant impact on the manufacturer-PBM rebate dynamic. Over ten years of gross-to-net data show that both Humalog and NovoLog have been subject to everincreasing discounts, and as of 2022 Q1, both Eli Lilly and Novo Nordisk were returning approximately 85% of Humalog and NovoLog list prices back to PBMs in the form of rebates (See Figure 1). Per their announcements, Eli Lilly and Novo Nordisk over time will reduce the list prices³⁶ of Humalog (by 70%) and NovoLog (by 75%), effectively transferring a substantial proportion of the discount from PBMs directly to patients, since patients' cost sharing obligations are typically tied to drugs' list prices. While it's still early to know the true impact of these actions, what is certain is how people will be tracking the industry closely and paying attention to the ripple effects of these announcements—not just on other manufacturers of insulin, but across drug classes.



Figure 1. Total Gross-to-Net Discounted Rate

Source: Data from SSR Health.

Note: Gross-to-net shows the percentage difference between WAC and estimated net price unit on a sales-weighted average.

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³⁴ Policy Statement of the Federal Trade Commission on Rebates and Fees in Exchange for Excluding Lower Cost Drug Products. (2022, June 16). Federal Trade Commission. https://www.ftc.gov/legal-library/browse/policy-statement-federal-trade-commission-rebates-feesexchange-excluding-lower-cost-drug-products

³⁵ Referenced earlier in the Regulation section

³⁶ Price paid by wholesalers to acquire the drug from manufacturers.



Patient Implications

Note: Patient scenarios are meant to be illustrative only. The goal of these scenarios is not to provide exact prices, but to demonstrate the patient experience while accessing their medications and the ways these prices are impacted by upstream incentives. Prices are based on publicly available information when possible (and cited accordingly) and based on good faith estimates when prices were not available.

In the scenarios below, we follow the journey of a 34-year-old female living with Type II diabetes, who uses fast- and long-acting insulin (Humalog, manufactured by Eli Lilly) to manage her condition. She has a high-deductible health plan through employer sponsored insurance. These scenarios will differ by time period to project the impact of Eli Lilly's planned reduction in Humalog's list price in Q4 2023. The result will have substantially different out-of-pocket costs for the patient.

Scenario 1

In 2023, prior to Eli Lilly's planned price reduction, the list price for 1,500 units of Humalog U-100 is \$530.40.³⁷ While individual dosing may vary, this patient uses 25 units per meal, for three meals, for a total of 75 units per day. As a result, the patient requires 2,250 units per month for a total of 18 prescriptions per year. Most pharmacies apply a markup to the list price of a medication to reimburse the pharmacy for stocking the medication and staffing the pharmacy. In this case we assume a 15% markup to cover these costs, which would lead to an annual cost of approximately \$11,000 for the patient to access the appropriate amount of their medication. Her insurance has an annual deductible of \$3,000 and a 20% patient coinsurance once the deductible has been met. As a result, the patient will pay the full cost of five prescriptions in order to hit the annual \$3,000 deductible. For the remaining 13 prescriptions, the patient will pay 20% of each prescription, for a total of \$1,600³⁸. In sum, the patient's out-of-pocket for the year (deductible plus coinsurance) is \$4,600, which breaks down to a monthly average cost of \$383.

Scenario 2

Effective Q4 2023, Eli Lilly will cut the list price of Humalog U-100 by 70% to approximately \$160 for 1,500 units. Assuming the same 18 prescriptions per year, 15% pharmacy markup, deductible, and coinsurance, the patient would pay the full cost of the first 16 prescriptions and coinsurance on the remaining two prescriptions. As a result, the patient's out-of-pocket for the year (deductible plus coinsurance) is \$3,074, which breaks down to a monthly average cost of \$256.

As a direct result of Eli Lilly lowering Humalog's list price by 70% in Q4 2023, the patient's annual spending on insulin decreased by \$1,526, and her monthly spending decreased by \$127.

³⁷ Humalog Insulin Price & KwikPen Cost | Humalog® (insulin lispro injection). (n.d.). https://www.lillypricinginfo.com/humalog

 $^{^{\}rm 38}$ \$530.40 with 15% markup added is \$610.00. 20% of \$610.00 is \$122.00



Scenario 1	Scenario 2	
Time period up to Q4 2023 (prior to Eli Lilly's planned Humalog list price reduction)	Time period Q4 2023 and beyond (factoring in Eli Lilly's Humalog list price reduction)	
The patient uses 25 units of Humalog per meal, 75 units per day, and 2,250 units per month. One prescription of Humalog is 1,500 units, so the patient requires 18 prescriptions per year.		
The patient's employer sponsored insurance is a high deductible health plan with an annual deductible of \$3,000 and a 20% coinsurance.		
Based on the pre-list price reduction, the patient's annual out-of-pocket to receive her insulin is \$4,600, which breaks down to a monthly average of \$383.	Based on the planned list price reduction, the patient's annual out-of-pocket to receive her insulin is \$3,074, which breaks down to a monthly average of \$256.	

Conclusion

Pricing for insulin products have come under intense scrutiny over the last decade, culminating in significant reforms associated with the IRA, directly applicable to the Medicare population and causing ripple effects into the commercial market. While this is great news for insulin users, these market forces and incentives still exist in other drug product categories and classes.

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