

# Insulin biosimilars



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## Abstract

Insulin was first purified in 1921 by Frederick Grant Banting and Charles Herbert Best at the University of Toronto. Soon after, the benefits of using insulin to treat diabetes was discovered, the patent was sold to the University of Toronto for \$1, and Eli Lilly received the contract to manufacture insulin. Banting believed that insulin must be widely available for treating diabetes. A century later, insulin is so expensive that 50% of the estimated 100 million patients that need it lack reliable access. With many of the patents for insulin expiring and forthcoming changes

to the US biosimilar regulations, things should be about to get better for people with diabetes. Biosimilar insulin products are expected to reach the US markets, and it will be interesting to see who achieves success.

Insulin was first purified from an animal pancreas in 1921 at the University of Toronto by Frederick Banting and Charles Best. Professor John MacLeod and biochemist J.B. Collip helped with this endeavour. Then in a paramount development in 1922, it was first used to treat a person with diabetes; the scientists went on to receive a Nobel Prize in 1923.<sup>1</sup> They soon recognised the significance of their finding to help people with diabetes mellitus and so sold their patent for \$1 to the University of Toronto. Banting wanted insulin to be mass-produced and widely available. He said "Insulin does not belong to me; it belongs to the world." Let's fast forward to 2019. An estimated 100 million people live with diabetes worldwide, yet more than half do not

have access to reliable and affordable insulin. High prices of insulin are a significant cause.<sup>2</sup>

## What is insulin and why is it important?

The cells in our body need sugar for energy to drive cellular metabolism and function. When we eat, carbohydrates are broken down into glucose (sugar), which is the primary source of energy. But the sugar cannot enter the cells directly. After a meal, glucose levels in the blood increase and beta cells in the pancreas secrete insulin, an important anabolic hormone. Insulin then attaches to the cells around the body, helping them to take up the circulating glucose from the bloodstream. When there is an excess of glucose in the blood, insulin helps store the excess glucose in the liver as glycogen. Between meals or while exercising, when the cells need more energy and blood glucose level is low, this stored glucose in the liver is made available and gets used up by the cells that need it.

Blood glucose concentration needs to be maintained in a narrow range to prevent long-term health issues, including weight gain, and for

overall wellbeing. Thus, insulin plays an important role in regulating the blood sugar levels and maintaining it within a narrow range.

Diabetes is a chronic condition; there are two types. Type 1 usually occurs in young people and type 2 develops in older people. Approximately 1.25 million children and adults in the US have type 1 diabetes.<sup>4</sup> People living with type 1 diabetes cannot maintain their blood sugar level in the normal range because the beta cells are damaged and the pancreas makes little or no insulin. It is an autoimmune disease initiated by cytokine rich natural killer cells. The regulatory T cells activity is compromised and cell mediated  $\beta$ -cell destruction via apoptosis dominates. Cellular and humoral components of the immune system involved in type 1 diabetes can be detected for months or sometimes years before the onset of clinical diabetes. It is believed to be caused by a combination of genetic and environmental factors.<sup>5</sup>  $\beta$ -cell death means type 1 diabetics need daily insulin therapy. In people with type 2 diabetes, either the pancreas does not produce enough insulin or the body does not use the insulin properly. Type 2 diabetics can initially control their blood glucose with diet and exercise and may need addition help with oral glucose-lowering medication. But as the condition progresses insulin therapy might become necessary to maintain blood glucose levels. Therefore, people with type 1 diabetes need insulin for survival and many with type 2 diabetes need insulin therapy as well.<sup>3</sup> Poor long-term blood sugar control has been shown to lead to complications such as cardiovascular disease, kidney failure, nerve damage, and eye problems.

Three large manufacturers (Eli Lilly & Company, Novo Nordisk, and Sanofi) hold 96% of the global insulin market share. These drug companies have successfully kept insulin under patent from 1923 to 2014 by making incremental improvements to their products, which has kept the current price of insulin high. The number of people living with diabetes in the US is 30.3 million as of 2015. In 2017, the US healthcare expenditure on people with diabetes was 15 billion dollars. However, as these patents have expired, the insulin market will open worldwide. Therefore, biosimilar insulins have been a subject of great interest for patients, healthcare community and governments.

