AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, participants will be able to

- Discuss the effect of high insulin costs on public health
- Describe the development of insulin as a treatment for diabetes and how its cost has evolved
- Characterize the factors contributing to the high costs of insulin
- Review the regulatory and legal issues which have had or will have an effect on the cost of insulin

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the post-test with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

ACPE UAN: 0009-0000-22-053-H03-P
0009-0000-22-053-H03-T

Grant funding: None
Cost: $7 pharmacists
$4 pharmacy technicians

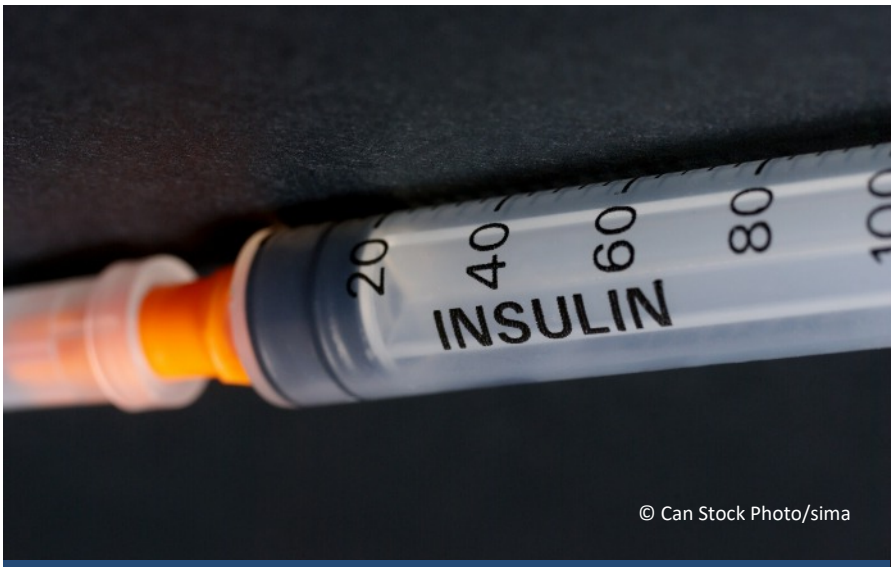
INITIAL RELEASE DATE: October 15, 2022
EXPIRATION DATE: October 15, 2025

To obtain CPE credit, visit the UConn Online CE Center https://pharmacyce.uconn.edu/login.php. Use your NABP E-profile ID and the **session code 22YC53-KXB43 for pharmacists or 22YC53-BXK34for pharmacy technicians** to access the online quiz and evaluation. First-time users must pre-register in the Online CE Center. Test results will be displayed immediately and your participation will be recorded with CPE Monitor within 72 hours of completing the requirements.

For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

TO REGISTER and PAY FOR THIS CE, go to: https://pharmacyce.uconn.edu/program_register.php

You Asked for It! CE



© Can Stock Photo/sima

LAW: CAN ANYTHING BE DONE TO MAKE A CENTURY-OLD DRUG MORE AFFORDABLE?

ABSTRACT: More than 100 years ago, insulin was found to be an effective treatment for diabetes, yet the disease continues to be a major public health concern. Many patients with diabetes undertreat the disease despite insulin's ready accessibility, due, in part, to the rapidly increasing cost of the medication. Significantly, the cost of insulin is subject to a complex, opaque price setting process with many stakeholders that encourages high list prices. There is also little competition in the insulin market, manufacturers aggressively protect their markets, and there are few alternatives to brand name products. Meanwhile, Congress is grappling with measures to lower out-of-pocket insulin costs, including capping copays on insulin products. This continuing education activity will review many of the factors that influence the cost of insulin and the consequences of high prices. It will also discuss regulatory and public health efforts to control costs and the role of the pharmacy team.

FACULTY: Gerald Gianutsos, PhD, JD, is an Emeritus Associate Professor of Pharmacology at the University of Connecticut School of Pharmacy

FACULTY DISCLOSURE: Dr. Gianutsos has no financial relationships with an ineligible company.

DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

"The skyrocketing cost of insulin has become a crisis in the US. Some people are dying because they can't afford the life-saving drug." Columnist Rachel Gillett.[1]

Diabetes is a rapidly growing global health problem with enormous health, social, and economic consequences.[1-3] This chronic metabolic disorder is characterized by prolonged hyperglycemia due to inadequate pancreatic production or utilization of the hormone insulin.[3] Approximately 6.5% of the global population (almost 300 million people) suffer from diabetes.[2] In the U.S., the Centers for

Disease Control and Prevention (CDC) estimates that 10.5% of the population (34 million people) have diabetes and that the prevalence rises to 26.8% among those aged 65 years or older.[4] Direct medical costs and lost productivity attributable to diabetes was estimated to be $327 billion in 2017, making it the most expensive chronic disease in the nation.[5,6]

Complications from diabetes are a serious public health concern. Diabetes is a principal cause of retinopathy, kidney failure, heart attacks and stroke, lower limb amputation, and ketoacidosis which can be fatal.[3] Individuals with diabetes are twice as likely to have heart disease or stroke than those without diabetes.[5] A total of 16 million emergency department (ED) visits were reported with diabetes as a listed diagnosis among adults aged 18 years or older in 2016.[4]

Management of diabetes is critical to preventing complications and high health care costs from the disease. However, many patients do not adequately manage their diabetes, in part due to high treatment costs. This continuing education activity will discuss some of the reasons behind the high costs of treating the disease and the impact that high prices have on patients. It will also review regulatory and public health efforts to reign in the rising costs of insulin.

