Biosimilar Insulins: A Potential Option in the Treatment of Diabetes

By

Turana Tabassum
ID: 17346050

A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
April 2021

© 2021. Brac University
All rights reserved.

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. We have acknowledged all main sources of help.

Student's Full Name & Signature:

Turana Tabassum
17346050

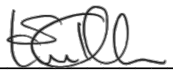
Approval

The thesis/project titled “Biosimilar Insulins: A Potential Option in the Treatment of Diabetes” submitted by Turana Tabassum (17346050) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on May 8, 2021.

Examining Committee:

Supervisor:

(Member)



Professor Eva Rahman Kabir

Chairperson and head, Department of Pharmacy

Brac University

Program Coordinator:

(Member)

Dr. Hasina Yasmin

Professor, Department of Pharmacy

Brac University

Departmental Head:

(Chair)

Professor Eva Rahman Kabir

Chairperson and head, Department of Pharmacy

Brac University

Ethics Statement

This study comprises no human or animal trial.

Abstract

Diabetes is one of the most common noncommunicable diseases in the world and insulin, a biologic, has been a successful treatment option for this disease. However, the cost of insulin treatment is expensive and thus a global burden. The introduction of biosimilar insulins (a highly similar copy of the biologic insulin) will not only reduce the cost but will also open door to patient access and choices of diabetes treatment. Several biosimilar insulins are already available in the market, and patient acceptability is expected to increase over time. Different countries with their stringent laws are working to establish this treatment option for the diabetic patients. A greater knowledge for the acceptance of biosimilar insulins is needed for the biosimilar insulin to be used in place of the biologic insulin. This paper aims to provide an overview on biosimilar insulins as a potential option for the treatment of diabetes.

Keywords: Diabetes; Biologics; Biosimilar insulin; Insulin Approval; Interchangeability; Insulin Glargine.

Dedication

Dedicated to my Beloved Parents & Respected Supervisor Dr. Eva Rahman

Kabir Madam

Acknowledgement

To begin, I am grateful to Almighty Allah for the good health and wellbeing during the project which was vital to complete the project work on time.

I wish to show my appreciation to my respected supervisor Professor Eva Rahman Kabir, Ph.D. (Chairperson, Department of Pharmacy, Brac University), to whom I am indebted for her expert, sincere and valuable guidance and encouragement extended towards me. Madam helped me to obtain deep insight into study, to explore and learn more. Her scholarly advice was the sustaining factors in carrying out the project successfully.

Also, I take this opportunity to express my gratitude to all the faculty members for their guidance, help and support throughout the last four years of my bachelors in department of pharmacy for whom I learned so much and could come this far. Their contribution to mold my life with knowledge and lessons will be always beholden.

I wish to extend my special thanks to Nashrah Mustafa (Teaching Assistant, Brac University) and Nahid Nausheen (Teaching Assistant, Brac University) for the assistance they provided, which were very helpful for me.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ADH	Anti- Diuretic Hormone
aBLA	Abbreviated Biologics License Application
BPCIA	Biologics Price Competition and Innovation Act
CCDE	Chinese Center for Drug Evaluation
EU	European Union
EMA	European Medicines Agency
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
INN	International Non-proprietary Names
NCD	Non-Communicable Disease
NMPS	National Medicines Policy Sector
NPH	Natural Protamine Hagedorn
NDA	New Drug Application
TEAR	Treatment-Emergent Antibody Response
PCO	Polycystic Ovary Syndrome
WHO	World Health Organization

Chapter 1 Introduction

Diabetes is a non-communicable metabolic disorder that is characterized by an increase in blood sugar level. If left untreated, the rise in blood sugar level can lead to the damage of several organs, including nerves, eyes, kidneys, etc. According to the diabetes statistics of 2021, about 422 million people all over the world suffer from diabetes, among which less than 10% people have Type 1 diabetes, 90-95% have Type 2 diabetes and 7% has gestational diabetes (Nicole Galan, 2021). Almost 88 million adults are found to have prediabetes, which is 1 in 3 people. In 2019, the prevalence of diabetes all over the world was estimated about 9.3%, where the prevalence was more in high-income countries and urban areas which is about 10.4% and 10.8% respectively (Saeedi et al., 2019).

It is estimated that the number of people suffering from diabetes may increase by 25% in 2030 and by 51% in 2045. However, most of the people living with this disease are unaware of having this condition. In the NDSR (National Diabetes Statistics Report) of 2020, it was found that the adults who were diabetic were 38% physically inactive people, 15% smokers, 37% had chronic kidney diseases, 25% had mild to severe chronic kidney diseases and 89% of the diabetic people were obese. The prevalence of diabetes among 10–19 year old people were stationary for non-Hispanic whites but the prevalence accelerates for the Hispanic blacks (DHHS, 2020). Moreover, about 1.5 million deaths occur due to diabetes worldwide (DHHS, 2020). People with a family history of diabetes are more likely to develop diabetes, and thus need to be extremely careful. People with a family history of diabetes are more likely to develop diabetes, and thus need to be extremely careful. Insulin is a treatment option for treating diabetes. However, taking insulin regularly may increase the risk of hypoglycemia. Moreover, the fast-acting insulin, that is currently available, may not provide rapid control of elevated glucose level in many patients. In such cases, the maintenance of

glucose homeostasis requires extra effort. Biologic drugs are large, complex proteins that are made from the living cells of different cells through highly complex manufacturing processes (Altasciences, 2019). The biologics include recombinant proteins, allergens or vaccines. Most biologics have a complete complex structure which is very hard to determine and are made with very sophisticated technologies such as monoclonal antibodies. A biosimilar is a biologic product which is derived from FDA approved biologic that demonstrates high similarity with the original product known as the reference product in terms of quality, safety and efficacy. The biosimilar should have no clinical differences with the reference product (pfizer, 2020). One of the benefits of using biosimilars is that they are relatively less costly than the biologics and thus have better access to patients (Windisch, 2015). The main difference between the biologics and biosimilars lie in their phases of undergoing clinical trials which reduces their development cost as shown in Figure 1. Both biologics and biosimilars are available for the treatment of several diseases, for example, cancer, diabetes, rheumatoid arthritis and other inflammatory diseases because of their target site specificity which makes them highly therapeutically efficacious (Chen et al., 2018).

	Biologics	Biosimilars
CLINICAL STUDIES	Phase 1-3 studies efficacy and safety	Pharmacokinetic studies in phase 3
TIME TO MARKET (YEARS)	8-10	7-8
DEVELOPMENT COST (USD)	800 million	100-300 million
POST AUTHORIZATION ACTIVITIES	Phase 4, risk management plan including pharmacovigilance	Phase 4, risk management plan including pharmacovigilance

Figure 1: Main differences biologic and biosimilar (Adapted from Luis & De La Cuerda, 2016).

Various treatment options are available to treat this non-communicable disease (NCD). However, as the occurrence of the disease is increasing globally, formulation scientists are performing continuous research to get better treatment options with better efficacy and lower cost (Yamada et al., 2018). To minimize the risk factors of the disease, a new treatment option has been developed named biosimilar insulin. Biosimilar insulins are highly similar to the original drug and are expected to have similar clinical effects on the body as the originator product (interchangeable biosimilars) (Thiruvengadam et al., 2020). Biosimilars have some advantages over the originator insulin including price drops of insulin in the market which ensures patient compliance (Kim & Bindler, 2016). In addition, introduction to biosimilar insulin adds another treatment strategy for patients and ultimately raises the patient's accessibility to treatment. As, biosimilars are cheaper than the originator drug, it could be the first choice of the healthcare provider or physicians, thus making it available to the patients (Polimeni et al., 2015a).

1.1 Aim

The aim of this review is to give an overview of the treatment options available for diabetes, with a focus on the biosimilar for insulin, designed to be highly similar to the original or reference insulin product, that will help promote competition and lower prices for drugs and thus be affordable to the patient.

1.2 Objectives

The objectives of this review on biosimilar insulins are to identify the importance of biosimilar insulins, its contribution as an accessible treatment option, comparison of the existing and new biosimilar insulins, the concerns associated with its clinical use, and finally

its future prospects. Addressing these would help the healthcare providers with an opportunity, to offer alternative and possibly personalized therapy in diabetes management.

1.3 Rationale

Biosimilars are biologics which are similar in terms of safety, purity and efficacy to the reference drug (biologics). They are expected to bring huge savings to the healthcare system and increase access to treatment in the coming years as expensive biologic drugs lose patent protection. The aim here is to provide an overview of biosimilars in its contribution to pharmaceutical science.

Chapter 2 An Overview on Diabetes

2.1 Diabetes

Among the NCDs, one of the most prevalent diseases is diabetes, characterized by high blood sugar (glucose) levels resulting from defects in insulin secretion or insulin resistance. In this metabolic disorder, the glucose obtained from the consumed food cannot be utilized well either because of the insulin insufficiency or due to unresponsiveness of the cells to insulin for glucose uptake (CDC, 2011). It is estimated that 422 million people are living with diabetes all over the world (CDC, 2011; Nicole Galan, 2021). It is a chronic health condition which can damage the organs eventually, if not timely treated.

There are two types of diabetes which are diabetes mellitus and diabetes insipidus. Diabetes mellitus is further divided into three kinds which are Type 1, Type 2 and gestational diabetes. Diabetes mellitus occurs when the pancreas is unable to produce optimum amount of insulin needed to control the glucose available in our blood. Type 1 diabetes is an autoimmune disorder where the immune system attacks and destroys the body's own insulin producing beta cells of the islets of Langerhans of pancreas. Its symptoms may start appearing from childhood or adolescence with acute symptoms or ketoacidosis. For this type of diabetes lifelong therapy is needed (NIH, 2016). In Type 2 diabetes, target cells do not normally respond to insulin and so glucose prevails in blood. It is caused by minor factors such as lifestyle and gene mutation or the major risk factors such as age (older), prediabetes, obesity, gestational diabetes, physical inactiveness, family history, PCO (Polycystic Ovary Syndrome), etc. (BMJ Publishing Group, 2020). On the other hand, gestational diabetes develops in pregnant women by the hormone which is secreted by the placenta contributing to insulin resistance in the late pregnancy period and occurs when the pancreas is unable to

produce enough insulin (NIH, 2016). During pregnancy either diabetes mellitus or gestational diabetes may occur in the condition where the woman is hyperglycemic. This condition can be treated with medical nutrition therapy or only with diet in some cases (BMJ Publishing Group, 2020). Another condition just before developing diabetes is known as prediabetes where the blood glucose level is not at the level of diabetes but it is higher than the normal level. This type of condition increases the chance of developing Type 2 diabetes. On the other hand, diabetes insipidus is a rare condition that has nothing to do with the pancreas or blood sugar. It may occur due to the damage caused to the pituitary gland or hypothalamus from any tumor, surgery, illness or head injury which affects the usual activity of ADH production, storage and release or inherited disorder is also responsible for such condition. This condition is associated with polyuria, thirst, hypotonic urine and polydipsia (Mayoclinic, 2019). Moreover, particular medication may also lead to diabetes (BMJ Publishing Group, 2020).

2.2 Treatment Options

There are a lot of treatment options available for treating diabetes. Simple management of diabetes includes oral medications, diet and exercise. For treating Type 1 diabetes, administration of insulin is necessary as the body cannot produce insulin hormone. Insulin is needed to be taken many times a day with meal or after meal. A convenient delivery system includes a pump that provides doses at small amounts throughout the day. However, Type 2 diabetes can be easily controlled with the help of healthy food choices and physical activity, but may require medications. Combination treatments are common and effective in diabetes management (Lecerf, 2016).

2.2.1 Medications (Drugs for Diabetes Treatment)

There are different forms of treatment options for diabetes. Diabetes can be treated by using different types of anti-diabetic medications including insulin. There are different classes of anti-diabetic medication to treat diabetes. Drugs of each class have a unique way to control elevated blood glucose level. Anti-diabetic drugs are available in different dosage forms. For example, some medicines can be taken orally whether some can be directly injected into the blood. Most classes of anti-diabetic drugs are for type 2 diabetes patients who have difficulty to control blood glucose level via exercise and strict diet alone. On the other hand, for patients with type 1 diabetes, sometimes metformin with insulin can be taken (Lecerf, 2016). General physicians can prescribe more than one anti-diabetic drug if a single drug is not sufficient to control blood sugar level. Efficacy of these drugs mostly depends on the strength of the dose and dosing regimen. Anti-diabetic drugs have different mechanisms to control blood glucose level (Mayo Clinic, 2020).

2.2.1.1 Glimepiride

Glimepiride with proper diet and exercise control high blood sugar level in people with Type 2 diabetes mellitus. It may also be used with other diabetes medications. This medication is taken by mouth with breakfast or the first main meal of the day as tablets. This drug increases insulin production by the pancreas. Other drugs of this class include -chlorpropamide, glipizide, glyburide, nateglinide, and repaglinide (WebMD, 2019).

2.2.1.2 Acarbose

Acarbose is an alpha glucosidase inhibitor which lowers intestinal absorption of carbohydrates and is used as an adjunctive therapy in the management of Type 2 diabetes. Its

available dosage form is tablet. Another type of drugs that decreases glucose absorption by the intestines is miglitol (WebMD, 2019).

2.2.1.3 Pioglitazone

Pioglitazone, an anti-diabetic drug (type of thiazolidinedione which is also called "glitazones"), is used with proper diet and exercise in order to control high blood glucose level in patients with Type 2 diabetes. Its activity includes lowering the blood glucose level by restoring the body's response to insulin. Its available dosage form is tablet. A similar drug that is found to be work well in diabetes is rosiglitazone (WebMD, 2021b).

2.2.1.4 Metformin

Metformin is often used to treat Type 2 diabetes. Sometimes it is also used with insulin or other medicines. The available dosage forms are tablet, immediate-release tablet, extended-release tablet and oral solution. The mechanism of action of metformin shows that it decreases the production of hepatic glucose by the moderate inhibition of the mitochondrial respiratory chain complex 1, it also decreases of the intestinal absorption of sugar. Metformin causes weight loss and this is one of the ways it helps bring blood glucose concentration back to normal (Sinha, 2020).

2.2.1.5 Linagliptin

Linagliptin increase insulin production by the pancreas and decreases glucose production in the liver. The drugs that fall under these criteria are alogliptin, dulaglutide, exenatide, liraglutide, lixisenatide, saxagliptin, semaglutide , and sitagliptin. It is used to treat Type 2 diabetes. Its available dosage form is tablet (WebMD, 2019).

2.2.1.6 Empagliflozin

These drugs, often referred to as sodium-glucose co-transporter 2 (SGLT2) inhibitors, block the reabsorption of glucose by the kidney and accelerates the glucose excretion in urine. They are also helpful in weight loss and bringing back blood glucose level to normal range. Other drugs that function similarly include canaglifozin, dapagliflozin, empagliflozin, and ertugliflozin. It is used to treat Type 2 diabetes. Its available dosage form is tablet (WebMD, 2019).

