From Bench to Market: A Multifaceted Examination of Insulin Pricing, Profit Margins, and Patient Advocacy

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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INTRODUCTION

Insulin is a therapeutic peptide produced by the pancreas to regulate blood sugar. Millions of individuals a year are affected by diabetes, Type 1 or Type 2, which affects their pancreas' ability to produce insulin and regulate blood sugar (Siew & Zhang, 2021). This is a critical biological process which regulates glucose and subsequently energy and other biological functions. The current solution for diabetes is the injection of insulin, which comes in a plethora of forms from a wide variety of manufacturers. The insulin market globally is massive – and is projected to continue increasing, with developing countries looking to take steps in addressing their diabetic populations that have largely been ignored (Beran et al., 2021).

My STS project will explore how pharmaceutical pricing strategies, profit margins, market dynamics, and political entities impact the affordability and accessibility of insulin for patients in developing countries. By tracing the interactions between various actors involved in the insulin supply chain, I aim to understand how decisions made by pharmaceutical companies, regulatory bodies, and advocacy groups shape the insulin market as well as the path from the manufacturing floor to the patient themselves not just in a modern context, but historically as well. My technical project aims to take this research and contextualize it by designing an insulin manufacturing process in the region of Sub-Saharan Africa, partially influenced by a previous capstone project (Iudica, B., 2023). My research questions center around the challenges and opportunities of insulin production in this region; I ask how the design and operation of an insulin manufacturing facility can be optimized to ensure cost-effective production while maintaining sustainability.

METHODS AND FRAMEWORK

My research methodology is centered on thoroughly exploring the factors influencing the affordability and accessibility of insulin for patients in developing countries. This discussion requires integrating technical manufacturing considerations with the sociotechnical landscape governing insulin production, distribution, pricing, and accessibility. At the heart of my investigation lies Actor-Network Theory (ANT), a robust theoretical framework in which human and non-human entities (such as technology, institutions, and objects) are considered as "actors" that exist in a constantly shifting network of relationships and influence. It emphasizes agency and the fluidity of power dynamics within networks.

In my research paper, various actors are examined to provide a holistic understanding of the insulin landscape. Pharmaceutical giants such as Novo Nordisk, Sanofi, and Eli Lilly are central players in the insulin market, chosen for their significant market share and influence over pricing and accessibility. These companies dominate the insulin production sector, with their patented manufacturing processes serving as critical focal points for understanding the economic drivers behind insulin pricing. Additionally, insurance companies and pharmacy benefit managers (PBMs) are scrutinized for their role in negotiating prices and shaping patient access to insulin. The complexity of insurance policies and the influence wielded by PBMs highlight the importance of examining these actors in the context of insulin accessibility. Patient advocacy organizations, exemplified by Diabetes Africa and the International Diabetes Federation, are integral actors in driving change and promoting equitable access to insulin. By amplifying patient voices and advocating for policy reforms, these organizations play a crucial role in addressing systemic barriers to insulin access.

By triangulating data from multiple sources, including quantitative cost estimations of insulin manufacturing processes and qualitative analysis of policy documents, the roles and relationships between actors are made clear. Additionally, another important focal point of this issue is intersectionality of factors such as sex, race, and gender with insulin accessibility, drawing on historical events, relevant literature review, and patient advocacy movements. All of this informs the development of targeted interventions and policy recommendations aimed at addressing systemic issues and improving healthcare outcomes for diabetic populations.

Quantitative data collection involves a review of available literature on pharmaceutical manufacturing operations and their economics to establish a foundational understanding of insulin manufacturing processes and the economics surrounding them. Downstream purification techniques are incredibly expensive, especially considering some of the criteria that government agencies require for the final product. Methods such as centrifugation, filtration, chromatography, pH adjustment, and various reactions throughout the process all need to be carefully fine-tuned so that they ensure the quality of medicine to an incredibly precise degree. Specific technologies in the process can also vary between countries depending on regulations. The research is used in an attempt to make cost estimations of these processes and then compare them against the economic conditions within countries with insulin accessibility issues.

Additionally document/policy analysis provides context regarding regulatory guidelines, corporate reports, and policy documents, aiming to trace the networks of relationships among stakeholders and discern their roles and influences. Network analysis techniques are employed to map out connections between various actors involved in the insulin supply chain, facilitating the identification of key nodes of influence. By making these identifications and mapping out this

information, they are presented in order to describe with specificity and detail what barriers stand between patients and the therapy they deserve.