INSULIN

Diabetes can be managed, and its consequences avoided or delayed with diet, physical activity, tobacco avoidance, and regular screening and treatment for complications.[3,5] Medication, of course, is also a key to management. Prescribers use many different classes of oral medications to manage diabetes,[7] but the emphasis in this activity will be on insulin. Insulin is the mainstay of therapy for individuals with type 1 diabetes, and many patients with type 2 diabetes also benefit from insulin therapy.[8] Prior to the discovery of insulin in 1921, diabetes was difficult to manage. The primary treatment consisted of highly restrictive diets, which compromised the immune system and stunted growth, and often led to death by starvation.[9]

In 1921, Frederick Banting, a Toronto surgeon without laboratory training, medical student Charles Best, physiologist John Macleod, and biochemist James Collip successfully isolated and purified insulin from a dog's pancreas and showed that it would normalize blood glucose levels when administered to diabetic animals.[10] Later, insulin was extracted in larger amounts from cattle and was first given to a 14-year-old dying diabetic patient who developed an allergic reaction. After the Canadian researchers purified it further, they gave a second dose to the patient 12 days later; the patient showed dramatic improvement as his blood glucose dropped to near normal levels with no obvious adverse effects.[10] This observation spurred widespread use of insulin in patients with diabetes. Banting and Macleod were jointly awarded the 1923 Nobel Prize in Physiology or Medicine in recognition of their life-saving discovery (The committee did not recognize Best, the lowly med student, for his contribution).[10] Banting, Collip, and Best were also awarded patents on insulin and the method used to make it in 1923. They all sold their patents to the University of Toronto for $1 each.[10] Banting famously said, "Insulin does not belong to me, it belongs to the world," proclaiming his desire that everyone who needed it should have access to it.[10]

Researchers at the university tried to manufacture insulin for distribution but realized they could not meet the demands of the North American market.[11] The university licensed the technology to Eli Lilly which possessed the expertise to produce large batches of insulin. Under the arrangement, Lilly was allowed to apply for U.S. patents on any improvements to the manufacturing process.[11] The university also established licensing agreements to produce insulin with other companies, including Nordisk and Novo which laid the foundation for the future domination of the insulin market by a few companies.[11] When the animal-based insulin patents began to expire, researchers developed new technologies. They bioengineered human insulin in 1982 and then analog insulin (insulin which has been genetically modified to improve its pharmacokinetic profile) and created new therapies and continued patent protection.[11] Today, approximately 7.4 million Americans use insulin, including roughly 1.4 million people who use it to treat type 1 diabetes.[9]

Pharmacists and technicians are aware that patients with type 1 and type 2 diabetes use a combination of short-acting, rapid-acting, intermediate-acting, and long-acting insulins to control their glucose levels. Today, the insulin analogs are widely prescribed and are the standard of care for people with type 1 diabetes and also a component of care for people with type 2 diabetes; the analogs are generally more expensive than other, older types of insulin.[9]

Even though diabetes is treatable and has been for more than a century, it remains the 7th leading cause of death in the U.S., accounting for 87,647 fatalities in 2019.[5,9] Despite the availability of this century-old treatment, many patients undertreat their diabetes, contributing to complications and high mortality from the disease. Results from an international survey of patients with type 1 diabetes found that approximately 25% of patients in the U.S. had rationed insulin in the previous year.[12] Why would patients show such low adherence to a proven, lifesaving medication?

One reason is cost. High-list prices, health plan structures, and high out-of-pocket costs make it difficult for many diabetic patients to adhere to their medications, especially insulin. Some patients maintain that they spend an estimated 50% of their monthly income on insulin and diabetes products.[11] Studies have found that approximately one of every four survey respondents in the U.S. report underuse of their insulin at least once within the previous year due to high cost.[12,13] This is the highest rate of insulin rationing of any high-income country in the world.[14] An international survey found that only 6.5% of respondents from

high income countries excluding the U.S. reported rationing in the previous year, compared with roughly 25% in the U.S.[14] In addition to rationing insulin, 33.5% of individuals from the U.S. reported rationing of blood glucose testing supplies.[14]

The financial burden is, not unexpectedly, especially acute for economically disadvantaged individuals who have a higher rate of diabetes. Rates of diabetes are higher among people living in impoverished regions of the U.S., such as Appalachia and the Mississippi Delta, and also among those who are eligible for Medicare and Medicaid.[9] Adults with less than a high school education are also more likely to be diagnosed with diabetes than those with at least a high school diploma.[9] Similarly, minority communities are also disproportionally affected by this disease, with Native Americans, Hispanics, Black Americans, and Asian Americans representing more than 45% of those diagnosed with the disease, despite these groups making up 39% of the U.S. population.[9] Cost-related rationing of insulin was the leading cause of hospital admissions for diabetic ketoacidosis among inner-city minority patients.[14] Approximately 24% of adults with diabetes earning below the poverty level use insulin, either alone or in combination with oral medications.[15]

An online survey performed by the American Diabetes Association in 2018 also found that a quarter of respondents reported that the cost of insulin had affected their purchase or use of insulin during the previous year. The percentage was even higher for dependent child insulin users (34%).[16] More than 20% of users admitted missing doses monthly or even weekly. They also had to choose between buying insulin or other health-related purchases such as physician visits (32%), health insurance (26%), or other medications (36%). Many also had to choose between purchasing insulin or other essential items such as utilities (30%), housing (27%), transportation (32%), as well as non-essential purchases like vacations (41%) and entertainment (43%).[16] Patients have also made employment decisions based on the availability of adequate health insurance to cover the cost of their insulin.[11] Patients also claim that they have been forced to make unhealthy food choices that can worsen the disease, purchasing cheaper alternatives due to spending on insulin.[11] The excessive costs also caused 23% of individuals to change to a less expensive insulin type or brand, while many skipped filling at least one insulin prescription.[16]

Moreover, surveys have found that insulin users for whom cost affected their purchase or use of insulin experience adverse health effects at higher rates than those for whom cost was not an issue. When cost was a factor, 72% of individuals experienced episodes of poor blood glucose control during the previous three months (compared with 42% in users who were not affected by the cost), and 80% had their most recent A1C level measured at 7.5 or higher (59% when cost was not a factor).[16] Patients have also claimed that they have intentionally allowed themselves to reach a state of diabetic ketoacidosis so that they would receive insulin in an ED instead of purchasing it.[11]

Not unexpectedly, 73% of individuals dealing with price increases also experience negative emotions (e.g., stress or anxiety), more than twice the rate of those not facing a price increase (31%).[16] There have even been reports of deaths in patients with type 1 diabetes due to a lack of affordable insulin.[14,17] The underutilization of insulin due to concerns over cost not only produces serious avoidable short- and long-term health consequences, but also raises overall costs for the U.S. health care system.[9,15] It is remarkable that this has occurred with a medication whose discoverers refused to profit from it.