2.2.1.7 Pramlinitide

This is a synthetic hormone which is given as injections for people who take insulin after meals to lower their blood sugar levels. It is basically used to treat Type 1 and Type 2 diabetes. Its available dosage forms are injectable solutions and pen-injectors. In pen injectors they might contain one or more types of medicines for diabetes such as recently approved empagliflozin/linagliptin which combines the SGLT2 inhibitor which blocks the reabsorption of glucose into the kidneys along with DPP-4 inhibitor. DPP-4 inhibitor accelerates the secretion of hormones that help the pancreas to produce insulin and reduces glucose production by the liver (WebMD, 2019).

2.2.2 Diet, Lifestyle and Exercise

Proper diet is vital in the management of any illness or disease. This is particularly essential in patients with diabetes, therefore regulating blood glucose level (Health Hub, 2019). The proper plan for a diabetic patient must include the following:

1. Intake of a consistent amount of meal every day.

2. Intake of less but regular food supplementing all kinds of nutrition.
3. Avoiding fat containing foods specially saturated ones such as butter, fatty foods and fried foods.
4. Including common carbohydrate and fiber containing meals which includes rice, oats, vegetables, legumes (beans, peas and lentils).
5. Experimenting with new healthy recipes. Eating the same food each day can cause boredom. One can then be tempted to move off their meal plan. Buying a cookbook with recipes suitable for diabetes management may be helpful.
6. Meals have to be eaten properly; no meal can be skipped.
7. Avoiding snacks unless it is recommended by the doctor as part of medication.
8. Cutting off alcohol consumption (Health Hub, 2019).

Achieving and maintaining a wholesome weight is crucial for people with diabetes. Weight management is crucial in treating Type 2 diabetes (non-insulin dependent) due to the fact greater body fats make it hard for sufferers to provide and use their own insulin. At least half an hour of mild exercise (for example-walking) on maximum days of the week and ideally each day is recommended to maintain a healthy weight. This will also help to increase responsiveness of the body to insulin (Health Hub, 2019). When a person is overweight, he/she could be advocated to shed pounds and agree on a weight reduction goal. In the beginning a loss of 5% to 10% of one's weight should be the target. Any weight reduction will help as the closer one gets to a healthy weight the higher the chance of having a long-term healthy life (NICE, 2020).

Lifestyle control is an essential factor for diabetes care. Adapting a proactive way of life can assist dealing with diabetes. For a few sufferers, simply following an individualized meal plan can yield enough outcomes. However, this is simpler said than being done. Diet and exercising are an intimidating pair to many people, and that they may be specifically daunting for sufferers with diabetes. Identifying what to devour is the difficult part in their care for many individuals. All people with diabetes have to be guided by a registered dietitian who can offer a customized method to accomplishing glycemic targets. After all, vitamin remedy has been proven to lessen A1C as much as 2% in folks with diabetes and is a protected gain below medical insurance plan. In addition to non-public medical insurance plans, sufferers can also acquire training advantages from Medicare (The Wellness Network, 2019). According to Medicare rules, a newly identified affected person is eligible to acquire 10 hours of diabetes training which incorporates vitamin intake within the first year and a pair of hours consistent with the year after that. Diabetes training in the past transformed into an outpatient setting, in which sufferers ought to get entry to registered dietitians and different professionals. Today, getting entry to a registered dietitian isn't constantly possible, so front-line practitioners want sensible pointers and gear to assist their sufferers to navigate meals picks within the interim. Not surprisingly, carbohydrate meals receive the maximum interest in those mini-consults due to their effect on blood sugar. However, rather than hackneyed recommendations like, “keep away from starches and sweets,” it's far satisfactory to recommend what to intake, in place of what not to eat.

Moreover, physical activity is another crucial part of diabetes control plan. When one exercises, one’s muscle cells use sugar (glucose) for energy production. Regular bodily activity additionally allows the body to use insulin more efficiently (Mayo Clinic, 2020). It has additionally been proven to enhance blood glucose control, further lowering the risk of

developing coronary heart disease and assisting in body weight reduction. The optimal "dose" is half-hour of cardio activity for maximum days of the week. The timing of workout is also important in weight management. Postprandial glucose spikes appear to lower if exercise is done immediately after a meal. Therefore, suggesting a brisk stroll after food is a sensible way to enhance activity in an impactful manner. In phrases of standard weight reduction though, the satisfactory workout for any affected person is the desk push-back (The Wellness Network, 2019).

2.2.3 Surgery

It has been observed that in some cases proper diet and use of oral hypoglycemic medicinal drugs have demonstrated inadequacy in diabetes treatment, while the most effective insulin solves the problem only temporarily. Alternative steps for diabetes management require cautious and accountable examination. A big frame of proof demonstrates that surgical treatment for Type 2 diabetes is effective in diabetes remission (Rubino et al., 2009).

2.2.3.1 Bariatric Surgery

Bariatric surgery is a type of surgery which is also referred to as weight loss surgical treatment or metabolic surgical treatment. Bariatric surgical treatment can also additionally assist a few human beings with weight problems and Type 2 diabetic patients lose a massive quantity of weight and regain ordinary blood glucose level. Some people with diabetes may also not require diabetes medicinal drug administration after bariatric surgical treatment. Researchers are studying the long-term outcomes of bariatric surgical treatment in patients with Type 1 and Type 2 diabetes (NIH, 2016).

2.2.3.2 Artificial Pancreas

Considering the global prevalence of diabetes and the need for an effective diabetes management treatment option, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has performed an essential function in developing “synthetic pancreas.” A synthetic pancreas is a sole gadget that watches over blood glucose level across the clock and presents insulin or an aggregate of insulin and a 2D hormone, glucagon, mechanically. In 2016, the FDA permitted a form of synthetic pancreas gadget referred to as a hybrid closed-loop gadget. This gadget monitors glucose level every five minutes throughout day and night, and mechanically offers the proper quantity of insulin. It continues to manually regulate the quantity of insulin the pump promises to release at mealtimes. The synthetic pancreas may also aid in unfastening the patient from a number of daily responsibilities needed to regulate the blood glucose, for instance, assist sleep at night time without the trouble to wake and check glucose level or take medicine. The hybrid closed-loop gadget was first introduced in the U.S. in 2017. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has funded numerous essential researches on one-of-a-kind forms of synthetic pancreas gadgets to efficiently assist human beings with Type 1 diabetes control. The gadgets might also assist human beings with Type 2 diabetes and gestational diabetes (NIH, 2016).

2.2.3.3 Pancreatic Islet Transplantation

One of the most prominent methods to treat Type 1 diabetes is pancreatic islet transplantation. It is an experimental remedy for poorly managed Type 1 diabetes. Pancreatic islets are clusters of cells within the pancreas that makes the hormone insulin. In Type 1 diabetes, the body’s immune cells attack the insulin producing cells of pancreas. A pancreatic islet transplantation replaces the destroyed beta cells of islets of Langerhans with new ones

that secretes normal insulin. This technique involves the transfer of islets from the pancreas of an organ donor to the patients with Type 1 diabetes. Based on the analysis of several research outcomes, this technique has been found to be most effective in diabetes treatment (NIH, 2016).

Chapter 3 Insulin

Insulin is an essential part of patients with Type 1 diabetes and additionally for many people with Type 2 diabetes. The intention of insulin intake is to maintain the blood sugar level within the normal range. Insulin is usually injected through the adipose layer beneath the skin the using syringe, insulin pen or insulin pump tubes. Different forms of insulin including rapid-acting, short-acting, intermediate-acting, long-acting and ultra-long-acting insulin are available on the basis of their onset of action, duration of action and time needed to reach their maximum therapeutic effect (Mayoclinic, 2019). The human insulin is used to regulate the blood sugar level in humans who've Type 1 diabetes (circumstance wherein the body no longer make insulin and consequently can't control the quantity of sugar in the blood) or in humans who've Type 2 diabetes (circumstance wherein the blood sugar level is excessive due to insulin that can't be managed with oral medicines alone. Human insulin is in a category of medicines referred to as hormones. It works by allowing the target tissues to take up more glucose molecules from the blood until the blood glucose concentration reaches normal. It additionally stops the liver from generating extra sugar (NIH, 2021).

3.1 Manufacture of Insulins

The manufacture of protein-based drugs makes use of recombinant DNA technology. The gene encoding for insulin is isolated from the DNA of human cells and inserted into a suitable vector followed by transformation of the recombinant DNA into the host organism, for example *Escherichia coli* or *Saccharomyces cerevisiae* for the expression of insulin. The expressed product is pro-insulin which is further modified using cellular machineries to produce insulin. The product is then recovered, purified, and processed for storage. There are many steps during the manufacturing process which can make the product prone to

contamination, therefore, it is very important to monitor the purity and stability of the product. The host cells or the cellular products may be quite sensitive to any changes in their surrounding environment such as temperature, pH, toxic byproducts and can bring about large modifications in the protein structure which ultimately may not provide the desirable therapeutic action or the product may have reduced efficacy (Sataloff et al., 2016).

3.2 Mechanism of Action

The mechanism of action of insulin starts off with its binding to the glycoprotein receptor on the surface of the cell membrane. This receptor includes an alpha-subunit, which binds the hormone, and a beta-subunit, that's an insulin-stimulated, tyrosine specific protein kinase. Activation of this kinase is thought to generate a signal that initiates the action of insulin on glucose, lipid, and protein metabolism. If there are any abnormalities in the insulin receptors then receptor kinase and its further post receptor steps changes due to the resistance (Kahn, 1985). The mechanism of action of insulin has been illustrated in Figure 2.

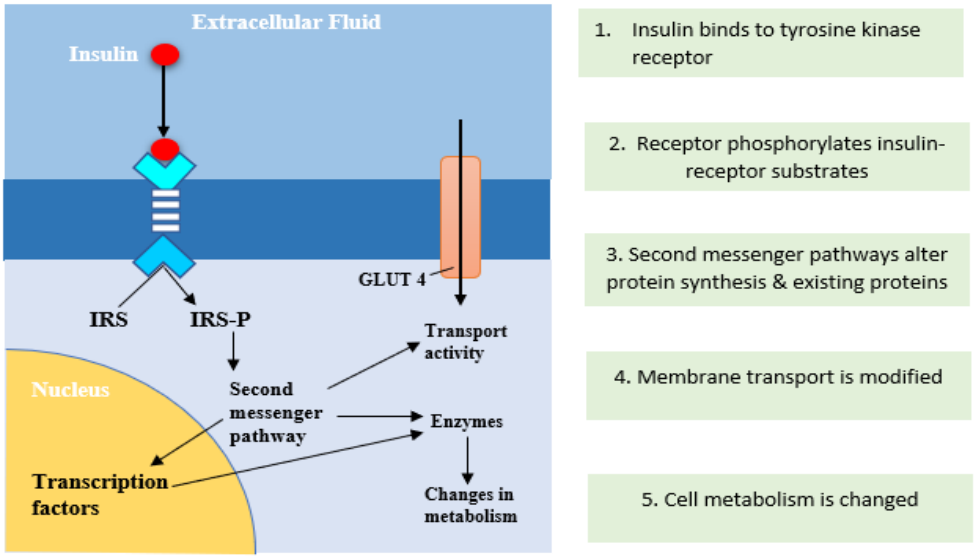


Figure 2: Mechanism of action of insulin (Adapted from Raid M. Al-Ani, 2018).

3.3 Insulin Development

Insulin performs a key function in the regulation of the blood glucose level. Lack of insulin production or inadequate response to insulin can result in the development of diabetes (State & Organisations, 2012). By Frederick Grant Banting and Charles Herbert Best Insulin was first purified in 1921. Banting believed that insulin should be extensively used for treating diabetes (Muthukumaran, 2019).

3.3.1 Types of Insulin

Due to the deficiency of insulin diabetes develops so it is necessary to maintain normal glucose level in the bloodstream. Three main groups of insulin are available which are as follows:

1. Fast-acting insulin: The body absorbs this kind insulin into the bloodstream from the subcutaneous tissue very quickly. It is used to decrease hyperglycemia, or excessive blood sugar, in addition to regulating blood sugar spikes after eating. This category of insulin consists of rapid-acting insulin analogs taken between 5 and 15 minutes after meal to have an effect) and ordinary human insulin (onset is between half-hour 30 minutes and 1 hour and its results remain on blood sugar for around eight hours) (Felman, 2018).
2. Intermediate-acting insulin: The hormone enters the blood at a slower rate, however provides a long-lasting effect. One of the examples of intermediate-acting insulin is NPH human insulin (Takes around 1 to 2 hours to onset) and reaches its peak within four to six hours of administration). Another example include Premixed insulin which

is a mixture of NPH with a fast-acting insulin, therefore having effects of both intermediate-acting and rapid-acting insulins (Felman, 2018).

3. Long-acting insulin: This form of insulin provides a long duration of action and incorporates a comparatively low peak. The “plateau” state of the blood glucose level may last throughout the day. It has an onset of action between 1.5 and 2 hours of administration and the effect lasts from 12 to 24 hours (Felman, 2018).

The three fast-acting insulins currently approved by the FDA are lispro, aspart and glulisine, have similar action curves, with an onset of 5 to 15 minutes, a peak at 45 to 90 minutes and a total duration of about 3 to 4 minutes (Hope Warshaw, 2014). There are currently two different long-acting insulin products: insulin glargine maintaining glucose level for up to 24 hours, insulin detemir for 18 to 23 hours (Watson, 2016).

3.4 Insulin Approval as a Biologic

March 23, 2020 was a milestone for patients with diabetes and other serious health conditions as insulin and some other biologics switched to a different regulatory path. This regulatory change, enforced by the Congress and FDA, is extremely important to patients. For the first time, the way will open for products offered as biosimilars and the products which are interchangeable. The availability of safe and effective biosimilar and interchangeable versions of these therapies, including insulin, is expected to improve patient accessibility, expand varieties to choose medicines and potentially reduce the cost of these essential treatments. Biologic drugs, including insulin, treat some of the most serious illnesses and conditions (US. Food & Drug Administration, 2020). Medicines administered today are used to treat, diagnose and prevent many of these diseases, including diabetes, respiratory distress syndrome, fertility diseases, Cushing's syndrome and deep vein thrombosis, Gaucher disease

and many others. But these life-saving drugs often increase healthcare costs dramatically. Historically, scientific considerations have hampered the development of generic versions of these drugs under the Federal Food, Drug, and Cosmetic Act (FD&C). Today's transition opens a new path for manufacturers to gain FDA approval and market biosimilar and interchangeable versions of insulin and other biologic products. When Congress established the Biologics Price Competition and Innovation Act (BPCIA) in 2009, Congress also created a 10-year program for stakeholders to prepare for a review of the regulation of products recognized by FD&C law. Now that the day has arrived, the FDA may receive biosimilar drug proposals for these licensed transitional biologics, including insulin products that millions of Americans rely on every day to keep their blood sugar stable. There is enormous potential for reducing healthcare costs, as evidenced by the growing supply of generics. When it comes to generics, it is evident from the FDA analysis that even a generic drug's price in the market is 31-39% lower than its competition (US. Food & Drug Administration, 2020).