Finally, I focus on the patients themselves. Any instances of patient advocacy movements or medically related political movements I included - more than that, though, the research is also used to focus on how things like sex, race, and gender have impacted the medical landscape with a focus on diabetic populations. This will be accomplished through research on historical events related to these topics, as well as literature review with texts like *Sweetness in the Blood: Race, Risk, and Type 2 Diabetes* by James Doucet-Battle.

A HISTORY OF INSULIN

Before the discovery of insulin by Frederick Banting and Charles West in 1921, the primary form of treatment for diabetes was the Allen diet, in which a patient was advised to be in a constant state of starvation or malnutrition (Beran et al., 2021). This treatment was able to extend the life of a diabetic for a few years, at best - and not healthily. Even today, 103 years after its discovery, lack of access to insulin affects millions of people globally with major discrepancies based on region. In the Sub-saharan region of Africa, the life expectancy of a child born with type 1 diabetes is as low as one year (Azvedo, 2008). This is in stark contrast with treatment outcomes in the United States, where individuals with type 1 diabetes have only about a 5 year difference in life expectancy compared to the average population (Beran et al., 2021).

The cycle of a medicine from discovery to use by a patient is a long and arduous process, with many barriers along the way impacting its accessibility. First, is manufacturing - insulin is a complex biological molecule that requires extreme care and precision in its manufacture. The equipment and workforce, as a result, is incredibly resource intensive compared to other

common therapeutics. Next, is marketing and regulation, referring to the companies that produce insulin and how they must follow the rigorous process of approval by a regulatory body to distribute their product and then the strategy and costs of marketing. While not all factors are described here, one more consideration is the distribution of insulin. This refers to the pipeline from when the insulin is finished on the manufacturing floor, all the way to its administration by a patient.

All of the hurdles I just mentioned in insulin accessibility are especially difficult to achieve for low and middle income countries (LMICs) and they vary wildly too (Beran et al., 2021). For example - data from the last 20 years showed the average government procurement price for a vial of 10 mL 100U/mL human insulin was $4.10 in Mozambique (2003), $8.40 in Kyrgyzstan (2008), and $9.71 in the UK (2013) (Beran et al., 2016). This difference in procurement prices still doesn't fully illustrate the differences in patient accessibility - there are still mark-ups in price before it reaches the patient, and these numbers also don't account for the income for people within these regions (Beran et al., 2016). Even with those considerations accounted for as well, accessibility comprises both price and physical accessibility - the latter still being an issue.

Patient advocacy has been historically limited in the space of pharmaceuticals. In the face of rising cases of diabetes within Sub-saharan Africa - from 3 million in 1994 to 7.1 million in 2000 - lack of strong economies, tools, and infrastructure have left this problem largely ignored (Azvedo, 2008). Some semblance of progress is being made, however, through efforts of the International Diabetes Foundation (IDF) which aims to provide training and education for patients in LMICs to spread information regarding patient's self-management and care (Azvedo, 2008). Although admirable, the efforts of the IDF have been insufficient. Studies have

demonstrated that a shortage in education and specific information on diabetic care have led to high non-compliance rates and complications in treatment (Azvedo, 2008). There is still work to be done in grassroots movement and organization for affected individuals in LMICs, as complex and difficult as it may be.

PHARMACEUTICAL COMPANIES AND MANUFACTURING

The landscape of insulin production is dominated by a handful of pharmaceutical giants, each wielding considerable influence over pricing and accessibility. Among the largest producers of insulin are Novo Nordisk, Sanofi, and Eli Lilly, collectively accounting for a significant portion of global insulin supply - specifically, 96% market share by volume and 99% by value (Beran et al., 2021). There are a few minor producers found in both India and China, but their production is relatively insignificant compared to the big three I mentioned. All of these manufacturing giants have extremely lengthy, technical, and thoroughly patent-protected manufacturing processes to create their insulins. Understanding the intricacies of insulin manufacturing processes employed by these companies is crucial and offers insights into the economic considerations driving pricing strategies.