PAUSE AND PONDER: How would you start a conversation about economic stress with a patient who appears to be underusing insulin?

ARE COSTS REALLY THAT HIGH?

There is a public perception that the cost of prescription drugs is out of control; indeed, Americans pay an average of three times as much as patients in the U.K. for the world's top 20 medications.[18] But is insulin, in the words of Representative Tom Reed (R., N.Y.), "the poster child of this broken marketplace"?[18]

Insulin in the U.S. is more expensive than anywhere else in the world. The average manufacturer price of insulin is more than four times higher in the U.S. than it is in the next most expensive country (Chile) and more than 10 times the average cost in the 32 developed countries surveyed.[19] In 2018, spending on insulin in the U.S. was $28 billion, compared with $484 million in Canada.[20] The average American insulin user spends almost five times as much annually than their Canadian counterparts. The average cost per unit of insulin in the United States increased by 10.3% between 2016 and 2019 compared with an increase of only 0.01% in Canada during the same time period.[20] By comparison, in 1923, two years after the introduction of insulin therapy, the U.S. had the lowest global price of insulin.[21] As recently as the 1960s, vials of insulin were available in the U.S. for 84¢, equivalent to $7.36 in today's dollars.[18]

The list price of insulin per milliliter in the United States increased, on average, 2.9% annually between 1991-2001, 9.5% per year from 2002 and 2012, 20.7% annually between 2012 and 2016, with a smaller increase from 2016 to 2018.[6] Analog insulins have seen the largest price increase, rising more than 1000% since the 1990s.[14,17] The average annual per capita cost of insulin now approaches $6,000.[6] (Note that the average yearly social security benefit in the U.S. is $18,458.)

The cost of insulin contributes an estimated $48 billion to the direct costs of treating diabetes (before accounting for any rebates or discounts) which represents 20% of the total spending.[6] If current trends continue, the cost of insulin could reach $121.2 billion by 2024, or $12,446 annually for each patient receiving insulin.[6]

WHY?

The reasons for the enormous increase in the retail price of insulin are complex and varied. It has been argued that one of the common justifications for the high price tag on prescription drugs, research and development costs, is not applicable to insulin.[17] Insulin is not a new drug and even the most commonly used modern analogs are 20 years old or more.[17] In addition, over the past 60 years, the increase in the cost of insulin exceeds the rate of inflation by nearly 43-fold.[18] If research and development costs are not driving the price increase, what is?

Notably, there is little competition in the insulin market. Only three companies, Eli Lilly, Novo Nordisk, and Sanofi, manufacture over 90% of the world's insulin and investigations have found that they generally raise their prices at the same time.[17,21-23] It should be pointed out, however, that the manufacturing of biologics, compared with small molecules, involves a higher level of engineering and facility requirements. Additional steps are needed to ensure compliance with good manufacturing practices, regulatory requirements and to minimize batch-to-batch variability, all of which would affect production costs.[21] The scale and optimization of production processes are also important to reduce the overall cost of the finished product which hinders smaller pharmaceutical manufacturers from entering the market.[21]

Other factors also contribute to rising insulin prices. An important trend over the past decade is a shift in insulin prescribing from less expensive human insulins to more expensive human insulin analogs.[15] More than 90% of privately insured patients with type 2 diabetes in the U.S. who receive insulin are currently prescribed the more expensive analog version.[17,21]

Price Setting

Another significant factor affecting the price of insulin is the large number of stakeholders (e.g., manufacturers, wholesalers, pharmacy benefit management services [PBMs], pharmacies, health plans, employers, and the Federal government) involved in the insulin supply chain and price setting, all of whom use varying degrees of negotiating power.[9,15] Multiple transactions occur among these stakeholders during distribution and payment and there is no one agreed-upon price for any insulin formulation.[15]

Although pharmacy staff are generally aware of the pricing dynamics, a brief review will place the insulin costs into context. Prices, rebates, and fees are negotiated among the stakeholders affecting the ultimate price paid by the patient with diabetes at the point of sale. The true cost of insulin can be difficult to pinpoint because of the complex nature and lack of transparency in the financial agreements among the stakeholders.[11,24]

Manufacturers set a list price for their product, but the list price is usually not what payers pay nor what the manufacturers receive.[15,24] The manufacturers, generally, receive the net price which is the list price minus fees paid to wholesalers, discounts

paid to pharmacies, and rebates paid to PBMs or health plans.[15] While manufacturers control the list price of insulin, a substantial portion of the negotiating power has shifted from manufacturers to PBMs.[15]

PBMs attempt to lower costs by leveraging formulary coverage. PBMs administer the prescription medication benefit for more than 266 million Americans and 70% of all prescription claims are managed by the top three PBMs.[15] PBMs have the power to provide exclusive formulary coverage and use this discretion to give them substantial clout in negotiations with manufacturers.[15] Insulin manufacturers compete fiercely, attempting to gain favorable formulary placement and maximize market share and revenue for their products.[9,15] They use rebates as one bargaining chip.[9,15]

These interactions give PBMs little incentive to discourage manufacturers from increasing their list prices since rebates, discounts, and fees PBMs negotiate are typically based on a percentage of a drug's list price.[9] There is an advantage for manufacturers to raise the list prices to provide bigger incentives (discounts) for the participants in the supply chain.[11] In other words, PBMs benefit when there is a larger "spread" between the list price and the real price paid by the health plan, so both the PBMs and manufacturer gain from higher list prices.[9,11,15] Since payers ultimately pay the "real" (discounted) price and not the list price, inflating the benchmark price does not increase the cost to the PBMs.[11]

A Senate investigation found instances in which insulin manufacturers were apparently discouraged from setting lower list prices for their products, which would likely lower out-of-pocket costs for patients, due to concerns that PBMs and health plans would react negatively.[9] Although it might be expected that rebates would reduce patient costs at the point-of-sale, they may be used instead by the employer or the health plan to reduce insurance premiums.[11] Significantly, insulin list prices have tended to rise more rapidly than the net price due to increasing rebates and discounts negotiated between stakeholders. In some cases, rebates and discounts may approach half of the insulin list price.[15,25] This suggests that participants in the distribution system are largely responsible for the increase in insulin costs.[25] It has been estimated that proceeds from insulin sales flowing to insulin manufacturers and insurers have decreased over time, while PBMs, pharmacies, and wholesalers have substantially increased their share of the funds.[25]