#### What are the differences between generics and biosimilars?

Generic drugs contain the same active ingredient as the originator product and are made from simple small, well-defined molecules that do not require complex modifications. However, the inactive excipient ingredients can be different. Generic drugs are administered in the same dose as the originator product and approved to treat the same disease. The manufacturing process is simple and must follow the same standard FDA good manufacturing practice regulations as the originator product. No preclinical or clinical studies are required and the approval process is straightforward. The investment required is around \$2 million to \$3 million.

On the other hand, biosimilars are complex molecules with post-translational modifications. They require a more complex manufacturing process. Unlike generics, they are not copies; they are similar to the originator product. The required investment is around \$3 billion and they take longer to reach the market. Biosimilars also have to go through a phase III clinical trial before reaching the market.

Biologics include products such as vaccines, antibodies, and blood components. They are complex molecules derived from micro-organisms, animals or through biotechnology techniques and contain sugars, proteins and nucleic acids. A biologic is different from chemically synthesised drugs where the structure is known. Insulin is a typical example of a biologic.

The manufacturing protocol for biologics is proprietary information known only to the originator pharmaceutical company. This is to prevent other manufacturers from producing copies that are identical to the originator biologic product. Therefore, biosimilars, which are very similar to the FDA approved originator biologic product, are manufactured differently. The clinical studies for biosimilars must show no difference in comparison to the reference product in terms of safety, purity and potency.<sup>6,7</sup>

#### Biosimilar Insulin and the FDA

In total, there are 11 biosimilars currently approved in the US. Basalgar is the only approved insulin biosimilar; however, it has been classified as a follow-on to the basal insulin Lantus. What

is a follow-on? Follow-on is a copy of an originator biologic product and is approved under the Food, Drug & Cosmetic Act (FD&C) 505 (b)(2) pathway. Basalgar was introduced by Eli Lilly & Company in 2015. To be approved, a product has to be shown to be bioequivalent to the reference biologic. The applicant relies on the safety and efficacy data from the published studies for the reference biologic to support the application. Additional clinical trials may be required for the FDA to approve follow-on biologics.

Manufacturing of biologics is challenging and well regulated. The Biologics Price Competition and Innovation (BPCI) Act of 2009 was signed into law via the Patient Protection and Affordable Care Act on March 23, 2010. The approval of biosimilars under these new regulations is challenging and requires a series of studies. For example, analytical studies demonstrating that the product is highly similar to the reference product, animal studies, toxicity studies and a range of clinical studies that include pharmacokinetic, pharmacodynamic and immunogenicity studies. Immunogenicity studies are significant, as even a small difference in the structure of the biosimilar could elicit an immune response. Immunogenicity study is important

for a product like insulin which would be taken by the patient on a regular basis.

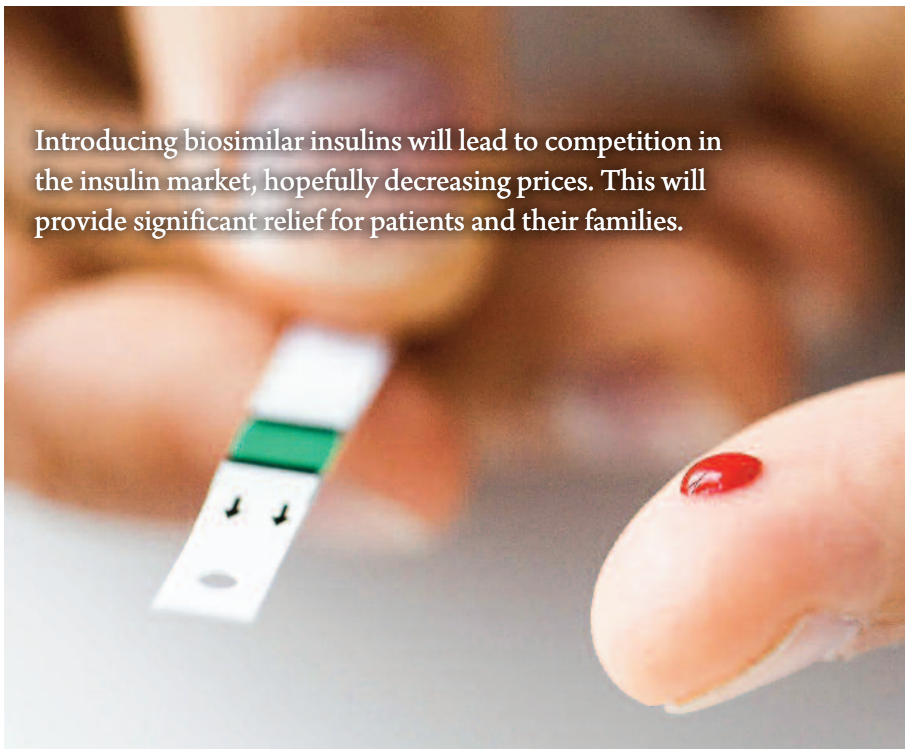
Any uncertainty must be addressed with additional studies.