Likewise, biosimilars sold in the United States are generally introduced with an initial prices list that are 15-35% lower than that of the reference products. For the past 10 years, the FDA has worked hard to create a robust biosimilar drug framework and interchangeable regulatory pathway, explaining to everyone involved what the transition means for them and how it could affect many of the stakeholders. The action plan was created to improve the efficiency of the development and approval process for biosimilars and interchangeable products, and to maximize scientific and regulatory transparency for the biosimilar developer community. In the past six months, several important steps were taken to facilitate the establishment of biosimilar medicines and in preparation for this transition from reference biologics to biosimilars, including working with the Federal Trade Commission to tackle false or

misleading claims and promotional messages from producers; business practices; supporting a competitive market for biosimilars; final rule, draft directive and final guide explaining the sector have been established; provide patients and healthcare professionals with information on what it means to switch to biosimilars; expand and digitize the FDA database with FDA licensed biological products, also known as Purple Book (US. Food & Drug Administration, 2020).

Chapter 4 Biosimilar Insulins

The treatment options for diabetes have been extended with the advent of biosimilars of insulin which are produced by the recombinant DNA. Biosimilar insulins cannot be called generics because the generics has particularly the same active ingredient like the reference drug having small molecular weight and are non-biological drugs (Ghosh et al., 2019). In the upcoming years patents of many branded insulins are about to expire that will create an opportunity for the biosimilars of insulin to pave their way towards the market. For several clinical conditions, biosimilars have already been approved and used because of their ability to successfully mimic the action of the reference products. Moreover, biosimilars of insulin have been recommended useful in terms of safety, clinical efficacy, immunogenicity showing no prominent differences with the originator insulin and short acting biosimilar insulins (Polimeni et al., 2015b). SAR342434, a biosimilar insulin is considered parallel to insulin lispro because it has been found equivalent in its safety, efficacy, pharmacokinetic (PKs) and pharmacodynamic (PDs), and is therefore, beneficial for the treatment of patients with diabetes mellitus (J. Hu et al., 2018a).

4.1 Development of Insulin Biosimilars

In 2014, the first biosimilar insulin was approved by the European union after which the second one was approved in 2016. In 2015, biosimilar insulin Basaglar by Eli Lilly was approved in the USA which corresponds to the originator insulin glargine by Lantus, Sanofi. After that in 2017 biosimilar insulin Admelog by Sanofi has been approved from the originator insulin lispro by Humalog, Eli Lilly (Schaffer, 2020).

The approval and development process differ for the generic and biosimilars such as a biosimilar drug can be approved when it will show absolutely no differences in, safety, purity. Moreover, any variation in their manufacturing process will have significant effect on the finished product and on the patients' feedback about it. The originator product and its biosimilar may have similar INN (International Nonproprietary Names) in the European Union. For instance, the originator product Lantus has the INN for insulin glargine whose biosimilars are Lusduna and Abasaglar. Lantus is manufactured by Sanofi-Aventis Deutschland GmbH, Frankfurt in Germany whereas Lusduna is made by Merck Sharp & Dohme Limited, Hoddesdon in United Kingdom and Abasaglar by Eli Lilly and Company, Indianapolis in USA. Due to this the health-care provider should be particular while providing the biosimilar or the reference insulin products emphasizing on the brand names. Having vast knowledge of these differences of biosimilar insulins shall help the health-care providers to make correct decisions to choose medications for the diabetic patients. Not only the health-care providers but also the patient should be aware of the information related to these biosimilar insulin (James et al., 2017). Developing biosimilars of insulin involves the engagement of supply chain logistics, modern in-process analytical methods and disposable technology for production (Tsuruta et al., 2015).

In 1922 insulin was isolated and since then its analogues have evolved itself in various magnitudes in terms of its pharmacokinetic and pharmacodynamic profile. Currently, the biosimilar insulin Abasaglar, being the first biosimilar insulin that was marketed is making noteworthy development in the biosimilar market. Other protein based drugs available as biosimilars include somatotropin, infliximab, filgrastim and erythropoietin (LLano Andrea, Fisher Miles, 2017). Figure 3 below demonstrates the approval steps of the first insulin biosimilar Abasaglar.

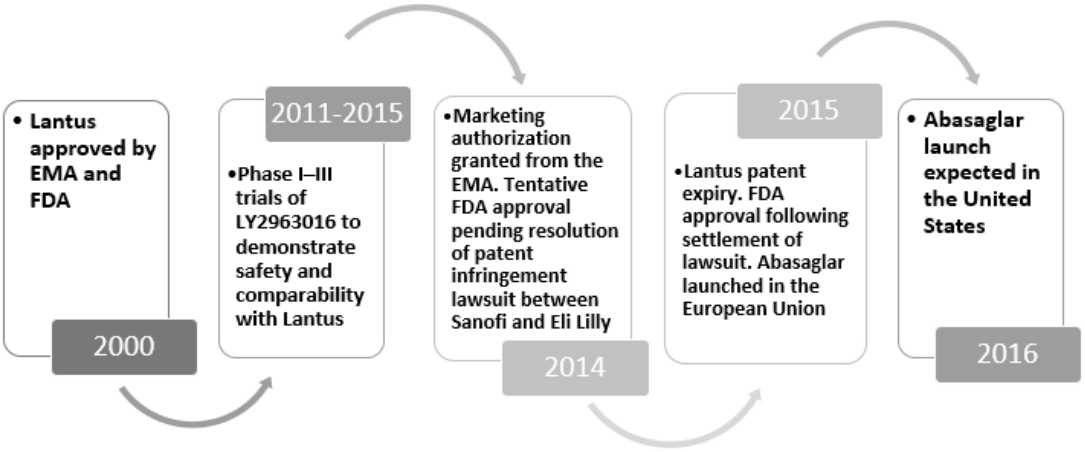


Figure 3: Timeline for the approval of the first insulin biosimilar Abasaglar (Adapted from LLano Andrea, Fisher Miles, 2017).

According to a study in USA, it has been observed that still not enough biosimilars of insulins are available in comparison to the available biologics of insulins. However, US FDA is expected to be working on building up a shaped regulatory framework for enhancing more insulin biosimilar production. The transition in the NDA pathway of insulin biosimilar in March 2020 was necessary as large companies such as Eli Lilly and Sanofi have already initiated to make insulin available for diabetic people in the USA. March 23rd of 2020 brought out a new regulatory pathway for the insulin biosimilars which will ultimately help in the cost reduction of originator insulin. Few numbers of companies are developing biosimilar insulin expecting them to inaugurate around this date. As such Mylan, Sandoz and Biocon have started to develop biosimilar insulin. Mylan has already inaugurated Semglee in Europe which is a insulin glargine which was launched in 2020 in the USA (Aideed, 2019). Table 1 shows the timeline of Insulin biosimilars in the United States.

Table 1: Insulin biosimilars timeline in the United States (Adapted from Aideed, 2019)

Reference brand	Biosimilar	Expected launch year
Lantus (insulin glargine) Sanofi	Basaglar (Eli Lilly/boehringer ingelheim) Semglee (Mylan/Biocon) Basalin (Sandoz/ Gan & Lee)	Launch 2016 2020 2020
Humalog (insulin lispro) Eli Lilly	Admelog (Sanofi) Insulin lispro generic (Eli Lilly) Prandilin (Sandoz/ Gan & Lee)	Launched 2018 2019 2020
Novo rapid (insulin Aspart) Novo Nordisk	SAR341402 (Sanofi) Biosimilar insulin Aspart (Mylan/Biocon) Biosimilar insulin Aspart (Bio genomics)	2020 2021 2022

4.2 Formulation of Biosimilar Insulins

Biosimilars are biologics having the same amino acid sequence and similar safety and clinical efficacy profile to its originator product (James et al., 2017). The manufacture of biosimilars is done within living organisms such as bacteria and yeast. This helps to restrict the production of the exact identical copies of the original biologic rather than produce a bulk amount of the large protein molecules using the living host mentioned in figure 4. There is a

lack of similarities entities of biologics and this would affect a lot in the production of biosimilars as even a slight difference in the production process may bring about huge differences between the biosimilar product and the originator medication (Kim & Bindler, 2016). The Biosimilar Medicinal Products Working Party of the EMA has ensured that the production process of biosimilar remains unique for different companies in order to maintain the identity which has made it more difficult to have the integrity of biosimilars similar to that of the reference product. To register for biosimilar approval, product evaluation and safety and clinical efficacy profile of the marketed reference product have to be presented (Kuhlmann & Schmidt, 2014).

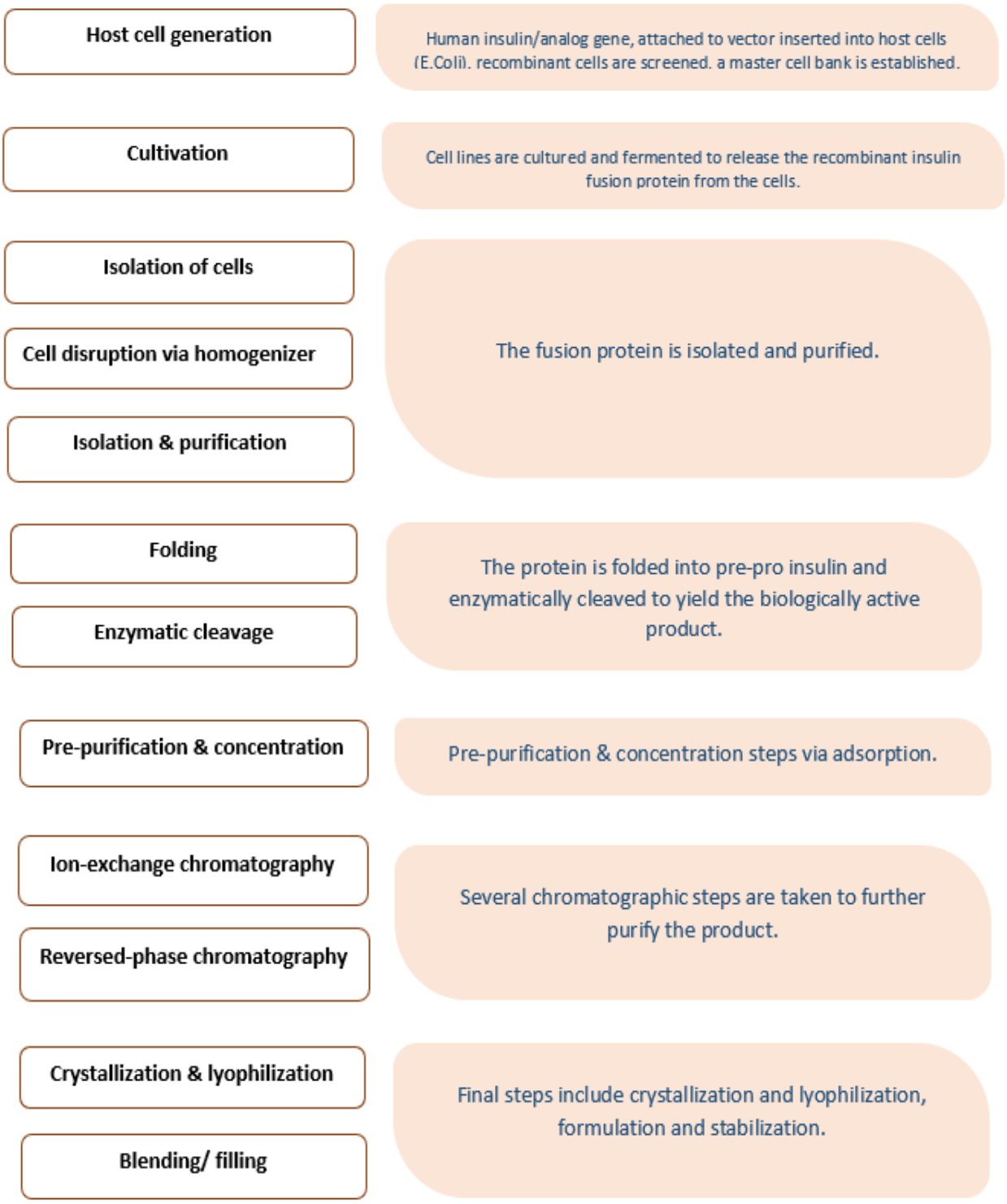


Figure 4: Manufacture of analog insulin using a bacterial host system (Adapted from Kuhlmann & Schmidt, 2014)

4.3 Critical Parameters

4.3.1 Interchangeability among Reference Insulin Analogues

Not all products are interchangeable but it is an important factor for consideration as it concerns patient health. For example, Basaglar has different acceptance patterns in different institutions. FDA did not yet mark Basaglar as an equivalent biosimilar whereas a management company of US called CVS Caremark have adopted Basaglar of Lantus. So, the pattern is varies among institutions and places (White & Goldman, 2019).

4.3.1.1 Interchangeability of Biosimilar Insulin in the Perspective of European Union

The regulation policy of biosimilars is quite different from other biologic molecules because the biologics have such a production process that slightest change or difference in the process can incur enormous changes in the pharmacodynamic and pharmacokinetic property of the product. Due to this the regulatory pathway of biosimilars are always changing and not all institutions can come to a conclusion for this. As it is an evolving medication it is necessary to make everyone understand about the importance of biosimilars, its benefits, safety profiles and that it can be used as a substitution of its reference product as it is interchangeable (switching to another medicine having similar effect). However, replacing any medicine with biosimilar without the supervision of any healthcare provider is not allowed in most of the countries. To show the possibilities of interchangeability among the biologic and biosimilar products more studies need to be conducted and people should be made aware of its difference and safety criteria (Dowlat et al., 2016). EMA has not given any conclusion on interchangeability of biosimilars rather left it to the national authorities like FDA, USA

federal law. Though EMA has stated that ‘Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional’ which contradicts the matter of seeking professionals’ advise before replacing a drug with its biosimilar (Dowlat et al., 2016). However, FDA gives another opinion upon its interchangeability. According to FDA it is normal to adopt biosimilar from pharmacy by replacing the originator which has been mentioned by the federal law in USA about this mechanism and requirements. Though FDA is on the go of making rules for the substitution of biosimilars but the USA have already established rules of replacing biosimilars in pharmacies (Dowlat et al., 2016).

Interchangeability of biosimilars and biologics would not be justified only if they are measured equivalent in terms of safety and efficacy, several factors such as cross-sectional studies are also necessary to support the interchangeability criteria. EMA have not yet established any rules of interchangeability of biosimilars. The euglycemic clamp test has been selected as the standard test by EMA to approve the interchangeability of biosimilars. The clinical studies regarding Abasaglar has already started in Europe and it shall pave the way to its regulatory structure (Dowlat et al., 2016).