Many participants in the pricing system benefit from the arrangement, but one essential participant who does not is the patient who needs insulin and is paying the artificially inflated list price. In particular, patients with high deductible insurances, Medicare recipients in the "donut hole," patients subject to coinsurance, and especially patients without health insurance are in jeopardy.[11,24] Over the past decade there has been a shift away from traditional health plans, which provided broad coverage, to high-deductible health plans, and the deductibles themselves have risen; even plans available under the Affordable Care Act can have high deductibles depending on the "tier." [11] Thus, it would seem that decisions made from negotiations between stakeholders that affect formulary choice may not be based on the patient's best financial or medical interest.[15]

Recently, the Federal Trade Commission (FTC) voted unanimously to conduct an in-depth probe of PBMs since, according to one commission member, "(f)or most Americans, pharmacy middlemen control what medicine you get, how you get it, when you get it, and how much you pay for it. Yet PBM practices are cloaked in secrecy, opacity, and almost impenetrable complexity."[26]

Patent Issues

Not only do a few companies dominate the market, they also maintain significant patent protection that limits incursion of competitive alternatives into the market. Currently, there are no patents on human insulin and most patents on first generation insulin analogs have also expired.[21] Manufacturers have made improvements with new formulations providing more reliable control of diabetes and more convenience for users. However, the newer formulations prolong the patent life and provide up to 37 years of market protection.[17] Companies also engage in what is known as "patent evergreening," where they continually apply for renewed patents for their drugs after making incremental (in some cases, insignificant) changes to their medications.[17,18,23,27]

For example, the long-acting insulin product insulin glargine (Lantus) was first patented in 1994 and was due to expire in 2015. Sanofi filed 74 patents for newer versions of the drug that can provide protection until 2031.[11,17,18] Sanofi maintains that the newer patents "are related to new and unique inventions" although there is evidence suggesting that the improvements are mostly minimal.[18] Sanofi also points out that while the list price for its insulin has increased, the actual price paid by consumers is lower than it was in 2006, due to the nature of the market.[18] In addition to modifying the insulin product, manufacturers have also filed and received patents for insulin delivery devices which effectively extends the patent life of the delivered insulin.[18,21]

Patent disputes can influence cost in many ways. The threat of a lawsuit alleging patent infringement would discourage other manufacturers from developing competing products even if the suit is without merit.[17] Even if the suit is litigated and found to be without merit, large litigation costs and marketing delays would occur.[22] In 2014, Sanofi filed a suit against Lilly alleging a violation of its patent on insulin glargine. The companies reached a deal under which Lilly agreed to delay the launch of its product until 2016 and pay royalties to Sanofi.[28]

Even more disturbing is the strategy of "pay-for-delay" patent dispute in which a competing manufacturer acknowledges the original patent and agrees to defer marketing its product for a specified period of time.[17,22] In return, the competing manufacturer receives a payment from the patent holder, a legal means for a manufacturer to pay a competitor not to enter the market.[22] When Merck filed a new drug application for its rival to insulin glargine, Sanofi filed a suit claiming that Merck violated 10 of its patents, including ones for the drug and its insulin delivery device.[28] After the suit was filed, Merck announced it would no longer pursue its interest in the drug, possibly reaching a deal to receive payments from the suing company.[22]

Biosimilars

Patents are not the only barrier to the introduction of alternatives to brand-name insulin. Insulin is a therapeutic biologic (not a chemically synthesized small molecule/drug) and the FDA treats alternative biologic products as biosimilars and not as generics; this leads to a more cumbersome and expensive regulatory approval process.[17,23] The FDA defines biosimilars as "a biological product that is highly similar to, and has no clinically meaningful differences from, a biological product already approved by the FDA." [29] Production and approval of biosimilars costs nearly as much as a new drug and requires similar testing and regulatory approval.[22,23] The development of a biosimilar takes five to nine years and costs at least $100 million,[30] leaving little financial incentive to develop cheaper options. The first insulin biosimilar, Basaglar, was introduced in the U.S. in December 2016, almost two years after the first biosimilar was approved in Europe, and requires that a prescriber supplies a new prescription.[17] A second biosimilar (Admelog) was approved in 2018.[17]

In 2021, the FDA approved Semglee (insulin glargine-yfgn) as the first interchangeable insulin biosimilar.[29] The "interchangeable" designation means that it can be substituted for Lantus (insulin glargine, approved in 2000) without the intervention of a prescriber, similar to pharmacist-initiated generic drug substitution for small molecules.[27,29]

PAUSE AND PONDER: What factors would you consider before substituting an interchangeable insulin? Would cost be one?

CAN ANYTHING BE DONE TO CONTAIN INSULIN COSTS?

The soaring cost of insulin has caught the attention of legislators, healthcare advocates, and the public.

Rising drug prices are a concern to the public at large. More than half of respondents in a March 2022 poll by the Kaiser Family Foundation agreed that limiting how much drug companies can increase the price of prescription drugs each year to the rate of inflation should be a "top priority" for Congress.[31] A majority of respondents also say placing a limit on out-of-pocket costs for seniors (52%) and, specifically, capping out-of-pocket costs for insulin at $35 a month (53%) should be top priorities for Congress in the coming months.[31] Several different approaches to reigning in costs involving multiple stakeholders have been proposed.

Congressional Actions

The most far-reaching proposal is the Build Back Better Act (BBBA) which was passed by the U.S. House of Representatives on November 19, 2021, but stalled in the Senate. This is a broad and complex 2,135-page bill with many provisions that would commit $2.2 trillion to a long list of health, social, and environmental

proposals.[32] The BBBA includes several provisions that would lower prescription drug costs for people with Medicare and private insurance and reduce drug spending by the federal government and private payers.[32,33]

The key proposals dealing with drug costs, if eventually passed, would include[33]

- Allowing the Federal Government to negotiate prices for some high-cost drugs covered under Medicare Part B and Part D
- Requiring rebates to limit annual increases in drug prices in Medicare and private insurance for drugs whose prices rise faster than the inflation rate
- Cap out-of-pocket spending for Medicare Part D enrollees by instituting a hard cap of $2,000 in 2024
- Eliminate cost sharing for adult vaccines covered under Medicare Part D
- Limit cost sharing for insulin for individuals with Medicare and private insurance.