Part 1: Manufacturing

Insulin manufacturing has evolved significantly since its discovery nearly a century ago. Initially derived from animal sources, modern production methods predominantly involve recombinant DNA technology. This process begins with the insertion of human insulin genes into bacterial or yeast cells, which act as "factories" for insulin production (Baeshen et al., 2014). Following a lengthy fermentation process, the cells are then broken up to release the insulin

produced. The real costs are found not in the production itself, but all of the steps following release of insulin from the cell. Strict regulatory guidelines dictate required purity and allowable levels of different components from the manufacturing process in the final product - insulin is most commonly injected, meaning there can be very little room for error.

After the cells are homogenized (broken up), the slurry is washed in a variety of patented solutes and buffers to separate material. The following solution is passed through a train of centrifuges, cation exchange chromatography columns, and reverse-phase chromatography columns (Rajkumar, 2020). At each point along the process, samples are collected and sent for laboratory analysis to ensure the outcome from each of the purification steps is as expected. The insulin then undergoes a series of reactions and modifications to become the final folded protein. One of these steps is cleaving some of the amino acids from the protein, typically done using cyanogen bromide. To illustrate the technicality of the process - cyanogen bromide is an incredibly hazardous compound, so just this minor step is very carefully planned and designed with many pieces of equipment and back-up measures employed. Finally, the transformed insulin once again goes through a series of buffer exchanges, washes, chromatography columns, and physical separations before it is packaged and formulated.

Part 2: Economic Incentives

While the production process is not wholly consistent across manufacturers and is continuously changing, current estimates indicate that a singular vial of insulin costs approximately $3-6 to produce (Hirsch, 2016). As corporations, these entities intend to maximize their profit as much as possible. Especially with how much dominance they have over the insulin market, their incentives are to exorbitantly upcharge their products. The price markups at the

source are particularly damaging, because there is still the consideration of every entity it passes through on the way to the patient requiring some compensation as well.

Many times in which a therapeutic is highly sought after on the market, the physical and economical accessibility constraints can be relieved via the introduction of a generic. This is a replicate compound to the brand name drug being sold, and is typically much cheaper to purchase. The challenge with insulin, however, is its status as a biologic rather than a small-molecule compound. Other than biological molecules typically being much larger, the primary difference between these two classes of drugs is that a biologic is produced from an organism, such as *E. Coli* or Chinese hamster ovary cells. A generic in this instance, would be called a biosimilar. One of the primary obstacles to developing a generic version of insulin as a biosimilar lies in its structural complexity. Insulin is a protein hormone comprising two peptide chains linked by disulfide bonds, with precise folding and post-translational modifications critical for its biological activity. These structural intricacies make it challenging to replicate insulin accurately, as even minor variations in its molecular composition can significantly impact efficacy and safety. Furthermore, the regulatory pathway for biosimilar approval differs from that of traditional generics (Beran et al., 2021). Biosimilars are subject to rigorous evaluation to demonstrate similarity in terms of structure, function, and clinical efficacy to the reference biologic (Beran et al., 2016). Given the complexity of insulin and the stringent requirements for biosimilar approval, manufacturers face substantial hurdles in proving biosimilarity to existing insulin products.

Furthermore, intellectual property rights and patent protection pose significant barriers to entry for generic and biosimilar manufacturers alike. Pharmaceutical companies holding patents on insulin formulations and production methods have historically wielded considerable control

over the market, limiting competition and innovation. While patents on older insulin formulations may have expired, manufacturers often introduce incremental innovations or modifications to extend patent exclusivity, further delaying generic or biosimilar entry into the market. To illustrate this control over the market, a collection of counties in northern Virginia late last year filed lawsuits against the big three insulin manufacturers, accusing them of colluding with middleman pharmacy benefit management entities to maintain the extreme prices of their products (Rizzo, 2023). Northern Virginia houses some of the wealthiest counties in America, however, and this kind of pushback from consumers or other pharmaceutical bodies is typically not feasible due to the cost of the lawsuits themselves.

POLICY & LEGISLATION

The accessibility and affordability of insulin are deeply intertwined with public policy and legislative measures aimed at regulating pharmaceutical markets, promoting competition, and ensuring patient access to essential medications. However, navigating the complex landscape of insulin pricing and accessibility requires a nuanced understanding of the various policy interventions and regulatory frameworks in place. Extensive lobbying by pharmaceutical companies, reliance on insurance companies by patients, and patent abuse are commonly identified as the policy issues that need to be focused (Rajkumar, 2020).

