



November 19, 2018

Insulin Products and the Cost of Diabetes Treatment

Insulin is a hormone that regulates the storage and use of sugar (glucose) by cells in the body. When the pancreas does not make enough insulin (type 1 diabetes) or it cannot be used effectively (type 2 diabetes), sugar builds up in the blood. This may lead to serious complications, such as heart disease, stroke, blindness, kidney failure, amputation of toes, feet, or limbs. Prior to the discovery of insulin treatment, type 1 diabetics usually died from this disease.

There were 23.1 million diagnosed cases of diabetes in the United States in 2015 according to the Centers for Disease Control and Prevention (CDC). Adding an estimated 7.2 million undiagnosed cases brings the total to 30.3 million (9.4% of U.S. population). People with type 1 diabetes, about 5% of U.S. cases, must have insulin injections to survive. For those with type 2 diabetes, about 95% of cases, many can control their blood glucose by following a healthy diet, losing weight, maintaining regular physical activity, and taking oral medications, but some require insulin injections to control their blood glucose levels.

Data collected in the 2010-2012 National Health Interview Survey from diabetics aged 18 or older indicate that 14% are treated with insulin alone, 14.7% are treated with both insulin and oral medication, 56.9% are treated with oral medication alone (not insulin), and 14.4% are not treated with either medication. The price of various insulin products has risen significantly. From 2001 to 2015, the price of one type of insulin (insulin lispro) increased 585% (from \$35 to \$234 per vial). One vial might last a patient less than two weeks. Given the number of Americans dependent on insulin, Congress may be interested in considering whether consumers have access at a reasonable cost.

Insulin Discovery and Development

Insulin was discovered nearly a century ago, in 1921, by researchers at the University of Toronto; their U.S. patent was later sold to the university for \$1. Manufacturing challenges resulted in collaboration with Eli Lilly in 1923 in order to make enough insulin for the North American market. They also licensed the right to produce insulin to other firms including a Danish company which eventually became Novo Nordisk.

Insulin is a small protein composed of 51 amino acids. Because it is made from a living organism, it is considered to be a biologic, or biological product. Like many other biologics (such as drugs or vaccines), insulin was obtained in the past by extraction from animals. Production has changed over the years as researchers have made alterations to insulin, easing its use by the patient.

The ideal treatment regimen for diabetics would closely mimic the way insulin secretion occurs in the body. This

would involve a consistent insulin level between meals combined with a mealtime level of insulin that has a rapid onset and duration of action to match the glucose peak that occurs after a meal. The original insulin, also called regular insulin, is a short-acting type of product with a duration of action of about 8 hours, making it less suitable for providing 24-hour coverage.

In the late 1930s through the 1950s, regular insulin was altered by adding substances (protamine and zinc) to gain longer action; these are called intermediate-acting insulins. One such advance (neutral protamine Hagedorn, or NPH) was patented in 1946 and is still in use today. It allowed for the combination of two types of insulin in premixed vials (intermediate-acting and regular insulin), making a single daily injection possible for some patients. In 1982, recombinant DNA technology allowed for the replacement of animal insulin extracted from cattle and pig pancreases by human insulin (Humulin R) made in a laboratory fermentation process using microorganisms. These advances still did not mirror the normal release of insulin.

Over the past few decades, slight modifications of the insulin molecule—called insulin analogs—have been developed. This has resulted in five types of insulin products on the market: long-acting, rapid-acting, intermediate-acting, short-acting (regular insulin), and premixed. In the early 2000s, the long-acting insulin analogs, Lantus (insulin glargine) and Levemir (insulin detemir), entered the market. In addition, the rapid-acting insulin analogs Humalog (insulin lispro) and Novalog (insulin aspart) were developed to allow for quicker absorption and shorter duration of action at mealtime.

The insulin analogs more closely replicate normal insulin patterns in the body and resulted in a greater number of patients using these new products. In 2000, of privately insured adults with type 2 diabetes using insulin, 19% were using analog insulins; by 2010, 96% were using these products. Studies indicate that the more expensive analogs do not seem to provide any advantage over regular insulin in controlling glucose levels or preventing diabetes-related complications, but they are more convenient for the patient.

Insulin Regulation and Production

In the past, all biologics, including insulin, were regulated by the National Institutes of Health (or its precursors) under the Public Health Service Act (PHSA). In 1941, Congress gave the Food and Drug Administration (FDA) authority over the marketing of insulin. As a result, insulin has been regulated as a drug under the Federal Food, Drug, and Cosmetic Act (FFDCA) rather than as a biologic under the PHSA. In the United States “generic” insulin products are referred to by FDA as “follow-on” products and are not called biosimilars (which are regulated under the PHSA).

However, under a provision of the Biologics Price Competition and Innovation Act (BPCIA) of 2009, biologics approved as drugs under the FFDCAs will transition to biological licenses under the PHSA in March 2020. BPCIA was enacted as Title VII of the Patient Protection and Affordable Care Act (ACA, P.L. 111-148).