4.3.1.2 Interchangeability of Biosimilar Insulin in the Perspective of USA

The biosimilars of the FDA approved originator products should be recommended under the supervision of a healthcare provider and the instruction for using the prescribed biosimilar has to be strictly followed. For the time being the term interchangeability is still not applicable for biosimilar products. To become an interchangeable product the insulin biosimilars, have to possess all the characteristics which are similar to FDA approved

originator insulin. For any certain patient the safety and clinical efficacy of the biosimilar and biologic must match to prove interchangeability. If any drug is given to a patient twice or more then it has to be taken under special consideration because it may have an effect on the immunogenicity. According to the FDA, interchangeability would include the knowledge about the effectiveness of the product and the risks and safety of the switch between biosimilar and biologic products. There are still no guidelines upon the safety concerns of the biosimilar products to demonstrate its interchangeability, the tests required are yet to be found. However, there are few studies which have been suggested to be performed for interchangeability of biosimilars such as crossover studies, randomized studies, double bind studies. For the patients who are switching products they need to be cautious about using the delivery devices. Whenever the biosimilar product gets the permission of being interchangeable right after that it can be provided by the pharmacist to the patients in place of the particular reference product and then no supervision from healthcare providers will be required. There are laws in each part of the US where they have legal structured requirements for replacing the reference product with the biosimilar product. Few parts of the USA are undertaking regulations for the replacement of biologics with biosimilars to reach them at pharmacies. In the USA the biosimilars will be considered interchangeable if it is considered interchangeable by the FDA. It will depend on time as the acceptance would require physician and patient retention time frame. More about the regulatory stature is mentioned in the Purple Book of FDA (it is an equivalent book of Orange Book containing drugs approved under FD&C act) which contains the biologic products, their biosimilars, their interchangeable that are licensed under FDA under PHS Act mentioning if the originator product which is licensed under Section 351(k) considered by the FDA to be a biosimilar or its interchangeable with reference to the originator products. Till 2020 there weren’t any

insulin biosimilar or its interchangeable in the market until new legislations were effective after that.

A study says that the pharmacists are supporting the use of insulin biosimilars using their name by the INN system of naming aligning the last name. The biologic naming system was created by FDA in January 2017. The rule of these names includes a non-proprietary name, a specific suffix (having no meaning), four lowercase letters, for example, Sandoz Inc's Zarxio which is a biosimilar of Amgen Inc's Neupogen (filgrastim) that functions as a bone marrow stimulant. The non-proprietary name of Zarxio is filgrastim-Sandoz. The buyers are more interested in buying the cheaper biosimilar and their follow on insulins (White & Goldman, 2019).

If there is no automated system then the prescribing of biosimilar relies on the health care provider. Studies shows that about 70% of the healthcare professionals are more prone to prescribe the biosimilars which are approved by FDA for both existing patients and new patients. The health care professionals are mostly considering the safety, efficacy and cost effectiveness profile of the biosimilars before prescribing them which are not always provided on their label as the guidelines of biosimilars suggests to keep the label only with related information as mentioned in the FDA standard product labelling system. If there are any unique information for any particular product then it can be added to the label. The clinical studies and comparative study results should not be included in the label as said by FDA as these are irrelevant to the physician's concern. However, there are many concerns related to the interchangeability of biosimilar product such as delivery device usage, monitoring patient support, etc. (White & Goldman, 2019).

The US Biologics Price Competition and Innovation Act of 2009 says a biologic would be accepted interchangeable if the biologic and the biosimilar has the same clinical efficacy for any patient. The biosimilars would be interchangeable if they possess no risk if there is a replacement made between the reference product and biosimilar product. If biosimilars are pronounced to be interchangeable then the switching can be made easier for people (Rotenstein et al., 2012).

4.3.1.3 Interchangeability of Biosimilar Insulin in the Perspective of China

The GMP (Good Manufacturing Practices) in China was mandated from 2016 ~~a~~ long after in the US and Europe. There are only few local companies in China with expertise in biologics let alone in the innovative biosimilar guidelines especially in terms of the clinical and technical settings. The NMPS (National Medicines Policy Sector) regulations have been adopted but is experiencing lag in implementation. The ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) members have already enforced the necessity to spot the manufacturing quality and clinical development of insulin biosimilar in China. Within the coming 2-5 years China is expected to put expand the biosimilar sector of their country (Deere, 2018)**.**

4.3.1.4 Interchangeability of Biosimilar Insulin in the Perspective of South-East Asia

In Asia about 68% of healthcare professionals agree to the interchangeability of biologic and biosimilars. However, only 37% of physicians agree to prescribe it to the new patients which indicates how important it has become to spread knowledge about biosimilars among people regarding its safety, efficacy and usefulness (Momin et al., 2017). The European Association for the Study of Diabetes and the American Diabetes Association have not given any

guideline to the launch of biosimilar but in 2013 Diabetes UK has given statements on the use of the proper insulin whose selection for use has to be made through consultation between the physicians and patients. In South East Asia the strategy is more insightful. For its profound usage patients should have the appropriate knowledge about the immunogenicity, safety, and efficacy of the biosimilars which will assist them in proper selection of the biosimilars. All the patients who have diabetes should know the disease well and the replacement pattern of the biosimilar insulin if it can be replaced with the innovator product. The replacement of biologic with biosimilar may lead to the arousal of adverse effects such as immunogenicity and hypersensitivity. To be cautious about this the prescribers must write on the prescription to dispense the medicine just as it is written. In South Asia the need for proper and cost-effective medical care for diabetic patients is in utmost need (Kaduskar, 2016).

4.3.1.5 Interchangeability of Biosimilar Insulin in the Perspective of Australia

The emergence of biosimilar in the market in recent years and the shift of biologics to biosimilars are considered to be a matter of concern in Australia. Interchangeability in Australia means shifting between two medicines which are clinically equivalent in terms of their activity having the similar therapeutic effect which is recommended by physicians. In Australia substitution means the replacement of one medicine with another medicine by not consulting with the physician rather with a pharmacist. In the USA interchangeability is a regulatory standard where a supervision from the physician is constantly needed to prescribe a biosimilar to the patients which contradicts the Australian usage of biosimilar. The shifting guideline of Australia is quite different from the interchangeable theory of biosimilar in the

USA, however, the USA have not given any interchangeability acceptance of biosimilar till date (Gregory et al., 2020; McKinnon et al., 2018).

4.3.2 Immunogenicity with Biologics and Biosimilars

The immunogenicity of a biologic refers to the immune response against the protein-based drugs if the immune cells of the body recognize any entity of the proteins as foreign resulting in adverse clinical effect. If there are immune responses towards the biologics then it can create ~~a~~ complications in the patient and compromise their safety (Biolabs, 2020). When insulin is used to treat the diabetic people then the formation of the produced insulin mediated antibody can pose a threat if it is produced in high amount causing insulin resistance, affecting metabolic regulations, inducing lipoatrophy and insulin allergy. As insulin biosimilars are manufactured using different sources and production processes, therefore a chance of dissimilarity in its stability and purity might exist. To study this immunogenicity pattern for the biosimilar insulins, post market pharmacovigilance needs to be performed. As biologics are created from living cells (Hamster cells, rabbit cells, bacteria such as *Escherichia coli*) the risk of having immunogenic reactions is possible as the body can easily find and neutralize foreign particles that enter into the body. If the insulin protein is more similar to the human protein, then the chance of immune response decreases. The detection of the immunogenicity pattern of the insulin antibodies can be six to twelve months long (Kroon et al., 2015). A study was conducted to assess the immunogenicity where patients with T1DM (Type-1 Diabetes Mellitus) (N = 535) and T2DM (Type-2 Diabetes Mellitus) (N = 756) were administered anti-insulin glargine antibodies to measure its percentage binding with the antibodies produce after treatment with external insulin. An open-label study was performed for 52-weeks and a randomized double-blind study was performed for 24-week. The T2DM group was again divided into two subgroups of patients

using insulin and the other pre-study insulin glargine treatment. Partial correlations and covariance were used to detect correlation between clinical results and the antibody presence by Wilcoxon rank sum. Fisher's exact test was used to do comparisons between TEAR (treatment-emergent antibody response) but no notable treatment dissimilarity was found for the antibodies of the T1DM and T2DM (insulin-naive subgroup) patients. However, a noteworthy distinction was found in the complete antibody detection but not in the endpoint or in the TEAR specially for the T2DM as the level of antibodies were lesser than 5 % for the both groups. Same immunogenicity was found between the LY Insulin Glargine and Insulin Glargine which were not related to the clinical results as antibodies were not very high in both the groups not affecting the safety and efficacy results (Ilag et al., 2016).

4.3.3 Naming of Biosimilar Insulin

In 2010, when framework concerning biosimilars was introduced, arguments on naming of biological products took place. Debates were going on whether the addition of suffixes to the biological products would ensure pharmacovigilance. On the other hand, some have opposed the idea of adding suffix as they thought that it could be an obstacle to the use of biosimilar products. FDA believes that biosimilars can lower healthcare costs, promote competition and allow greater access to biologics. Thus, FDA updated their policies to achieve the goal of a high-quality, robust and competitive market for these biosimilar products (M.D., 2019). FDA established a guideline in January 2017 stating the concerns upon the distinction of suffix for the right names of the reference products with their aim of obtaining patient safety. They chose a suffix that will not provide any misinterpretation of the product name or any name which is not superior to the originator. FDA also stated that they are updating the names of the existing biologics (M.D., 2019).

Biological products which are licensed or approved under the Public Health Service Act are not intended to be modified by the FDA. The FDA has no intention on the nomenclature to the actual names of transition biological products. In addition, the FDA develops a proper name by combining core name and a distinguished suffix which has lack of meaning and comprises four lowercase letters. Thus, it will help to ensure pharmacovigilance and using this strategy FDA can successfully monitor all the biological products and ensure patient safety. Biosimilar, originator and interchangeable products have distinct nonproprietary names to assist adverse drug event report tracking. Moreover, in the updated policy, products which are first licensed as biosimilar and later termed as interchangeable will retain its nonproprietary names (M.D., 2019).

To use the biosimilars in pharmacy level the unique four-letter suffix is added to the biologics and biosimilar to help the physicians and patients to easily distinguish and understand the effectiveness and safety concern of the biosimilars. The unique suffixes that are given to the reference product and the originator play key role for the FDA to keep a track on the product's activity and easily get hold of its adverse events. The distinguishable name helps the patients to understand the interchangeable products for instance all 17 biosimilars which have been approved have been given 4 letter suffixes similar to the 27 proper biologic products. In 2017 guidance FDA could later find that changing names of existing biologics can cause confusion among the people to understand the names of medicines (M.D., 2019). So, they decided that they will apply this suffix addition theory to the new drugs rather than to the older products. FDA now concentrates on adding suffixes to the newly licensed products and the biosimilar and its interchangeable products. FDA is working on making the people understand that the naming has no effect on the product quality as the biologics and biosimilars are the same products having no significant clinical differences (M.D., 2019). The

agencies launched new policies in December 2018 to promulgate new policies of naming systems for biosimilars along with the new pathway for the transition of the biologic product to biosimilar product under the BLAs introduced on March 23, 2020. The recent updated guideline provides transparency to the nonproprietary naming of the biosimilars and their interchangeable (M.D., 2019).

4.4 Production Cost and Potentiality

Diabetic treatment has always been costly specially for the people who take insulin (about 50% people) as it has to be given on a daily basis at a certain time, so on an average it becomes very costly. It is expected that the cost of treatment would reduce through the advent of insulin biosimilar in the market. The biologic insulin and biosimilar insulin have a difference in their molecular structure due to slight variation in their amino acid sequences but similarity in their production process. From the bacterial culture, inclusion bodies originating from the host cells are purified. The insulin precursor is then enzymatically cleaved in a tube which is done mostly for the regular human insulin and its analogues. The total cost of developing biosimilars and the approval application process for introducing biosimilar insulin in the market would cost about USD 100–200 which is gauged by the US Federal Trade Commission. Within 5 years the cost was expected to be USD 100. Moreover, about one million Type 1 diabetic patients would buy insulin from the biosimilar producers which is parallel to the cost of one year purchase of insulin in developed countries which leads to addition of more 20 dollars for each patient. Insulin producers calculate their total expenditure of production cost in sales percentage as it is not possible to accurately calculate per unit expenditure of its manufacture so all the reports are considered for the calculation. The cost of insulin per year would cost USD 133 and for biosimilar regular human insulin

and insulin NPH would cost 72 dollars which is much less than the insulin analogue (Gotham et al., 2018).

Table 2: Estimated insulin prices (Gotham et al., 2018)

Compound	*Price of API per kg (USD)*	*Typical dose per day (mg)*	*API cost per day (USD)*	*Estimated cost of production for 10 ml (100 units) phials (USD)*	*Estimated price for 10 ml (100 units) phials (USD)*	*Estimated price per year (USD)*
Regular human insulin	24750	1.40	0.03	2.28-3.37	3.29-4.86	48-71
Insulin NPH	23282	1.56	0.04	2.32-3.42	3.35-4.93	49-72
Glargine	68757	1.46	0.10	3.69-5.13	5.32-7.38	78-108
Lispro	100000	1.40	0.14	4.52-6.16	6.52-8.87	95-130
Aspart	100000	1.40	0.14	4.51-6.16	6.50-8.86	95-129
Glulisine	100000	1.40	0.14	4.47-6.11	6.44-8.80	94-128
Detemir	100000	5.68	0.57	13.47-17.35	19.40-24.99	283-365
Degludec	100000	1.46	0.15	4.66-6.34	6.71-9.13	98-133

The manufacture of biosimilar insulins specifically RHI and NPH insulin is possible with USD 72 or even less and biosimilars of reference insulin Aspart, glargine, lispro, glulisine for USD 133 for each patient yearly. If the competition rises then the price for biosimilar human insulin would jump to USD 48 and for originator insulin USD 78 to USD 98 as shown on

Table 2. With such price comparison it is evident that the marketers can sell the biosimilar insulins at lower prices yet making profits (Gotham et al., 2018).

4.5 Pharmacokinetic/Pharmacodynamic Bioequivalence of Approved Biosimilar Insulins

The novel insulin biosimilar is established on the basis of its pharmacokinetic and pharmacodynamic parameters which shows its clinical efficacy and safety to advance its way from preclinical to clinical trials. The duration of action of the newly developed insulins are tested through the euglycemic clamp technique which is chosen by the regulatory authority. The glucose data obtained from the euglycemic clamp technique study help to determine the pharmacodynamic activity of biosimilar insulin (Krentz et al., 2019). The European regulatory body also requires the euglycemic clamp technique for evaluating the pharmacodynamic parameters of biosimilar insulin in order to compare it with the innovator product (Home, 2015).

The development of biosimilars strictly requires comparative studies; this comparison is made by a bit-by-bit process which is unique for each of the biosimilar products. The stages include initial quality comparability studies followed by the determination of the duration and type of nonclinical studies and thirdly clinical studies which paves the way to the development of the biosimilar product. These stages help to demonstrate the dissimilarities between the biologic and biosimilar product. In the first stage the functionality analysis is done by studying the chemical, biological and physical characteristics of the biosimilar *in vitro* to collate the amino acid and biologic structure with the technique (Ghosh et al., 2019). Between the biologic and the biosimilar product, the dissimilarity is detected by these studies' sensitivity which are more specific than clinical trials. Then the second stage where

nonclinical comparison data analysis is done *in vitro* to detect the effect of physiological changes in the cells. If there is a scarcity of animal models then *in vitro* models can also be utilized. The toxicological studies are required for special cases when the biosimilar is produced within a special cell or with different formulation. Finally, the third stage is clinical study where the priority is to demonstrate the bio-similarity of the insulin rather than its safety and efficacy profile (Ghosh et al., 2019).

4.5.1 Clinical Trials of Pharmacokinetic/Pharmacodynamic Studies

Clinical studies include

1. **Phase 1 study (Pharmacokinetic/Pharmacodynamic):** Shows similarity in PK and PD profiles by the insulin clamp study which is expected to be the main technique to validate the similarity in efficacy between biosimilar and reference insulin.
2. **Phase 3 study:** A comparative study in terms of efficacy and safety in patients with Type 1 diabetes mellitus (T1DM) and insulin naive Type 2 diabetes mellitus (T2DM) are endorsed (Ghosh et al., 2019).