Part 1: Insurance

While insurance coverage can provide essential financial support for insulin therapy, the intricacies of insurance policies, including coverage limitations, copayments, and formulary restrictions, can pose barriers to access for many patients. Copayments and cost-sharing

requirements imposed by insurance policies can contribute to the financial burden on patients requiring insulin therapy. High copayments for insulin prescriptions may result in medication non-adherence or discontinuation, as patients struggle to afford the out-of-pocket expenses associated with their treatment (Rajkumar, 2020). Cost-sharing arrangements, such as tiered formularies or coinsurance, may disproportionately impact patients with chronic conditions like diabetes, who require ongoing access to insulin. In tandem with the insurance companies, are pharmacy benefit managers (PBMs) who negotiate the price of insulin between retail pharmacies and the manufacturer themselves. These middlemen have then come to wield considerable influence on which drugs are sold and at what price, further hiking the final price for the consumer (Rajkumar, 2020).

All of this is especially concerning, because it results in a total reliance on the health insurance system for access to medication that people's lives are dependent on. For those in LMICs, this network of insurance and profit sharing is typically non-existent and subsequently lacks any major incentive for these manufacturing giants to focus distribution of their products there. In America, where the medication can be price-gouged, individuals without insurance are forced to pay prices that they may not be able to afford in many cases. While some pharmaceutical entities are implementing programs to assist those in the most dire of need, it is still not adequate to ensure complete equity in access.

Part 2: Patent Abuse

Insurance policies often include coverage limitations that may impact access to specific insulin formulations or brands. Formulary restrictions, for example, may limit coverage to certain insulin products, necessitating patients to switch to alternative medications that may not

be as effective for their individual needs. Coverage limitations are made even more straining on a patient, due to the patent practices of these major manufacturers. Minor adjustments in formulation for what is essentially the same exact drug allow the manufacturer to continue filing patents for continued monopoly of the drug - Lantus, a long acting form of insulin, has had upwards of 70 patents filed on it since it was first introduced (Rajkumar, 2020). This practice is called patent evergreening. The issue of patent abuse and evergreening in the pharmaceutical industry exacerbates monopolies, delays the introduction of affordable generic or biosimilar alternatives, and impedes access to essential medications, including insulin, for patients in need.

PATIENT FOCUS

Patient advocacy plays a pivotal role in raising awareness, influencing policy, and driving change to improve access to insulin for individuals living with diabetes. Advocacy efforts are led by patient organizations, healthcare professionals, and individuals affected by diabetes, who work tirelessly to address barriers to insulin access, promote affordability, and advocate for the rights and well-being of patients. By amplifying the voices of patients and sharing their lived experiences, advocacy organizations advocate for policy changes that prioritize patient needs and ensure equitable access to insulin for all.

Patient advocacy organizations actively engage in policy advocacy and legislative action to promote patient-centered healthcare policies, improve insulin affordability, and address systemic barriers to access. Advocates work collaboratively with policymakers, legislators, and regulatory agencies to propose and support legislation aimed at lowering insulin prices, increasing transparency in drug pricing, and protecting patient rights. Diabetes Africa, a non-profit organization, is dedicated to raising awareness and improving diabetes care and access

to insulin in African countries. They empower healthcare professionals, support patient education, and advocate for policy changes to address diabetes challenges in the region (Diabetes Africa, n.d.).

Patient advocacy efforts extend beyond policy and legislation to encompass grassroots education and infrastructure improvements aimed at empowering individuals with diabetes and enhancing access to care. Organizations like the World Diabetes Foundation (WDF) play a crucial role in supporting such initiatives. The WDF focuses on diabetes prevention, education, and capacity-building in low- and middle-income countries, working closely with local communities, healthcare providers, and government agencies. Through collaborative projects, the WDF strengthens healthcare infrastructure, raises diabetes awareness, and enhances the skills of healthcare professionals in diagnosing and managing diabetes effectively (World Diabetes Foundation, n.d.). Another prominent organization engaged in grassroots advocacy is the IDF that I mentioned previously. With a global network of member associations, the IDF implements community-based programs and initiatives to promote diabetes awareness, education, and self-management skills. By empowering individuals with diabetes and their communities through education and support, the IDF contributes to improved access to care and better health outcomes for people living with diabetes worldwide (International Diabetes Foundation, n.d.).