Currently, three firms—Eli Lilly, Novo Nordisk, Sanofi Aventis—account for over 90% of the global insulin market and produce the entire insulin supply for diabetic patients in the United States. For the most part, insulins produced by these companies are brand-name drugs. In general, brand-name drugs cost more because the drug manufacturer has free rein in setting the drug price due to a government sanctioned monopoly for a defined period of time. Brand-drugs are protected from market competition by (1) patents issued by the U.S. Patent Office and (2) a regulatory exclusivity period granted by FDA under the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), also called the Hatch-Waxman Act. According to some analysts, lack of price competition in the U.S. insulin market is a contributor to the high cost of this vital drug.

The price of a drug is directly affected by the number of *different* manufacturers marketing the drug. According to an FDA analysis of generic chemical drugs, “the first generic competitor prices its product only slightly lower than the brand-name manufacturer. However, the appearance of a second generic manufacturer reduces the average generic price to nearly half the brand name price. As additional generic manufacturers market the product, the prices continue to fall, but more slowly. For products that attract a large number of generic manufacturers, the average generic price falls to 20% of the branded price and lower.”

One “generic” insulin product—or what FDA calls a “follow-on” product—is being marketed in the United States. Eli Lilly received tentative approval for Basaglar from FDA in August 2014. Final approval occurred in December 2015 following resolution of patent issues with Sanofi-Aventis, maker of the brand product, Lantus (insulin glargine). The Basaglar application was submitted to FDA under Section 505(b)(2) of the FFDCAs and relied on the FDA’s finding of safety and effectiveness for Lantus. Eli Lilly began marketing Basaglar in the United States in December 2016; by the end of December 2017, Basaglar had captured about 17% of the U.S. Lantus volume share.

Because three firms manufacture all the insulin used in this country, the market behaves differently from the usual case in pharmaceutical markets where generic competition results in price reductions following patent expiration and the end of the exclusivity period granted by FDA under Hatch-Waxman. Basaglar, the only follow-on insulin available in the United States, is made by one of the three insulin-making firms, Eli Lilly. Basaglar’s approval has not resulted in a *new* insulin manufacturer on the U.S. market.

Industry observers believe that as other pharmaceutical companies enter the insulin market, price reductions may begin to occur. In July 2017, FDA granted tentative approval to a second insulin glargine product, Lusduna Nexvue, made by Merck. However, in October 2018 Merck

announced that it is discontinuing Lusduna. Some industry analysts believe Merck’s decision was due to the drug rebates offered by the three manufacturers of insulin products. For drugs such as insulin with a high list price, manufacturers may use a high rebate to gain placement on an insurance company formulary. This results in making the drug more affordable for insurance plans, but the drug remains expensive for the uninsured, as well as for those with high cost-sharing insurance plans.

Price of Insulin, Cost of Manufacture, and Profit

The price of a drug often has very little basis in the cost of manufacturing a drug. Also, it is very rare to find data on manufacturing costs; this is considered to be proprietary information. However, a 1995 paper in *Biotechnology and Bioengineering* focused on the process used by Eli Lilly in the commercial production of insulin using *E. coli* bacteria. The authors found that the total cost involved in making enough insulin to treat one patient per year is \$33.60. This amount would be altered by inflation, but would be offset by process improvements.

Most of the manufacturing cost (94.2%) is associated with the recovery and purification of insulin; the remainder (5.8%) is the fermentation process using *E. coli*. The economic analysis includes the cost of raw materials, product separation materials, facility overhead (depreciation and maintenance of the facility), treatment and disposal of waste materials, and labor of plant operators and laboratory scientists who perform analysis of the process and product (quality control/quality assurance). It does not account for other costs, such as the cost of vialing and quality assurance of vialing, distribution costs, promotion and advertising costs, and briefly mentions research and development cost recapture.

In the case of insulin, however, much of the initial basic research—original drug discovery and patient trials—was performed 100 years ago. Other more recent costs, such as developing the recombinant DNA fermentation process (over 35 years ago) and the creation of insulin analogs (about 20 years ago) may account for some portion of the current price of insulin products, but exactly how much is known only by the manufacturers. The pricing of insulin could also reflect accounting for research costs of other drug products, both the past costs of drugs that were not successful as well as future products that are currently under development.

A September 2018 study published in *BMJ Global Health* calculates that a year’s supply of human insulin could be \$48 to \$71 per person and between \$78 and \$133 for analog insulins; this amount would cover production costs and still deliver a profit to the manufacturer. How much profit is fair is another piece of the drug pricing puzzle. A November 2017 Government Accountability Office (GAO) report found that the average profit margin was 20% in 2015 for the largest 25 drug companies, compared with 6.7% for the largest 500 companies in general. The three insulin manufacturers are among the largest 25 drug companies.

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