Currently, Part D and private insurance plans vary in terms of the insulin products they cover and what enrollees pay for insulin products. Under the BBBA, participating plans would cover insulin products at a monthly copayment of $35. Participating plans would not have to cover all insulin products at the $35 monthly copayment but would include one of each dosage form (vial, pen) and insulin type (rapid-acting, short-acting, intermediate-acting, and long-acting).

Since the large BBBA endeavor has not progressed in Congress, the House of Representatives passed a scaled back version (Affordable Insulin Now Act) in March of 2022 that specifically addressed insulin costs.[34] The bill would cap cost-sharing under the Medicare prescription drug benefit for a month's supply of covered insulin products at $35 and cap private health insurance cost sharing for selected insulin products at $35 or 25% of a plan's negotiated price (after any price concessions). The cap would become effective in 2023. At the time this activity was

prepared, the effort was awaiting Senate action. A modified bipartisan Senate bill with a $35 co-pay cap has been introduced.

The industry trade group, the Pharmaceutical Research and Manufacturers of America (PhRMA), does not favor the act, calling the proposed law heavy-handed and flawed. PhRMA's position is that it would make the "broken insurance system worse and throw sand in the gears of medical progress" and "doesn't address perverse incentives in the system that are leading to higher costs for patients."[35]

Biosimilars

The previously discussed biosimilars also aim to encourage more affordable insulin substitutes.[23] Before 2010, the U.S. lacked a regulatory pathway for the development of biosimilar medications.[15,36] In 2010, the Biologics Price Competition and Innovation Act (BPCIA) was signed into law as part of the Affordable Care Act. This new law created an FDA approval pathway for biosimilar and interchangeable biologic products while preserving incentives for the development of new medications.[36,37] Typically, biosimilars marketed in the U.S. have launched with initial list prices 15% to 35% lower than comparable list prices of the original reference products.[29] The BPCIA provides two separate pathways for a biological product to compete with a reference product: either as a biosimilar or as an interchangeable. Interchangeable products are subject to more stringent requirements.[23,36]

To be considered a biosimilar, the route of administration, dosage form, and strength must be the same as the reference product.[36,38] The sponsor must show that it is "highly similar" to the reference product and that no clinically meaningful differences between the biosimilar and the reference product exist in terms of safety, purity, and potency of the product.[38] Only minor differences in clinically inactive components are permitted in biosimilar products.[30]

The biosimilar must also possess the same mechanism of action as the reference product for the condition it is intended to treat, and the manufacturing conditions and facilities must meet standards to ensure safety, purity, and potency.[36,38] To be interchangeable, the manufacturer must demonstrate two things[36,38]:

- That the product produces the same clinical result as the reference product in patients.
- If it is to be used more than once in a given individual, any safety risks or diminished efficacy from switching between the reference substance and the biosimilar is no greater than the risks from using the reference product alone.

Pharmacists should take note of an important difference between biosimilars and generics. Generics (small molecules) only need to demonstrate bioequivalence, while biosimilars need to demonstrate therapeutic equivalence.[36] The equivalence must be based on data derived from animal studies, clinical studies, and analytics that show a similarity to the reference product.[36] As noted above, meeting the biosimilar criteria requires much more time and expense than substantiating generic equivalency. Pharmacists also need to appreciate that even if a product is defined as "interchangeable," it is not possible to create identical versions of reference biologic medicines due to their complexity.[30]

The BPCIA also has market exclusivity provisions that address manufacturers' concerns.[36] Applicants for biosimilar products cannot submit an application until four years after the date on which the reference product was first licensed. Further, the FDA cannot approve the biosimilar or interchangeable until 12 years after the date on which the reference product was first licensed. In addition, the applicant must provide the manufacturer of the reference product with notice of intent 180 days before marketing the product. The first interchangeable product also has market exclusivity for at least a year.[36]

FDA approval of biosimilars, however, is not the only obstacle to marketing insulin substitutes. As noted above, biosimilars must contend with patent evergreening.[17,27] Biosimilars will also not necessarily grab a large market share.[27] Lilly, Novo Nordisk and Sanofi have launched their own "authorized generics," essentially their own drugs repackaged and marketed at discounted prices.[27] Lilly and Sanofi produced the first two (Basaglar and Admelog), which provides little in the way of competition; they are priced only about 15% to 20% less than their respective original forms.[17,39]

More significantly, the complex price setting maneuvering that affects the cost of insulin could also impede cheaper biosimilar acceptance. Since PBMs can make more money from discounts on brand name products, they have more to gain from prioritizing the dominant brands and little incentive to include biosimilars in formularies.[17,27,39] In addition, since pharmacists can substitute interchangeable products, pharmacists have the discretion whether or not to dispense the less expensive formulation.

Over the Counter

Pharmacy personnel should recall that when Congress established federal prescription drug regulations in 1951, the types of insulin available at that time, unlike the more recent analogs, did not require a prescription.[40] Human insulin injection is available over the counter in 49 U.S. states and the District of Columbia and about 15% percent of U.S. patients who buy insulin purchase it over the counter without a prescription.[40,41] This presents a dilemma for patients and clinicians.[40,41] On one hand, this provides an opportunity for patients to obtain insulin without delay, especially in an urgent situation,[41] at a more affordable price (average price of $54.09, compared with $114.40 for prescription short-acting insulins.[19]). On the other hand, it could be dangerous for a

patient to adequately assess the appropriate dosage and timing for optimal glucose control without training or guidance from a health care provider especially if they are switching between different versions of insulin.[40] Physicians may not be aware that insulin can still be purchased OTC and may be puzzled by a patient's sudden change in blood glucose.[41] The FDA maintains that the older insulins were approved for OTC sale because they are less concentrated and did not require medical supervision for safe use.[41]

State Activities

States have also taken measures to influence insulin cost and use while waiting for federal actions.