RACE AND GENDER AS A BARRIER

The intersectionality of race, gender, and sexuality adds layers of complexity to the already challenging landscape of insulin accessibility. Research indicates significant disparities in diabetes prevalence and outcomes across racial and ethnic groups, with marginalized communities often bearing a disproportionate burden of the disease. For example, studies in the

United States have highlighted higher rates of diabetes prevalence, poorer glycemic control, and increased risk of complications among African American, Hispanic, and Indigenous populations compared to their white counterparts (Rodriguez, 2017). James Doucet-Battle's seminal work, "Sweetness in the Blood: Race, Risk, and Type 2 Diabetes," delves into the sociocultural dimensions of diabetes among African American communities, shedding light on the historical, structural, and environmental factors that contribute to health disparities. He challenges the assertion that racial categories are beneficial in reducing diabetes rates and mitigating health disparities, contending instead that their usage contributes to the exacerbation of such rates by obscuring the historical factors responsible for inequalities. In a society driven by consumption and capital, everyone faces equal biological susceptibility to diabetes. The differentiating factor lies in the structural circumstances of one's life: their geographical and occupational environment, the resources available to them, the affordability and accessibility of food, and their access to quality healthcare—all of which are outcomes of "the historical circumstances of unequal exchange that perpetuate societal, racial, and gender disparities" (Doucet Battle, 2021, p. 120).

Furthermore, gender disparities in insulin access and diabetes care have been widely documented, with evidence suggesting differential treatment outcomes and healthcare utilization patterns between men and women. Transgender and gender-nonconforming individuals face unique challenges in accessing appropriate diabetes care, including hormone therapy interactions with insulin and discrimination in healthcare settings (Safer, 2019). While limited research specifically addresses the intersection of gender identity and insulin accessibility, broader studies on transgender healthcare disparities highlight the urgent need for inclusive and affirming healthcare practices. Addressing gender disparities in insulin access requires a multifaceted

approach that considers social, economic, and healthcare system factors, alongside promoting gender equity in diabetes research and healthcare delivery.

CONCLUSION

The complexities surrounding insulin accessibility and affordability highlight the urgent need for comprehensive strategies to address systemic challenges and ensure equitable access to this life-saving medication for individuals with diabetes worldwide. While technological advancements in insulin manufacturing offer opportunities for improved efficiency and product quality, they also contribute to higher manufacturing costs, posing barriers to affordability. Efforts to mitigate these costs must prioritize innovation and collaboration while ensuring that the benefits of automation and robotics translate into tangible improvements in insulin affordability and accessibility. Additionally, addressing insurance-related barriers to insulin access requires proactive policy reforms that focus on capping out-of-pocket expenses, expanding coverage for essential medications, and increasing transparency in insurance formularies. Legislative measures aimed at curbing patent abuse and evergreening practices are essential for promoting competition, fostering transparency, and protecting patient access to affordable insulin. By reforming patent laws, strengthening regulatory oversight, and promoting generic or biosimilar competition, policymakers can help alleviate the financial burden on patients and improve insulin accessibility. Furthermore, grassroots advocacy efforts, supported by organizations like the World Diabetes Foundation and the International Diabetes Federation, play a vital role in empowering individuals with diabetes, raising awareness, and driving community-based initiatives to improve diabetes care and access to insulin. Through collaborative efforts across various sectors, including healthcare, policy, industry, and advocacy,

we can work towards a future where insulin is accessible and affordable for all individuals living with diabetes, regardless of their socioeconomic status or geographic location.

Limitations and Future Work

While I have explored various aspects, such as manufacturing costs, insurance policies, and patent abuse, there are still significant gaps in the knowledge and research. Firstly, understanding of the intricate dynamics of insulin pricing, particularly in low- and middle-income countries, remains limited. Further research is needed to delve into the specific factors driving disparities in insulin affordability across different regions and socioeconomic contexts. Additionally, while we have discussed the role of patient advocacy in promoting insulin access, there is a need for more comprehensive studies evaluating the effectiveness of grassroots advocacy efforts and community-based interventions in improving insulin accessibility. Moreover, my discussions on manufacturing costs and manufacturing technologies were based solely on my experience in the industry, and are general in nature. While these topics, general as they may be, highlighted the potential benefits of automation and robotics in insulin production, there is a lack of research exploring the long-term sustainability and scalability of these technologies, particularly in resource-constrained settings. Future studies should address the feasibility and cost-effectiveness of implementing advanced manufacturing technologies in low-resource environments, considering factors such as infrastructure requirements, workforce capacity, and environmental sustainability.

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