Clinical trials required to demonstrate comparability of biosimilar insulin to its innovator

1. **European Medicines Agency (EMA)** - Pharmacokinetic/Pharmacodynamic study, Phase 3 study in patients with T1DM with duration of six months.
2. **U.S. Food and Drug Administration (USFDA)** - Pharmacokinetic/Pharmacodynamic study, Phase 3 study in patients with T1DM with duration of twelve months, determination of primary efficacy parameter at six months, Phase 3 study in insulin naive patients with T2DM with duration of six months, Interchangeability study (guidance pending).

3. **Pharmaceutical and Medical Devices Agency (PMDA), Japan** - Pharmacokinetic/Pharmacodynamic study, Phase 3 study in T1DM with the duration of twelve months, determination of primary efficacy parameter at six months.
4. **Central Drugs Standard Control Organization (CDSCO), India**- Pharmacokinetic/ Pharmacodynamic study, Phase 3 study in T1DM (Ghosh et al., 2019).
5. **World health organization (WHO)**- Pharmacokinetic/Pharmacodynamic study, Phase 3 study.

Biosimilars have their own dose range by the originator due to which phase 2 study is not required as it needs to collate the phase 3 of the innovator product. Insulin guidelines are provided by EMA which gives an overall idea about the preclinical, clinical and non-clinical studies for comparing biologic and biosimilar drugs (Ghosh et al., 2019).

Requirements for Pharmacokinetic/Pharmacodynamic study

1) **Study design:** Double-blind, crossover, hyper insulinemic euglycemic clamp study with the help of single doses of test and reference insulins.
2) **Study population:** Normal-weight healthy volunteers/patients with T1DM.
3) **Equivalence margin:** Pharmacokinetic/Pharmacodynamic needs equivalence testing which can compare the 90% or 95% confidence interval (CI) of the measured treatment dissimilarity among the biosimilar and originator product with a given equivalence margin (Ghosh et al., 2019).

4) **For primary PK endpoints (AUC_{0-t}, C_{max}):** the 90% confidence interval of the ratio test/reference should lie within the given equivalence margins of 80% to 125% (0.8–1.25).

5) **For primary PD parameters (AUC_{GIR0-t}):** the 95% confidence interval of the ratio test/reference should lie within the given equivalence margins (0.8–1.25) (Ghosh et al., 2019).

4.5.2 Equivalence Trial of Pharmacokinetic/Pharmacodynamic Studies

The Pharmacokinetic/Pharmacodynamic clinical analogy for the originator and innovator are based on their equivalence testing whose goal is the statistical and hypothetical deduction of the differences from the traditional tests. The null hypothesis lies within the equivalence test which uses a two-sided test depending on the predetermined span which is either lower to the originator product or better than the originator product depending on the predetermined span.

This helps to find out if there is any clinically significant dissimilarity in the effectiveness of the biosimilar and biologic product with a CI of 90% or 95%, however the higher or lower limits of this test should normally be similar. This equivalence test is made to remove the null hypothesis to maintain the treatment options which are the same. This test equals the CI and this is handled by the statistical estimation of the history of the innovator and clinical activity (Ghosh et al., 2019).

4.6 Therapeutic Efficacy of Biosimilars over Biologics (Insulin)

4.6.1 Comparison Between Two Glargine Products (Biosimilar vs Reference)

Since 2006 the biosimilar products are in use in the European by demonstrating its preclinical, clinical, analytical, safety and efficacy profiles. In 2014 insulin glargine got approved to be a long-acting insulin and LY IGlar as a biosimilar insulin of insulin glargine. The phase 1 study of these insulins were carried out where the bioequivalence test to check the pharmacokinetic and pharmacodynamic characteristics were observed to be the same. Afterwards in Type 1 and 2 patients, phase 3 clinical trials were carried out and similarity were observed with no dissimilarities in terms of immunogenicity, hypoglycemia and other adverse effects. The end results showed that to treat Type 1 and Type 2 diabetes LY IGlar can be used as a substitute to insulin glargine in terms of tolerability, efficacy and safety showed in figure 5 and 6 (Mönnig et al., 2016).

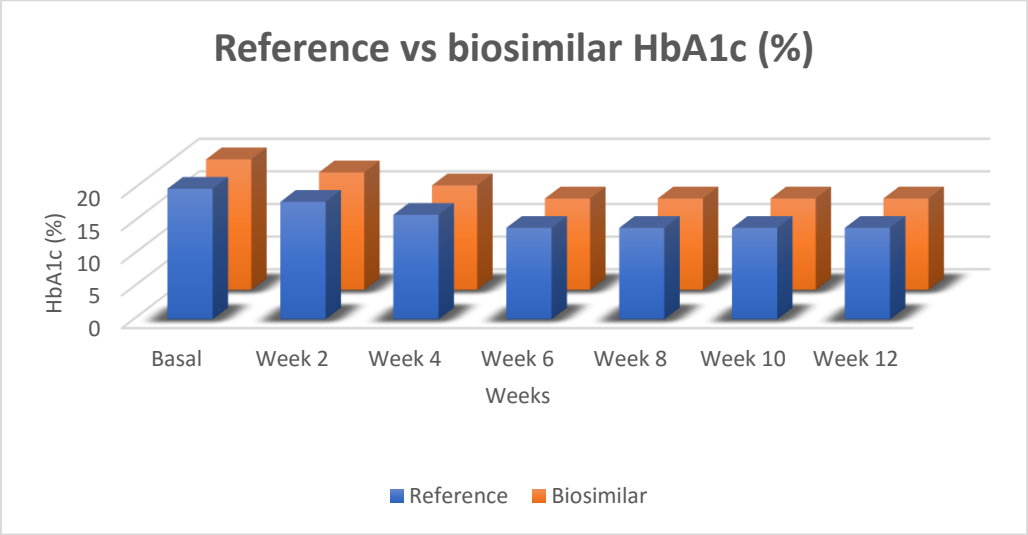


Figure 5: Levels of HbA1 during the 12 weeks of following both insulins (Reference and Biosimilar). No significant differences were found between both groups. (Adapted from Mönnig et al., 2016).

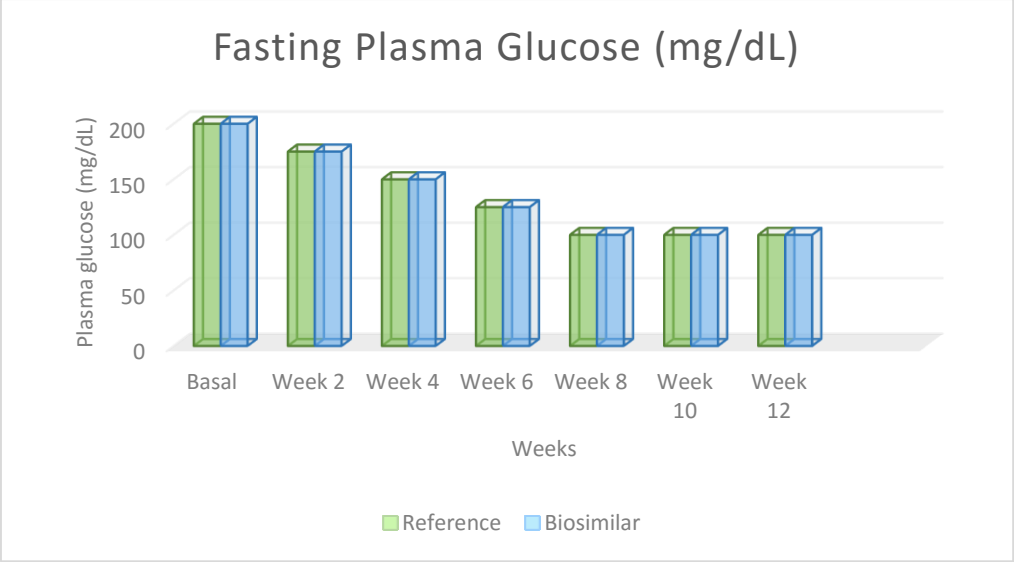


Figure 6: Levels of Fasting Plasma Glucose during 12 weeks of treatment with insulin glargine Reference and Biosimilar. No significant differences were found. (Adapted from Mönnig et al., 2016).

Regulatory framework for biosimilars has made it easier for mass people to get access to the biologics at a relatively lower cost. The human insulin, insulin glargine maintains plasma insulin level for a long time. This study gave a comparison of the efficacy and safety of the originator product and the reference product for Type 2 diabetes. A comparative study of 102 people with 28 males and 64 females were conducted by giving them reference insulin glargine subcutaneously at a dose 0.4 to 0.7 IU/Kg per day for twelve weeks. The assessment was done by developing a questionnaire and evaluating Hb1Ac, lipid profile and FBG (Fasting blood glucose) for both groups. No prominent dissimilarities were found in body weight rather improvement in physical and mental state were observed. The cross over studies between antibodies and hypoglycemia shows no correlation. The HbA1c test of 80.8% patients with biosimilar treatment was less than 7.5%, 66.6% and 69.5%. So, it can be concluded that the biosimilar of insulin glargine showed similarity in terms of safety and

efficacy with its reference insulin and is suitable for treating patients with diabetes mellitus (Antonio Hernández-Bastida, 2014).

4.7 Impact of Biosimilar Insulin on Healthcare

Economic Impact of Diabetes: The cost of diabetes management is very high worldwide and puts a burden on the financial condition of a family and its member. For instance, in India about 70% of the total population lives in rural areas and it is very difficult for them to get access to proper healthcare services due to their financial insolvency (Ghosh et al., 2019).

Biosimilar and Competition: Once the biosimilar insulin gets into the market then the mass people will be able to understand its significance which might raise a competition among the insulin market. Moreover, biosimilar insulin increases accessibility and reduce the cost of diabetes therapy (Ghosh et al., 2019)

Approved Quality with State-of-the-Art Technology: The technology used to manufacture biosimilar insulin has been used since the beginning in the production of innovator biologic products this is why it is termed as ‘State-of-the-Art Technology’ which implies that the quality of the product is maintained throughout the manufacturing of the finished product (Ghosh et al., 2019).

Substantial Cost-Benefit: To develop and introduce a biosimilar product in the market it takes about 8 to 10 years so it requires a good amount of expenses for such processes which is more than the generic drugs but once it is established in the market their development cost reduces (Ghosh et al., 2019).

An Exciting New Reality: The innovator companies have also started to produce biosimilars and so now more than 450 biosimilars are manufactured worldwide and more than 250 are in

the serial to be introduced in the market which led to the fact that by 2025 the market value of biosimilar will rise to USD 25 to 35 billion. FDA approved the biosimilars Zarxio (Sandoz) of the biologic filgrastim, Erelzi (Sandoz) biosimilar of etanercept, Renflexis (Celltrion's Inflectra and Samsung Bioepis) biosimilar of infliximab, Amjevita (Amgen) biosimilar of adalimumab. In USA, Japan and Europe insulin glargine of Lilly and Boehringer has been approved and Merck, Biocon and Mylan insulin glargine has been approved after the Phase III trial and now Phase 1 clinical trial of biosimilar lispro has been initiated by Sanofi (Ghosh et al., 2019).

Chapter 5 Biosimilar Insulin Products

In USA, the biosimilar insulin Basaglar (Eli Lilly) of the reference insulin glargine Lantus (Sanofi) was approved in 2015, biosimilar Admelog (Sanofi) of the reference insulin lispro Humalog (Eli Lilly) was approved in 2017 biosimilar Semglee (Mylan and Biocon) of the reference insulin glargine Lantus (Sanofi) was approved in August 2020. In 2018 Mylan and Biocon launched Semglee in UK in the form of a prefilled pen 100 units per mL (Diabetes UK, IDF, Korea Biomedical Review, 2018).

In South Korea, biosimilar Glarzia of the reference insulin glargine was approved in November 2018 by GC pharma and in March 2018 by Korean Ministry of Food and Drug Safety (MFDS). It was made by Biocon in 2016 but GC Pharma in Korea got special rights for its commercialization (Diabetes UK, IDF, Korea Biomedical Review, 2018).

In China, Biosimilar Basalin of the reference insulin glargine was approved by Gan & Lee in 2020.

5.1 Insulin Glargine and its Biosimilars

5.1.1 Insulin Glargine

Insulin glargine is equivalent to human insulin and exhibits a long duration of action (long-acting insulin) through the maintenance of blood glucose level in a stationary state for a longer time compared to the regular insulin. It can be used in combination with other medications or as a short acting insulin. Its mechanism of action includes increased uptake of glucose by the cells for the body to reuse it as a source of energy (WebMD, 2021). It binds to the insulin receptor which is a heterotetrametric protein comprising alpha and beta subunits. Insulin binds to the alpha unit and stimulate tyrosine kinase signaling cascades. The

phosphorylation of protein occurs simultaneously by IRS protein, APS, Gab 1 whose signaling starts with activation of PI3 kinase and Akt (which regulates GLUT4 and PKC) (D. R. Owens & Bolli, 2008). This insulin is a prescription medicine that can be injected by the patients themselves. The available brands for this insulin are Lantus, Basaglar, Soliqua and Toujeo. For Type 1 diabetic patients the insulin glargine is used with short/rapid acting insulins and for Type 2 diabetes insulin glargine can be used alone (UIC, 2018). Insulin glargine was first made in the Frankfurt-Hochst at Sanofi-Aventis and currently the company distributes its products ~~to~~ in 100 countries to more than 3.5 million diabetic patients (Rendell et al., 2013). Glargine is soluble in pH 7.4. When given subcutaneously it neutralizes by micro precipitation and is released at regular time interval at a constant rate. This release pattern retains the basal insulin level in the body (D. R. Owens & Bolli, 2008). Insulin glargine also functions to inhibit proteolysis, lipolysis in adipose tissues and promote the synthesis of protein. The insulin analogue of glargine, Lantus whose patent expired in 2014 opened the door for biosimilars in the market (PubChem, 2021). FDA and EMA approved originator Lantus of Sanofi in April 2000 and June 2000 respectively. Lantus bought USD 6.4 billion globally in 2015 (GaBI Journal Editor, 2019). The Table 3 below shows the Biosimilars and non-originator biologicals of insulin glargine approved or which are in development process.

Table 3: Biosimilars and non-originator biologicals of insulin glargine approved or in development (Adapted from GaBI Journal Editor, 2019).

Company name, Country	Product name	Stage of development
Biocon/Mylan, India/USA	Basalog/Semglee (MYL-1501D)	Similar biologic launched in India in 2009. Received Japanese approval in March 2016 and launched in July 2016. Approved by EC and Australia's TGA in March 2018 and by FDA in June 2020. Launched in South Korea and the UK in November 2018 and in Australia in October 2019.
Eli Lilly/Boehringer Ingelheim, USA/Germany	Abasaglar/ Basaglar (LY2963016)	Approved by EC in September 2014, by FDA in August 2014, by Japan in January 2015 and by Australia in May 2015. Launched in Korea in April 2017.
Gan & Lee, China	Basalin	Copy biological launched in China in 2005
GC Pharma (Biocon), South	Glarzia	Received Korean approval in March 2018.