In 2019, Colorado became the first state to limit co-pays for patients who use insulin, capping individual prescription at $100 for a 30-day supply ($200 if patients use two types of insulin), although payers have exploited some loopholes.[42] The law applies to private insurers but not to patients on Medicare. Since then, seven other states (Illinois, Maine, New Mexico, New York, Utah, Washington, West Virginia) have enacted similar measures and five others (Connecticut, Florida, Kentucky, Tennessee, Virginia) are contemplating similar legislation.[42] In New Mexico, the cap is set at $25.

Pharmacy staff are also reminded that, generally, individual state laws govern generic substitution.[42] Some states have become concerned that biosimilars are not "identical" to the reference product, consequently pharmacy staff should become familiar with their state's regulations regarding biosimilar substitution.[43] At least one U.S. state (Indiana) does not permit OTC sales of insulin due to the safety concerns noted above.[19,41]

Individuals

Insulin prices have risen to such an extent that patients have taken matters into their own hands. The disparity in price has motivated many Americans to travel to Canada to purchase their insulin where the price may be as little as 1/10 the cost in the U.S.[1,9,44] Governmental policy controls insulin prices in Canada, including price caps and negotiations with manufacturers and often insulin does not require a prescription.[44]

PAUSE AND PONDER: How would you advise a patient who is contemplating purchasing insulin from Canada as a cost-saving measure?

In another approach to reducing the cost of insulin, biohackers have been attempting to make insulin by converting proinsulin obtained from yeast to insulin with the hope of providing a method for do-it-yourself production that could be shared online.[18,45] If they are successful, anyone, hypothetically, could construct a lab and manufacture open-source insulin in a garage at a lower cost.[18] However, they could still run afoul of FDA regulations and need to conform to Good Manufacturing Practices.[18,45]

PAUSE AND PONDER: How would you respond to a patient who asks you about OTC or "homemade" insulin?

Patients are also filing lawsuits challenging manufacturer's "schemes" to unlawfully inflate the benchmark prices of rapid- and long-acting insulins.[11]

SUMMARY AND CONCLUDING REMARKS

Insulin maintains a critical place in the treatment of diabetes more than 100 years after the discovery of its beneficial effects, yet the disease is poorly managed in many patients, in part due to the escalating cost of newer forms of the drug. Insulin prices in the U.S. are far higher than in the rest of the world, fueled by a pricing system riddled with disincentives to keep prices low. Patients with no or low-quality health insurance are particularly impacted. Congress and states are examining possible solutions to the problem, notably by placing caps on out-of-pocket spending on insulin.

Pharmacy staff, as the point of contact with patients receiving insulin, are ideally situated to help patients who are struggling with adherence to their medication. Patients would benefit from pharmacists who can advise them about the different forms of insulin and delivery devices.[46] The Endocrine Society recommends that pharmacists learn about lower cost options offered by manufacturers and share their findings with patients and prescribers.[24] Pharmacists should also be ready to discuss the pros and cons of OTC insulin products. Pharmacists have also gained an opportunity (and responsibility) to manage costs with the approval of the first interchangeable insulin product.

Another helpful role would be to educate patients about available patient assistance programs especially since many patients may be unfamiliar with them or unsure about whether they qualify and how to apply.[46] This is a function that pharmacy technicians can fulfill. It is also vital that pharmacy staff remain familiar with Congressional and State efforts to lower out-of-pocket costs of insulin described above and some may choose to serve as patient advocates. Finally, if open-source methods of manufacturing insulin prove to be successful, it could potentially introduce opportunities for compounding pharmacies to make insulin at a lower cost.[18] Insulin may never be as affordable as Frederick Banting hoped, but at least encouraging signs suggest that fewer patients will find it necessary to forego their life-saving treatment because of the expense.

As this activity was being prepared for posting, the Senate passed the long-debated Inflation Reduction Act which dealt with climate, taxes, and health care. The relevant features will allow the government to negotiate costs for certain drugs paid for by Medicare (10 in 2026 and 20 in 2029) and will cap out-of-pocket expenses for insulin at $35 per month for Medicare patients but not for private insurers.

Figure 1. Applying Information about Insulin in Everyday Practice

Best

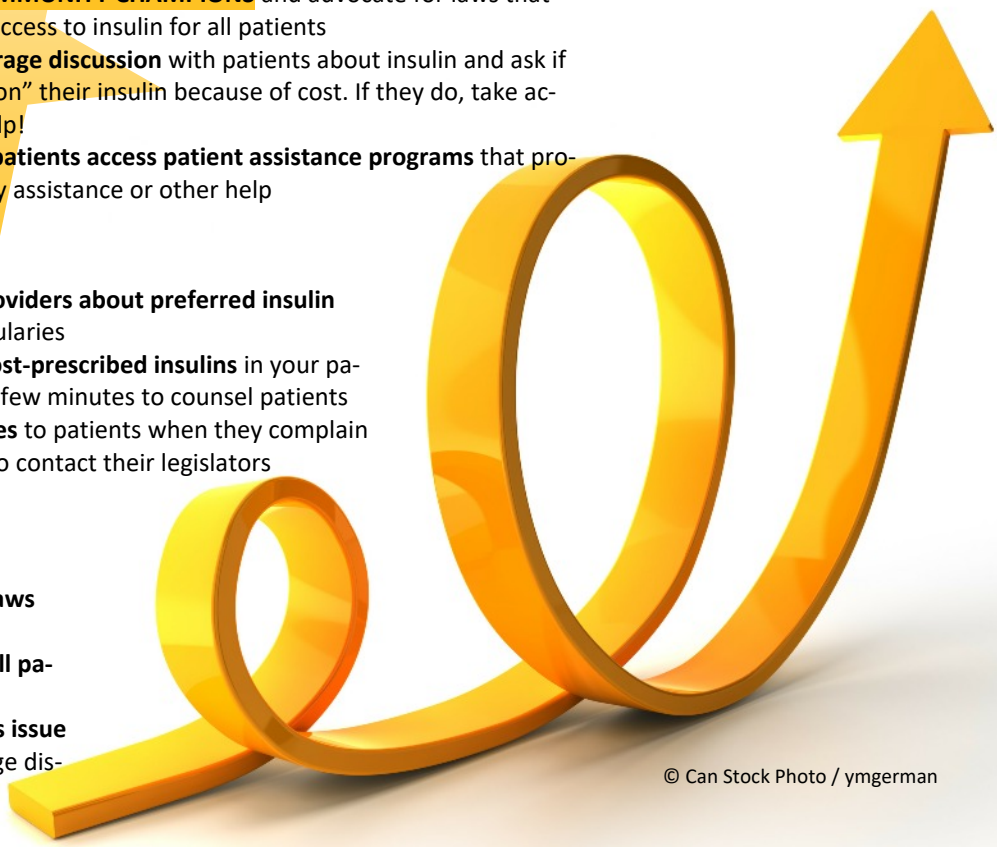
❶ **Be COMMUNITY CHAMPIONS** and advocate for laws that increase access to insulin for all patients
❷ **Encourage discussion** with patients about insulin and ask if they "ration" their insulin because of cost. If they do, take action to help!
❸ **Help patients access patient assistance programs** that provide copay assistance or other help