Currently, there are separate approval pathways in the US, one for biosimilars and one for follow-on biologics. However, the less stringent

FD&C (follow-on) act will soon give way to the more stringent BPCI Act (biosimilar). When the BPCI Act was initiated, it came with a 10-year transition period. During the transition period, a biosimilar product application must include a reference product approved under section 351 of the Public Health Service (PHS) Act. However, no insulin has yet been approved under the PHS Act as an exception was made during this transition period, where applications for drugs such as insulin could be submitted as follow-on biologics until March 23, 2020. For the follow-on biologics application, there is no need to present a reference product approved under section 351 of the PHS Act. This is how Eli Lilly was able to get the approval for Basalgar as a follow-on insulin. The safety and efficacy of

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Lantus was used to support the application. With March 23, 2020, approaching, the pharmaceutical companies are waiting. They do not want to submit a follow-on biologic application as we are nearing the cut-off date. The applications for biosimilar insulins have to wait as well.

Many clinical trials with biosimilar insulins are being carried out in the US. For example, Basalgar has been subjected to various clinical trials and has undergone pharmacokinetic, pharmacodynamic and immunogenicity studies. Three other potential biosimilar insulins have completed their phase 3 clinical trials.<sup>6</sup>

#### **Biosimilar Insulin and EMA:**

LY2963016 insulin glargine was the first biosimilar introduced in Europe. Following this, many biosimilar insulins have been introduced to the European market. EMA developed the guidelines for biosimilars 10 years ago. It involves both preclinical and clinical evaluation. Pre-clinical evaluation includes physical characteristics, structural characteristics, and analysis of the purity and impurities. The evaluation process also includes phase I and phase III clinical trials. This would include pharmacokinetic, pharmacodynamic and immunogenicity studies. Any uncertainties had to be supported by additional studies in the application.<sup>7</sup>

#### **Interchangeability:**

Interchangeability will be a major concern with

insulin biosimilars. It will address questions such as, can a prescriber switch between the reference product and a biosimilar? What will happen if the patient substitutes the reference product without a prescriber's consent? The current European regulations do not require studies showing evidence of interchangeability. With the new FDA guidelines, applicants for biosimilar products can submit studies that would classify them interchangeable.<sup>6,7</sup>

### **Conclusion**

When all the regulatory hurdles are overcome by biosimilar insulins, a huge market is awaiting them. Introducing biosimilar insulins will lead to competition in the insulin market, hopefully decreasing prices. This will be significant relief for patients and their families. Once biosimilars reach the market, the transition is not expected to be smooth. To help overcome the hurdles of substitution and interchangeability, all necessary support and education must be given to physicians, nurses, and the patient community. They must understand that biosimilars are similar to the originator products but not the same. Patients should be made clearly aware about the product they are prescribed and how it might differ from the product they were using before. If there is an adverse event, the patient should know which product they took. Comfort and familiarity of the delivery devices used with biosimilar insulins will also play a role in their

success. We do not know what the initial cost differences would be when the biosimilar insulin enters the US market or how prices will change over the years. The costs of insulin in most of Europe is one-sixth of what it is in US. Insulin prices have tripled in US in the last decade. This has led to people cutting back and skipping insulin doses, putting their health at risk. Now we just have to wait and watch and hope for relief for the patient community.

### **Conflicts of interest**

The author declares no conflict of interest related to this article.

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