Korea (India*)		Launched in South Korea in November 2018.
Kalbe Pharma, Indonesia		Copy biological launched in Indonesia March 2017.
Polus Biopharm, South Korea	PDP808	Primary target
Samsung Bioepis, South Korea	Lusduna (SB9/MK 1293)	Approved by the EU in January 2017. Tentative approval for follow-on biological granted by FDA in July 2017. Merck pulled out of the deal in October 2018.
Wockhardt, India	Glaritus	'Similar biologic' launched in India in March 2009.
EC: European Commission; EMA: European Medicines Agency; EU: European Union; FDA: US Food and Drug Administration; TGA: Therapeutic Goods Administration		

5.1.2 Biosimilar Semglee

In USA, Mylan and Biocon launched Semglee which is the biosimilar of insulin glargine on August 31, 2020. This biosimilar is long acting, available in prefilled pens and vials. Dr. Thomas Blevins did the clinical trial for Lantus and drew the conclusion that it is safe to use and can control glucose level for both Type 1 and Type 2 diabetic patients (Nicole Corey, 2020). In March 2018 it achieved marketing authorization by European Union (CHMP, 2018). The protein structure and hypoglycemic effect is similar to the reference product as it has been approved in forty-five countries including Japan, European Union, South Korea and Australia. However, FDA has still not tagged Semglee to be similar or interchangeable to Lantus so it is now considered to be a basal insulin (Karena Yan, 2020).

Initiation of Semglee therapy

1) Type 1 Diabetes- For Type 1 diabetic people Semglee has to be provided simultaneously with short acting insulins. The initial dose has to be 1/3 of the regular insulin required for Type 1 diabetic patients. The remaining dose needs to be fulfilled with short acting insulin (Of et al., 2008).
2) Type 2 Diabetes- The initial dose will be 0.2 units per kg or up to 10 units once daily for those who aren't taking insulin currently. The timing and quantity of the short/rapid acting insulin needs to be adjusted accordingly (Of et al., 2008).

Semglee is available as pre-filled disposable pens. It is a prescription drug. The injection is inserted beneath the skin of the thigh, belly and upper arm. It is a substitute for insulin because it works just like the body's own insulin and has a long duration of action (CHMP, 2018).

Benefits of Semglee

The insulin glargine of Lantus is equivalent to Semglee in terms of purity, chemical structure, absorption rate and biological activity. Semglee being a biosimilar has the safety and efficacy profile close to insulin glargine. A survey stated that Type 1 diabetic patients experiences the same therapeutic effect with both Semglee and Lantus. In a HbA1c test, patients were given Lantus which controlled the blood glucose level and continuing this treatment with Semglee for the next twenty-four hour kept the control level at the same rate (CHMP, 2018).

5.1.3 Biosimilar Abasaglar

In April 2018 Abasaglar was approved as a biosimilar of insulin glargine in European Union which is also Basaglar in the USA, administered once daily subcutaneously. Biosimilar Abasaglar of reference insulin glargine showed the same activity in Phase I Euglycemic clamp test including the same functional and structural properties in the preclinical studies, duration of action and pharmacodynamic and pharmacokinetic studies. It also showed equivalent glucose control activity in the Phase III trial for the mealtime insulin of Type 1 diabetes and for oral antidiabetic medication for Type 2 diabetes. The safety profile also demonstrated the tolerance property of Abasaglar with reference to insulin glargine. The immunogenicity of insulin glargine also matched with the biosimilar Abasaglar in the Phase I and II trials. All these points out that Abasaglar is a choice of drug for Type 1 and Type 2 diabetic patients at a low cost (Lamb & Syed, 2018). This is a modified insulin of insulin glargine and the dosing regimen is 100 units per mL once daily (Blevins et al., 2015; Rosenstock et al., 2015).

5.2 Insulin Lispro

On May 22, 2019 Eli Lilly launched Humalog in USA which is a biosimilar of insulin lispro with a lower price than the originator product (Eli Lilly, 2019). On May 19, 2017 EMA Committee for Medicinal Products for Human Use (CHMP) approved biosimilar insulin lispro by Sanofi and on December 11, 2017 FDA approved Admelog biosimilar of insulin lispro. Mylan and Biocon combinedly developed the three insulin products which are Lantus, Novolog which is insulin Aspart (Novo Nordisk), Humalog which is insulin lispro (Eli Lilly) (Derbyshire, 2017). Another biosimilar of insulin lispro is SAR342434 approved by the EU as it has same activity like its reference insulin lispro having same pharmacokinetic and pharmacodynamic properties. It is administered subcutaneously and improves glucose control for both Type 1 and Type 2 diabetes. It is under Phase III of clinical trial now but till now it has shown similarity in every aspect. The main advantage of this biosimilar insulin would be cost reduction as it is cheaper than the originator product and gives greater access to treatments (Hu et al., 2018). Table 4 shows the biosimilars and non-originator biologicals of insulin lispro approved or which are in development.

Table 4: Biosimilars and non-originator biologicals of insulin lispro approved or in development (Adapted from Derbyshire, 2017).

Company name, Country	**Product name**	**Stage of development**
Biocon/Mylan, India/USA	N/A	'Similar biologic' currently under preclinical/ scale-up development.
Sanofi, USA	Insulin lispro Sanofi (EU)/Admelog (US)	Approved by EMA in May 2017. Approved by FDA in December 2017.
EMA: European Medicines Agency.		

Admelog and Humalog are of the same type but one is biosimilar insulin and another is the follow on, this difference occurs due to the difference in the production procedure but both are equally effective and safe. The long-acting biosimilar insulins Basaglar and Lusduna are the biosimilars of reference insulin glargine and Admelog (rapid acting) is the first follow on insulin approved in July with the name 'insulin lispro Sanofi'. The pricing is such that Admelog will be less costly than Humalog. Biosimilar and its follow on drug tends to be around 15% to 30% cheaper than brand name drugs such as Basaglar which is around 15% less costly than brand name Lantus (Amelia Dmowska, 2018).

5.3 Upcoming Products in 2021 and 2022

The abbreviated registration process (a comparison of information of originator and biosimilar drug to show similarity) approves the biosimilars. On January 7th, 2021 CHMP (Committee for Medicinal Products for Human Use) reviewed a list of twelve applications of biosimilars which were under the evaluation by EMA's committee CHMP. One of the applications reviewed were for rDNA as it has not been approved in Europe yet (GaBI, 2020).

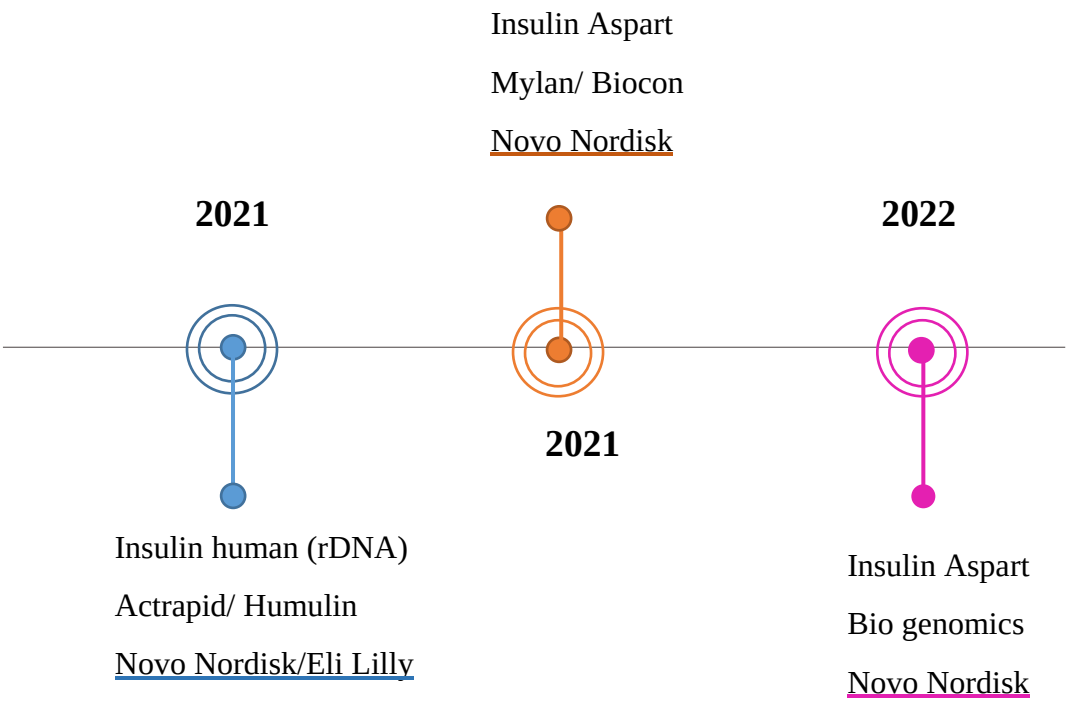


Figure 7: Timeline of the new insulin products to be launched (Adapted from GaBI, 2020).

FDA and Lannett, in their meeting about Type II biosimilar biological product development gave a positive review over the clinical, manufacturing, controlling progress of biosimilar insulin glargine which was constant throughout their formulation. By 2022 the expected biosimilar application is hoped to fulfill the requirement in terms of development activity, clinical trials, safety profiles and so on which are shown in figure 7 (Stanton Mehr, 2020).

Chapter 6 Global Regulatory Guidelines

The manufacture of biosimilar insulin has to follow the basic framework for proving the similarity with the reference product with respect to safety, efficacy, clinical properties and marketing data. The similarity has to be evident at every stages of development to prove it as an alternative of the originator medicine. Moreover, while doing the validation studies if any doubtful event is observed then further analysis has to be conducted to clear the confusion and draw an exact conclusion of the product being similar (Rotenstein et al., 2012). Table 5 shows the definition of Biosimilars as per different regulatory agencies.

In the peer reviewed scientific papers the regulatory pathways are not given rather they are found by exploring in the internet to relate the originator and its biosimilar (Heinemann et al., 2015). Till now there is no biosimilar that has been presented following this guideline. Therefore, conclusion cannot be drawn yet regarding its actuation (Rotenstein et al., 2012). Figure 8 shows the timeline of regulatory pathway of different biosimilar insulins.

Table 5: Definition of Biosimilars as per different regulatory agencies (Ghosh et al., 2019).

Agency	Definition
US-FDA	Highly similar to US-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences in terms of safety, purity, and potency.
EMA	Similarity to reference medicinal products in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.
PMDA (Japan)	Biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived product of innovator. Comparability with respect to quality, safety and efficacy, or other relevant data should be established.
CDSCO (India)	"Similar" in terms of safety, efficacy and quality to a reference biologic, which has been granted marketing authorization in India by DCGI or is approved in ICH countries (i.e., EU, Japan, US, Canada etc.).
WHO	A biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.

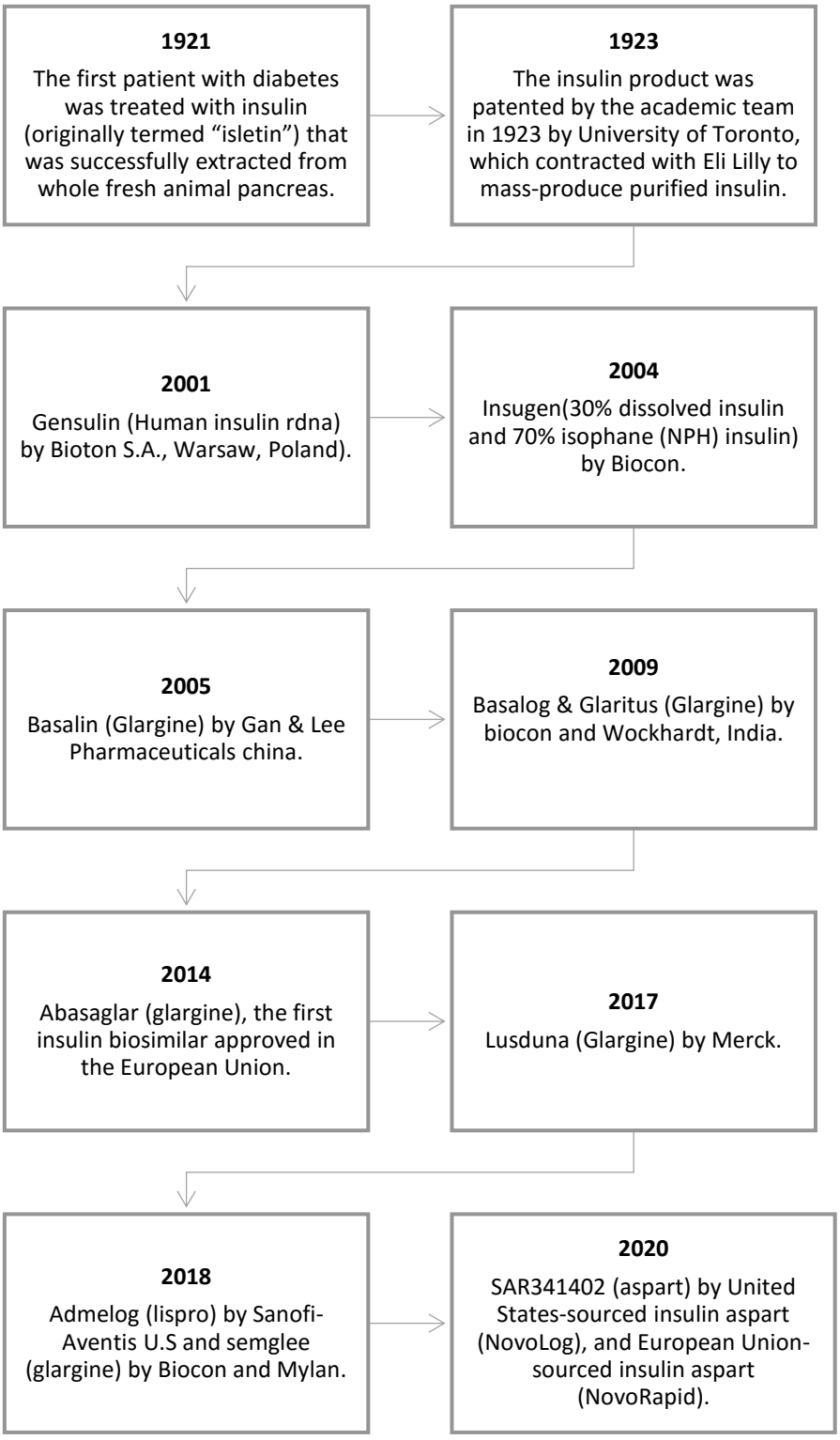


Figure 8: Timeline of regulatory pathway of different biosimilar insulins (Adapted from Altman et al., 2018; Hu et al., 2019; Kapitza et al., 2020; Kim & Bindler, 2016; Owens et al., 2012).

6.1 Asia Guidelines

Among the Asian subregion, South Asia is considered as the factory of drugs in the entire world as the countries India, Bangladesh and Pakistan serve the domestic and international medication needs. That's why almost every country of South Asia has well established regulatory guidelines regarding biosimilars as for instance, India considers a biosimilar to be exactly the same with its reference drug, their Organization of Pharmaceutical Producers have position papers to compare their biosimilar guidelines with those of WHO and Sri Lanka also follow the WHO guidelines for GMP (Good Manufacturing Practice). They conduct the quality, safety, efficacy, control tests and trials for the applied biosimilars for further confirmation which results in weak biosimilars losing their license (Kalra et al., 2016). Table 6 includes the biosimilar insulins and insulin analogs marketed in South Asia.