Better

❶ **Talk to patients and providers about preferred insulin products** on common formularies
❷ **Be familiar with the most-prescribed insulins** in your patient population and take a few minutes to counsel patients
❸ **Explain the pricing issues** to patients when they complain about cost and urge them to contact their legislators

Good

❶ **Be familiar with federal and state laws** concerning insulin pricing caps
❷ **Know that caps may not apply to all patients**
❸ **Understand that insulin is a serious issue for millions of Americans** and encourage discussion



REFERENCES

1. Gillett R, Gal S. One Chart Reveals How the Cost of Insulin Has Skyrocketed in the US, Even Though Nothing About It Has Changed. *Business Insider*. September 18, 2019. Accessed September 15, 2022. https://www.businessinsider.com/insulin-price-increased-last-decade-chart-2019-9

2. Kaul K, Tarr JM, Ahmad SI, Kohner EM, Chibber R. Introduction to diabetes mellitus. *Adv Exp Med Biol*. 2012;771:1-11.

3. World Health Organization. Diabetes. November 10, 2021. Accessed September 15, 2022. https://www.who.int/en/news-room/fact-sheets/detail/diabetes

4. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Accessed September 15, 2022. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

5. America's Health Rankings – Diabetes. United Health Foundation 2021 Annual Report. AmericasHealthRankings.org. Accessed September 15, 2022. https://www.americashealthrankings.org/explore/annual/measure/Diabetes

6. Hayes TO, Farmer J. Insulin Cost and Pricing Trends. American Action Forum. April 7, 2020. Accessed September 15, 2022. https://www.americanactionforum.org/research/insulin-cost-and-pricing-trends/

7. Nauck MA, Wefers J, Meier JJ. Treatment of type 2 diabetes: challenges, hopes, and anticipated successes. *Lancet Diabetes Endocrinol*. 2021;9(8):525-544.

8. American Diabetes Association Position Statement. Approaches to Glycemic Treatment. *Diabetes Care*. 2016;39(Suppl 1):S52-S59.

9. Insulin: Examining the Factors Driving the Rising Cost of a Century Old Drug. United States Senate Finance Committee Staff Report. January 14, 2021. Accessed September 15, 2022. https://www.finance.senate.gov/imo/media/doc/Grassley-Wyden%20Insulin%20Report%20(FINAL).pdf

10. Diabetes UK. 100 Years of Insulin. Accessed September 15, 2022. https://www.diabetes.org.uk/research/research-impact/insulin

11. Class Action Complaint. *Chaires v Sanofi*. United States District Court District of Massachusetts. Filed January 30, 2017. Accessed September 15, 2022. https://static01.nyt.com/science/01-30-17_Insulin_Class_Action_Complaint_Hagens_Berman.PDF

12. Pfiester E, Braune K, Thieffry A, *et al*. Costs and underuse of insulin and diabetes supplies: Findings from the 2020 T1International cross-sectional web-based survey. *Diabetes Res Clin Pract.* 2021;179. https://doi.org/10.1016/j.diabres.2021.108996 Accessed September 15, 2022. https://www.sciencedirect.com/science/article/pii/S0168822721003557

13. Herkert D, Vijayakumar P, Luo J, et al. Cost-Related Insulin Underuse Among Patients with Diabetes. *JAMA Intern Med*. 2019;179(1):112–114.

14. Costs and Rationing of Insulin and Diabetes Supplies: Findings from the 2018 T1international Patient Survey. T1International. Accessed September 15, 2022. https://www.t1international.com/media/assets/file/T1International_Report_-_Costs_and_Rationing_of_Insulin__Diabetes_Supplies_2.pdf

15. Cefalu WT, Dawes DE, Gavlak G, *et al*. Insulin Access and Affordability Working Group: Conclusions and Recommendations. *Diabetes Care.* 2018;41(6):1299–1311.

16. American Diabetes Association. Insulin Affordability Survey, 2018. Accessed September 15, 2022. http://main.diabetes.org/dorg/PDFs/2018-insulin-affordability-survey.pdf

17. Rajkumar SV. The High Cost of Insulin in the United States: An Urgent Call to Action. *Mayo Clin Proc*. 2020;95(1):22-28. https://www.mayoclinicproceedings.org/article/S0025-6196(19)31008-0/fulltext

18. Burningham G. The Price of Insulin Has Soared. These Biohackers Have a Plan to Fix It. *Time*. October 24, 2019. Accessed September 15, 2022. https://time.com/5709241/open-insulin-project/

19. Mulcahy AW, Schwam D, Edenfield N. Comparing Insulin Prices in the United States to Other Countries: Results from a Price Index Analysis. Santa Monica, CA: RAND Corporation, 2020. Accessed September 15, 2022. https://www.rand.org/pubs/research_reports/RRA788-1.html

20. Schneider T, Gomes T, Hayes KN, et al. Comparisons of Insulin Spending and Price Between Canada and the United States. *Mayo Clin Proc*. 2022;97(3):573-578.

21. Keeping the 100-year-old Promise: Making Insulin Access Universal. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO Accessed September 15, 2022. https://www.who.int/publications/i/item/9789240039100 Link to download.