Table 6: Biosimilar insulins and insulin analogs marketed in South Asia (Adapted from Kalra et al., 2016)

Country	**Biosimilar insulins**	**Biosimilar insulin analogs**		
		Glargine	***Aspart***	***Lispro***
Sri Lanka	None	None		
Pakistan	Insuget R, 70/30, N Innogen R, 70/30, N Zansulin R, 70/30, N	Basagine		
Nepal	Wosulin R, 70/30, N	Glaritus		

India	Insugen R, 70/30, 50/50, N Humstard 30/70 Humarap Lupisulin R, M30, M50, N Recosulin R, 70/30, 50/50, N Human fastact, Mixact 30/70 Wosulin R, 70/30, 50/50, N	Basalog Basugine Glaritus		
Bangladesh	Insul R, 70/30, 50/50, N Maxulin R, 70/30, 50/50, N Ansulin R, 70/30, 50/50, N Diasulin R, 70/30, 50/50, N Insulet R, 70/30, 50/50, N	Glargin Glargin C Vibrenta Insulet glargine Glarine	Glyset R, Glyset Mix, Acilog Acilog R, Insulet Asp, Insulet Asp 30/70	Insul Lispro, insul Lispro C

6.2 China and South Korea Guidelines

The regulatory process of approving biosimilars is yet to be published in China, that is, the drug approval procedure and regulatory pathway are ought to be established. Since December 2011 about forty biologics were approved in China among which some were copies of the biologics. Then in 2011 and 2012, about forty-one companies were involved in the research of these copies in China. In October 2014, the CCDE (Chinese Center for Drug Evaluation)

made a guideline for discussion on the approval process of biosimilars however the copies of the biologics will keep undergoing the drug approval procedure. The South Korean guidelines for testing biosimilars are as such that to correctly find out the safety, efficacy profile of the biosimilar with its reference product it has to undergo double-blinded or blinded clinical trials in the lesser groups' or in parallel groups or randomized. All these tests can be concluded only if the pharmacokinetic and pharmacodynamic properties have well established ranges to detect the dissimilarities between the reference and the biologic product. Again the Korean FDA has a guideline which says that there should be predefined safety variables among many people to find out the safety outline which may also contain the frequency, type, adverse events or its severity because alone the safety information is good enough to judge the biosimilar product but still all types of product justifications are necessary for the post marketing part of the products (Heinemann et al., 2015).

6.3 EU Guidelines

When the patent expiry occurs for any product for instance insulin then the biologic products are provided for further authorization and specially for biosimilars this sector needs strict monetization for the regulation of the therapeutic arenas. Through internet search and other sourcing, the available guidelines for the regulatory pathway of biosimilars were found out to check the approval status of biosimilar insulin. Up to August 2014 the guidelines for biosimilar insulins were found among 34 countries which have raised in numbers now. Most of the guidelines came from EMA by covering the pharmacokinetics and pharmacodynamic, pre-clinical and clinical outcomes of the biosimilar insulin and biologics. In the US FDA biosimilar guidelines, not only pharmacokinetics and pharmacodynamic, pre-clinical and clinical profiles are considered but also the invitro studies are also demonstrated. In Mexico,

guidelines are more comprehensive. At a glance globally, the drug regulatory pathway aims to synchronize the needs to establish biosimilar insulins (Heinemann et al., 2015).

Several scenarios are considered that are based on either EMA policies and/or sound clinical and statistical reasoning.

6.3.1 Scenario A: One Clamp Study and Two Efficacy Trials (Based on HbA1c Endpoint)

The initial point where the drug development procedure starts with an insulin product in which the one to two clamp study works in early phase where two efficacy trials (type 1 and type 2) for diabetic patients were carried out. The change of HbA1c baseline leads to the efficacy trials for the time period of 26-52 weeks. About 450-550 participants are considered in this test. To test the immunogenicity, at least 250 candidates are taken into account (Heinemann et al., 2015).

6.3.2 Scenario B: One Clamp Study (Type 1) and One Efficacy Trial (Type 2)

Scenario A is the conventional way of testing bio-similarity of insulins, there are more ways of finding the drug development procedure which can assist the similarity assessments. The Type 1 and Type 2 diabetic people should show equivalent activity for both reference and biosimilar products. The majority (90-95%) of diabetic cases are Type 2 so the efficacy for Type 1 should also be effective for Type 2. Nevertheless, the study has to be done in Type 1 as well to check its efficacy in Type 1 patients. EMA has adopted this strategy of approving pharmacokinetics and pharmacodynamic results and glucose control trials such as FPG.

Additionally, it also requires another test for knowing the immunogenicity of the biosimilar insulin (Heinemann et al., 2015).

6.3.3 Scenario C: One Clamp Study (Type 1) and One Abbreviated Efficacy Trial (Type 2)

Two types of tests can be done with Type 1 and Type 2 diabetic people. For Type 1 one clamp study can be done to know the efficacy and for Type 2 immunogenicity (one abbreviated safety trial) can be conducted. The number of candidates can be 250 in order to test the biosimilar product (Heinemann et al., 2015).

6.3.4 Scenario D: One Clamp Study (Type 1) and Efficacy Plus Interchangeability Trial (HbA1c)

The new insulin products should be as such that they can be prescribed because this can help the prescriber to understand if the biosimilar insulin products are actually worth prescribing or not and whether they are interchangeable or not with their originator medicines. This is necessary to know because this is a lifelong medication system. It is obligatory for patients and physicians to know if the biosimilar insulins are interchangeable or not and so this has to be strictly monitored by the regulatory authority (Heinemann et al., 2015).

6.3.5 Scenario E: One Replicated Design Crossover-Clamp Study and One Safety Trial

The scenario D is population dependent, the bioequivalence study for each drug is based upon the variability of individuals and requires both the biologic and biosimilar product. This

case, clamp studies are required mainly for the time period and the relationship between HbA1c and FPG ranges. The bio-similarity test is necessary for understanding the efficacy of biosimilar insulins (Heinemann et al., 2015).

6.4 USA Guidelines

In February 2012, the US FDA brought out the need that a biosimilar producer must adopt the guideline of license regulatory pathway (three draft guidance). In these guidelines it is expected that the companies distributing and manufacturing biosimilar insulins would give a detailed demonstration of the structural, physiochemical, manufacturing, quality control evaluations and comparison of the originator and biosimilar product. Then it is expected that the preclinical and clinical toxicology, immunogenicity, safety, clinical efficacy, pharmacokinetics and pharmacodynamic studies will also be assessed. The pre (finds the major dissimilarity of two products) and post marketing (finds the detailed dissimilarity) immune response test has to be conducted. FDA have not yet given any specific guideline on the pharmacovigilance study of biosimilar insulin but it has given priority to the extensive evaluation of every aspect of biosimilar insulin to be conducted prior to its marketing (Rotenstein et al., 2012). Biosimilar makers need to market and position their biosimilars as best as possible for the earliest launch. However, there are several challenges and litigations that biosimilar makers face before the product can be approved to be available in the market. Interchangeability standards to be clear and in place as well for the biosimilars to be interchanged when needed, so that they can be substituted in the same way as a small molecule generic.

Chapter 7 Constraints and Challenges in Access to Biosimilar Insulins

7.1 Patent Dance

The pre-litigation process for information/s to be exchanged between the biosimilar applicant and the reference biologic product manufacturer is known as patent dance. If there is any patent debate regarding any product, it needs to be solved right after the application to the FDA for biosimilar approval (Fogel & Hanna, 2014). There is an outline given by BPCIA which contains all the necessary steps for reviewing the application alongside the originator product by cross studying the important clinical data submitted in the aBLA (Abbreviated Biologics License Application) throughout which the candidate and the sponsor finds out the patents that needs to be taken under legal action for the upcoming legal proceedings. During these phases firstly the sponsor may point out violence that could be found throughout the patent dance, then in the next phase the candidate sends the sponsor a notice of commercial marketing, even any unresolved patents can also be identified by the sponsor in this phase. It generally takes about 8 months or almost 250 days to complete the patent dance for the candidates and the sponsor. If any candidate backs out from this ongoing procedure, then there are ramifications that the candidate would have to face. The candidates who are part of the dance will get the opportunity of reserving a file for them where they can challenge the validity of the recognized patents. However, if the candidate gives up then the opportunity goes to the sponsor to take legal actions for the violence of the enforcement and validity of the patents concerning the biologic product (Winston & strawn, 2021). Figure 9 shows the process of the biosimilar launch and patent dance. The stages of the process are listed as follows:

1. The FDA reviews the abbreviated application of the proposed biosimilar, after which the candidate has to give the reference product sponsor the access to the biosimilar product confidentially to review its production processes within 20 days.
2. The sponsor needs to provide the details of patents that the sponsor thinks is violated and which of the patents can be given to be licensed for the biosimilar which has to be provided within 60 days.
3. After the candidate receives the details of the complaints given by the sponsor, the candidate has to mitigate the claims mentioned by the sponsor within 60 days with evidence and data that proves its basis.
4. The biosimilar candidate within that same 60 days gives a sponsor a detail of the patents which could be related to the patent violence that are claimed.
5. When the sponsor receives the details within 60 days it will start to create reciprocal lists that demonstrate the claim, the legal bases of the patents that are claimed to be violated, even to an answer of the enforcement or the validity.
6. After all these there will be 15 days for the sponsor and candidate to negotiate and bring down the patent within the list that were considered to be a part of patent violation action (Fogel & Hanna, 2014).

The expiry date of the patents is still in development than that of the products which are already in the market. Even the patents approved will expire by 2030, therefore, the patents and its application are filed in more places of the world in comparison to the insulins present in the market (Beall et al., 2016).

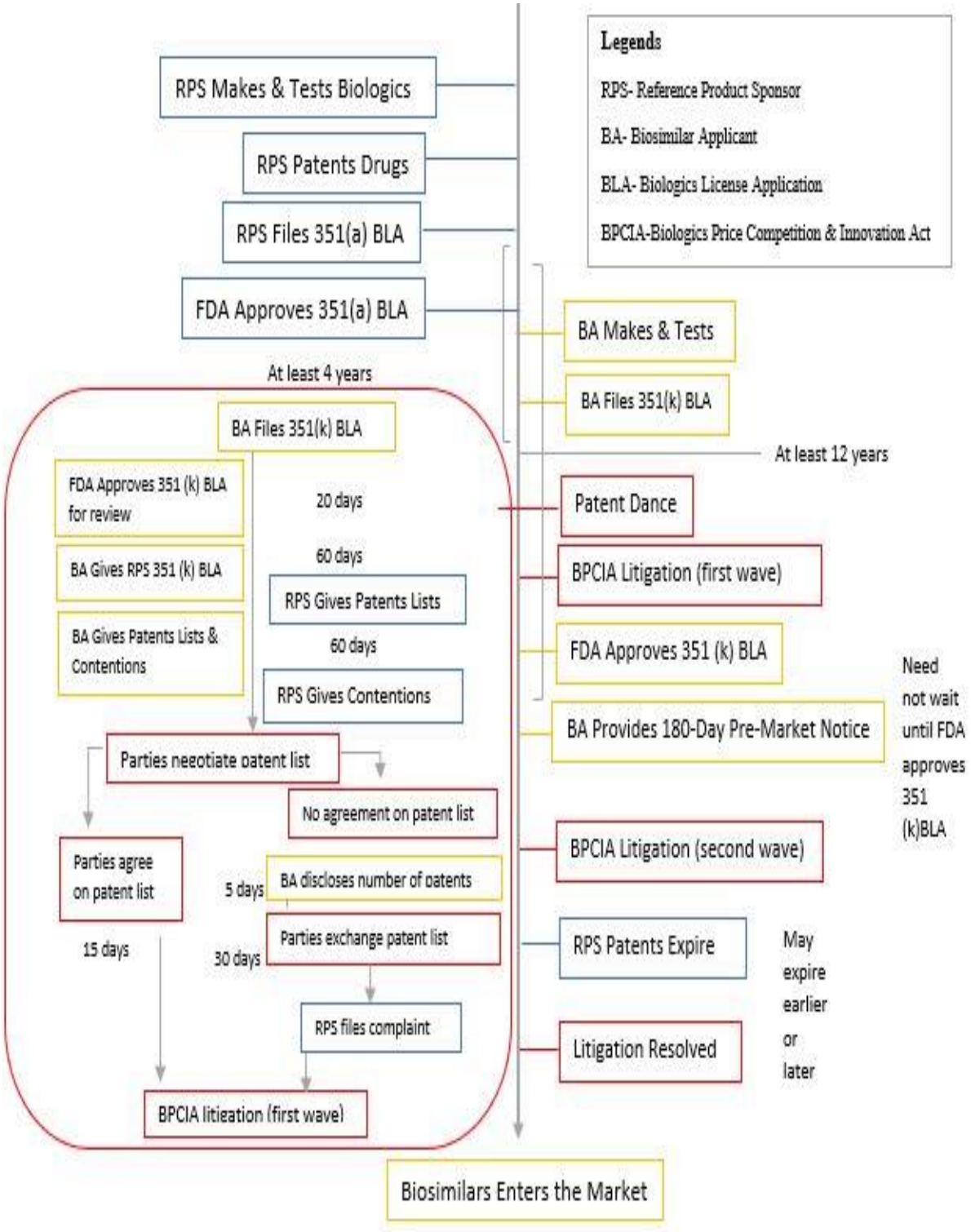


Figure 9: Biosimilar launch and Patent Dance (Adapted from Cheryl Wang, 2020)

7.2 Perception on the Evolution of Biosimilar Insulins

Biosimilar insulin's introduction in the market will require an adequate amount of knowledge and awareness about. It is necessary that all types of professionals such as physicians, pharmacists, regulatory authorities, patients and counselors are aware of the differences between biosimilar and reference insulins (Kalra et al., 2016).

Insulin is vital for the patients with both Type 1 and Type 2 diabetes but the needs has not been met yet due to various global restrictions and drawbacks (Beran et al., 2016). Though insulin was discovered in 1921, it is still not yet accessible to all the diabetic people. The price of insulin is also still high due to the manufacturing costs, taxes and supply chain and local chain costs.

In a survey it was found that there are approximately forty independent manufacturers of insulin biosimilars in 17 countries that include China, India, Mexico, Egypt and Russia. Six of these manufacturers could actually suffice to supply insulin worldwide. However, biosimilar insulins have to go through stringent regulatory pathway than that of biologics because they need more assessments to prove their efficacy which adds up to the increase in cost of the biosimilar's entry into the market. The rules of using biosimilars are more stringent in USA and Europe rather than in India, Mexico or China. In 2015, biosimilar insulin glargine got approved from Japan's Ministry of Health, Labor and Welfare for marketing which was remarkable as even after not being a multinational company they achieved this novel challenge (Perrin et al., 2017). A set of questionnaires showed that people with diabetes are hopeful of the use of biosimilars where 1637 insulin users were asked about their willingness of using biosimilar insulin which is a less expensive version of the biologic insulin. The results show that 37% of the participants are willing to use it and 30% answered

in affirmative in using biosimilar insulin. Again, in another study, 415 professionals were asked about their willingness to prescribe biosimilar insulin to patients. About 41% assured about prescribing and 42% are willing to prescribe having further questions about the biosimilars. But this willingness of people will not work alone; further strict regulatory rules are to be made between the originator and biosimilar products before letting the biosimilars enter into the pharma giant markets. To retain in the market biosimilars have to first obtain loyalty to the prevailing brands in the major company timelines (LS Rotenstein, 2012).