22. 8 Reasons Why Insulin is so Outrageously Expensive. T1 International. January 20, 2019. Accessed September 15, 2022. https://www.t1international.com/blog/2019/01/20/why-insulin-so-expensive/

23. Zelitt J. Pay or Die: Evaluating the United States Insulin Pricing Crisis and Realistic Solutions to End It. *Stetson Law Rev.* 2021;50:453-489. Accessed September 15, 2022. https://www2.stetson.edu/law-review/wp-content/uploads/2021/04/Zelitt.PayorDie.pdf

24. The Endocrine Society, Addressing Insulin Access and Affordability: An Endocrine Society Position Statement. *J Clin Endocrin Metab.* 2021;106(4):935–941.

25. Van Nuys K, Ribero R, Ryan M, Sood N. 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.* 2021;2(11):e213409. doi:10.1001/jamahealthforum.2021.3409 Accessed September 15, 2022. https://jamanetwork.com/journals/jama-health-forum/fullarticle/2785932

26. Rowland D. FTC Agrees to 'Shine A Light' on How Drug Middlemen Impact Your Prescription Prices. *Columbus Dispatch*. June 9, 2022. Accessed September 15, 2022. https://www.dispatch.com/story/news/2022/06/08/drug-prices-heart-new-ftc-investigation-pharmacy-benefit-managers-pbms/10002565002/

27. Insulin — the New Battleground for Drug Pricing. *Nat Biotechnol*. 2022;40:1. https://doi.org/10.1038/s41587-021-01203-z Accessed September 15, 2022. https://www.nature.com/articles/s41587-021-01203-z

28. Bisserbe N, Landouro I. Sanofi Files Suit Against Merck, Claiming Patent Infringements. *WSJ*. September 19, 2016. Accessed September 15, 2022. https://www.wsj.com/articles/sanofi-files-suit-against-merck-on-patent-infringements-1474285467

29. U.S. Food and Drug Administration. FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes. July 28, 2021. Accessed September 15, 2022. https://www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-product-treatment-diabetes

30. Pfizer. Let's Take a Closer Look at the Characteristics of Biosimilars. Accessed September 15, 2022. https://www.pfizerbiosimilars.com/characteristics-of-biosimilars

31. Kirzinger A, Kearney A, Quasem M, *et al*. KFF Health Tracking Poll – March 2022: Economic Concerns and Health Policy, The ACA, and Views

of Long-term Care Facilities. Kaiser Family Foundation. March 31, 2022. Accessed September 15, 2022. https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-march-2022/
32. H.R.5376 - Build Back Better Act. 117th Congress (2021-2022). Accessed September 15, 2022. https://www.congress.gov/bill/117th-congress/house-bill/5376
33. Cubanski J, Neuman T, Freed M. Explaining the Prescription Drug Provisions in the Build Back Better Act. Kaiser Family Foundation. November 23, 2021. Accessed September 15, 2022. https://www.kff.org/medicare/issue-brief/explaining-the-prescription-drug-provisions-in-the-build-back-better-act/
34. H.R.6833 — 117th Congress (2021-2022). Affordable Insulin Now Act. Accessed September 15, 2022. https://www.congress.gov/bill/117th-congress/house-bill/6833
35. Pharmaceutical Research and Manufacturers of America. House Drug Pricing Plan Will "Throw Sand in the Gears of Medical Progress." November 19,2021. Accessed September 15, 2022. https://phrma.org/resource-center/Topics/Cost-and-Value/House-Drug-Pricing-Plan-Will-Throw-Sand-in-the-Gears-of-Medical-Progress
36. Koballa KE. The Biologics Price Competition and Innovation Act: Is a Generic Market for Biologics Attainable? *Wm & Mary Bus Law Rev*. 2018;9(2):479-520. Accessed September 15, 2022. https://scholarship.law.wm.edu/cgi/viewcontent.cgi?referer=https://www.google.com/&httpsredir=1&article=1150&context=wmblr
37. Biologics Price Competition and Innovation Act. Accessed September 15, 2022. https://www.dpc.senate.gov/healthreformbill/healthbill70.pdf
38. Regulation of Biological Products 42 U.S. Code § 262. Accessed September 15, 2022. https://www.law.cornell.edu/uscode/text/42/262
39. Bagley D. Devil in the Details: The Impact of the First Interchangeable Biosimilar Insulin. *Endocrine News*. August 2021. Accessed September 15, 2022. https://endocrinenews.endocrine.org/fda-approves-first-interchangeable-biosimilar-insulin-product-for-treatment-of-diabetes/
40. Goldstein JN, McCrary M, Lipska KJ. Is the Over-the-Counter Availability of Human Insulin in the United States Good or Bad? *JAMA Intern Med.* 2018;178(9):1157–1158.
41. Tribble SJ. You Can Buy Insulin Without a Prescription, But Should You? Kaiser Health Network. December 14, 2015. Accessed September 15, 2022. https://khn.org/news/you-can-buy-insulin-without-a-prescription-but-should-you/
42. Yan K. Eight States Pass Legislation to Place Caps on Insulin Price; Five More Await Ruling. *diaLogue*. diaTribe Foundation. Accessed September 15, 2022. https://diatribe.org/foundation/about-us/dialogue/eight-states-pass-legislation-place-caps-insulin-price-five-more-await-ruling
43. National Conference of State Legislatures. State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars. May 3, 2019. Accessed September 15, 2022. https://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx
44. Rauhala E. As Price of Insulin Soars, Americans Caravan to Canada for Lifesaving Medicine. *Wash Post*. July 31, 2019. Accessed September 15, 2022. https://www.washingtonpost.com/world/the_americas/as-price-of-insulin-soars-americans-caravan-to-canada-for-lifesaving-medicine/2019/06/14/0a272fb6-8217-11e9-9a67-a687ca99fb3d_story.html
45. Osterath B. Do-It-Yourself Insulin: Biohackers Aim to Counteract Skyrocketing Prices. *DW*. May 24, 2019. Accessed September 15, 2022. https://www.dw.com/en/do-it-yourself-insulin-biohackers-aim-to-counteract-skyrocketing-prices/a-48861257
46. Gogineni HP, Gogineni RV. Increasing Insulin Prices - Role of Pharmacists in Assisting Patients with Diabetes to Enhance Access. *Biomed. J. Sci. & Tech. Res.* 2018;8(2) :1-4. DOI: 10.26717/ BJSTR.2018.08.001633. Accessed September 15, 2022. https://biomedres.us/pdfs/BJSTR.MS.ID.001633.pdf