7.3 Factors Affecting the Constraints on Biosimilar Insulins

Efficacy and Safety

The quality of insulin can differ from variation in its source, manufacturing procedure, or equipment used to produce it. The bioequivalence characteristics may get affected if there enters any impurity from the host, or production steps. If inulin products undergoes variation then insulin neutralizing antibodies might be formed resulting in insulin resistance (Kalra et al., 2016).

Labeling

The products available in the market should have proper names and labels on it containing the particular information conveying whether they are biosimilars or biologics and their process of manufacturing. The preparation process of insulin glargine and Aspart are not same though but can be differentiated with trade name and nonidentical names as the biological and generic product prescription is different from each other which has to be clarified further by the proper information in the literature of the products (Kalra et al., 2016).

Substitution

Replacement of biologic products are often harmful, therefore, without proper clinical indications replacement of insulins cannot be done and close monitoring of glucose level after replacement of medicines has to be done (Kalra et al., 2016).

Pharmacovigilance

Pharmacovigilance post marketing is necessary to keep track of any adverse events from the use of the biosimilar insulins as safety and efficacy concerns are associated with this. Even studies showed that the control of glucose can be achieved more with higher dose of biosimilar insulins (Kalra et al., 2016).

Chapter 8 Future Implications

The health care providers need to be aware of the concerns with biosimilar insulins, particularly with regard to interchangeability of the biosimilars and their reference biologic. A number of biosimilar insulins are expected to be launched in 2021, and it is essential that awareness of these products is done for patients to have access to them. This will lead to the acceptance of biosimilars as a novel medication system (Kim & Bindler, 2016). Though biosimilar insulin is facing barriers from regulatory bodies, development authorities, and commercial sectors, it will surely be significant in serving the diabetic patients. The use of biosimilar insulins plays a crucial part in determining how the delivery devices are to be used, their labeling and regulatory interchangeability. As soon as the number of biosimilar insulins increases it will also increase the confusions among people regarding it. But this can only be addressed through a consolidated effort of the players to disperse knowledge regarding the biosimilar insulins among its stakeholders. The first generation biosimilars (filgrastim, somatotropin, epoetin) had faced many hurdles for their establishment and so biosimilar insulin would also face this. All these can create confusion in people because the interchangeability and legislation property are still not established properly yet. Post market surveillance is much needed to look over the safety and efficacy profile of the marketed biosimilar insulin and so the mechanism of action of biosimilars in terms of its immunogenicity and adverse effect needs to be considered for both the generic and biosimilar product. If automatic switching is to be enabled, then sufficient evidence to prove its part shall be established. The cost of medications will keep increasing but it is necessary to know and see that whether the pricing is justifying the activity or not, if the production cost is low then the total cost also should be low which will in overall call for a price reduction of

biosimilars than biologics. With increase in the number of people with diabetes in the USA even a lower amount of change in the price can be very helpful and beneficial for the health care sector concerning diabetes. Many biosimilar insulins have been approved while many are in development phase and they will be entering the market very soon. Hence, the concerns related to these products are to be considered for investigating the biosimilar insulin products (White & Goldman, 2019).

8.1 Opportunities and Patient Compliance

The expiry of biologics has paved the way forward for biosimilars. The development of the biosimilars market is expected to grow, particularly due to the cost-effectiveness of the biosimilars. Thus, the future of biosimilar insulins is also significant because they can bring a revolutionary change in the diabetic sector especially in countries such as Europe, Japan and USA, etc. where the affordability is a concern. Both the developed and the developing countries are more likely to accept biosimilars rather than their reference biologics. For example, China and India have been developing biosimilars for a very long time but their biggest hindrance is the implementation of a transparent and stringent regulatory pathway, unlike the developed countries. Also, in the developed countries, the physicians are found to prefer affordable medications which opens doors to opportunities. Biosimilar insulins are thus expected to enter the market as the number of diabetes cases are increasing, high costs of biologic insulins and patent expiry of the reference biologics. When the insulin biosimilars enter the market, the treatment option for diabetes will increase because these biosimilars will be more affordable and available, increasing market competition (Market, 2017). The advantage of biosimilar insulin is that it will have the same clinical benefits as the current reference product at a cheaper price, allowing the patients to get more effective treatments.

However, to ensure patient adherence to these biosimilars, it is necessary that the treatment regimen and the potential issues are resolved at the earliest (Edelman et al., 2014).

Chapter 9 Conclusion

The copy of biologic products approved in the pharmaceutical market is known as a biosimilar product. They are well known because of their high similarity in terms of quality, safety and efficacy. However, there are concerns amongst the healthcare providers whether or not the copy (the biosimilar) and the original reference product (the biologic) have clinical similarity or not. On the other hand, the expiration of biologics is shaping the entrance of biosimilars to the market. India and China are already ready to introduce insulin biosimilars in the market (Jennifer Zahn, 2016). In the upcoming years, biosimilar insulins are expected to change the insulin market scenario, with a significant impact in the treatment of diabetes, reducing cost, raising competition and increasing accessibility to patients though there are concerns in the regulatory landscape and commercial fronts. Debate continues whether or not biosimilar insulins will have a significant impact in the USA market or not. With the regulatory pathways becoming more transparent, chances of its acceptance shall become high and by reducing cost biosimilar insulins will start holding their own space in the diabetes cure options. The biosimilar timeline shows that the issues and patent disputes are complications that could be overcome with better commercialization of the product. The most significant part of introducing biosimilar insulin would be its affordability and impact in the high-quality patient care for diabetic patients. The regulatory development of biosimilars is very much on point and stringent in the USA, Japan and Europe. Different tests like biological and physicochemical tests will also help in characterizing the clinical studies done by the investigators. For patient safety, efficacy and quality of the reference insulin and biosimilar insulins have to be tested in a well-defined manner. Currently, six countries are working with biosimilar insulin production with both the combination of natural protamine Hagedorn (NPH) and insulin mixture.

The growth in biosimilar market share from late 2018 until now has been remarkable. Twenty of the 28 FDA-approved biosimilars are physician-administered drugs covered under a patient's medical benefit. And, there is the potential for the first therapeutically interchangeable insulin biosimilar to come to market in 2021, as insulin has gained a new pathway to increase competition (Joshua Cohen, 2020). The launch of biosimilars offers the opportunity to further lower the costs of long-acting insulin analogues to benefit all key stakeholder groups. Their availability has enhanced their use among Asian countries including Bangladesh, India and Malaysia, as well as among European countries (Godman, 2021). We didn't anticipate seeing interchangeability for biosimilars until 2023, when several biosimilars referencing Humira are slated to come market. Seeing the first interchangeable insulin biosimilar could eventually lead to more conversations around evolving the process for applying for interchangeability for large molecule biosimilars. Studies show that costs could decrease by nearly 30% if biosimilar uptake continues at the current rate (Sean Mc Gowan, 2021). Wholesale acquisition costs and average selling prices for biosimilars (net of discounts) are 15%-37% and 3%-24% lower than the reference product, respectively, according to Amgen Biosimilars (Wire, 2021).

The post marketing programs will also impact the cost effectiveness. But it is a fact that even the slightest change in cost will be helpful in the diabetes treatment. It is unknown how the introduction of biosimilar medications will exactly change the insulin market, but what is known is that more biosimilar medications will be coming to the market in the near future which will be convenient for the patients with regard to availability and affordability.

References

Aideed, H. (2019). *Will Biosimilars Solve The Insulin Cost-Conundrum In The US*. https://www.biosimilardevelopment.com/doc/will-biosimilars-solve-the-insulin-cost-conundrum-in-the-u-s-0001

Altasciences. (2019). *Are Biosimilars Destined to Replace Biologics? | Altasciences*. https://www.altasciences.com/blog/are-biosimilars-destined-replace-biologics

Altman, J. J., Chevalier, N., Delemer, B., Travert, F., & Benabbad, I. (2018). LY2963016 insulin glargine: The first biosimilar insulin approved in the European Union. *Presse Medicale*, *47*(10), 854–866. https://doi.org/10.1016/j.lpm.2018.06.004

Amelia Dmowska, P. M. (2018). *FDA Approves Admelog, the First Biosimilar Mealtime Insulin | diaTribe*. https://diatribe.org/fda-approves-admelog-first-biosimilar-mealtime-insulin

Antonio Hernández-Bastida, R. M.-M. de O. (2014). *Equivalence on Efficacy and Safety of Two Formulations of Insulin Glargine (Biosimilar and Reference) in the Treatment of Patients with Type 2 Diabetes Mellitus | Semantic Scholar*. https://www.semanticscholar.org/paper/Equivalence-on-Efficacy-and-Safety-of-Two-of-and-in-Hernández-Bastida-Oca/e7736f516c7920f2761aa3fa18f851b5566e723f

Beall, R. F., Nickerson, J. W., Kaplan, W. A., & Attaran, A. (2016). Is patent "evergreening" restricting access to medicine/device combination products? *PLoS ONE*, *11*(2). https://doi.org/10.1371/journal.pone.0148939

Beran, D., Ewen, M., & Laing, R. (2016). Constraints and challenges in access to insulin: A

global perspective. In *The Lancet Diabetes and Endocrinology* (Vol. 4, Issue 3, pp. 275–285). Lancet Publishing Group. https://doi.org/10.1016/S2213-8587(15)00521-5

Biolabs, C. (2020). *Immunogenicity Overview of Therapeutic Biologics*. 4–7. https://www.creative-biolabs.com/blog/index.php/immunogenicity-of-therapeutic-biologics/

Blevins, T. C., Dahl, D., Rosenstock, J., Ilag, L. L., Huster, W. J., Zielonka, J. S., Pollom, R. K., & Prince, M. J. (2015). Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: The ELEMENT 1 study. *Diabetes, Obesity and Metabolism*, *17*(8), 726–733. https://doi.org/10.1111/dom.12496

BMJ Publishing Group. (2020). *Overview of leukemia - Summary of relevant conditions | BMJ Best Practice US*. https://bestpractice.bmj.com/topics/en-us/534

CDC. (2011). Diabetes: What is diabetes ? *CDC National Center for Chronic Disease Prevention and Health Promotion*, 1–3. http://www.niddk.nih.gov/

Chen, B. K., Yang, Y. T., & Bennett, C. L. (2018). Why Biologics and Biosimilars Remain So Expensive: Despite Two Wins for Biosimilars, the Supreme Court's Recent Rulings do not Solve Fundamental Barriers to Competition. *Drugs*, *78*(17). https://doi.org/10.1007/s40265-018-1009-0

CHMP. (2018). *Semglee (insulin glargine)*. www.ema.europa.eu/contact

Deere, D. (2018). *Biosimilars and Healthcare Policy: What China Can Learn from the EU and US*. https://www.biopharminternational.com/view/biosimilars-and-healthcare-

policy-what-china-can-learn-eu-and-us

Derbyshire, M. (2017). Patent expiry dates for biologicals: 2016 update. *GaBI Journal*, *6*(1), 27–30. https://doi.org/10.5639/gabij.2017.0601.006

DHHS. (2020). National Diabetes Statistics Report, 2020. *National Diabetes Statistics Report*, 2. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html

Diabetes UK, IDF, Korea Biomedical Review, M. (2018). *Insulin glargine biosimilars launched in UK and South Korea / News / Biosimilars / Home - GaBI Online - Generics and Biosimilars Initiative*. https://www.gabionline.net/Biosimilars/News/Insulin-glargine-biosimilars-launched-in-UK-and-South-Korea

Dowlat, H. A., Kuhlmann, M. K., Khatami, H., & Ampudia-Blasco, F. J. (2016). Interchangeability among reference insulin analogues and their biosimilars: regulatory framework, study design and clinical implications. *Diabetes, Obesity and Metabolism*, *18*(8), 737–746. https://doi.org/10.1111/dom.12676

Edelman, S., Polonsky, W. H., & Parkin, C. G. (2014). Biosimilar insulins are coming: What they are, what you need to know. In *Current Medical Research and Opinion* (Vol. 30, Issue 11, pp. 2217–2222). Informa Healthcare. https://doi.org/10.1185/03007995.2014.952718

Eli Lilly. (2019). *Eli Lilly launches lower-priced insulin lispro / General / Biosimilars / Home - GaBI Online - Generics and Biosimilars Initiative*. https://www.gabionline.net/Biosimilars/General/Eli-Lilly-launches-lower-priced-insulin-lispro

Felman, A. (2018). *Insulin: Function and types*. https://www.medicalnewstoday.com/articles/323760#what-is-insulin

Fogel, L. E., & Hanna, P. H. (2014). *The Biosimilar Regulatory Pathway and the Patent Dance(1)*.

GaBI. (2020). *Biosimilars applications under review by EMA – January 2020 / General / Biosimilars / Home - GaBI Online - Generics and Biosimilars Initiative*. Generics & Biosimilars Inititaive. https://www.gabionline.net/Biosimilars/General/Biosimilars-applications-under-review-by-EMA-January-2021

GaBI Journal Editor. (2019). Patent expiry dates for biologicals: 2018 update. *Generics and Biosimilars Initiative Journal*, *8*(1), 24–31. https://doi.org/10.5639/gabij.2019.0801.003

Ghosh, S., Bose, S., Gowda, S., & Mukhopadhyay, P. (2019). Biosimilar insulins - What a clinician needs to know? In *Indian Journal of Endocrinology and Metabolism* (Vol. 23, Issue 4, pp. 400–406). Wolters Kluwer Medknow Publications. https://doi.org/10.4103/ijem.IJEM_180_19

Godman, B. (2021). *Report for the 2021 WHO Expert Committee on Selection and Use of Essential Medicines on recent insulin price trends in a sample of countries (including but not necessarily limited to low-and middle-income countries), exploring key issues and suggestions f*.

Gotham, D., Barber, M. J., & Hill, A. (2018). Production costs and potential prices for biosimilars of human insulin and insulin analogues. *BMJ Global Health*, *3*(5), e000850. https://doi.org/10.1136/bmjgh-2018-000850

Gregory, G. P., Carrington, C., Cheah, C. Y., Hawkes, E. A., Irving, I. M., Siderov, J., & Opat, S. (2020). A consensus statement on the use of biosimilar medicines in hematology in Australia. In *Asia-Pacific Journal of Clinical Oncology* (Vol. 16, Issue 4, pp. 211–221). Blackwell Publishing Ltd. https://doi.org/10.1111/ajco.13337

Health Hub. (2019). *Diabetes: Diet and Lifestyle*. https://www.healthhub.sg/live-healthy/886/diabetes-diet-and-lifestyle

Heinemann, L., Khatami, H., McKinnon, R., & Home, P. (2015). An overview of current regulatory requirements for approval of biosimilar insulins. In *Diabetes Technology and Therapeutics* (Vol. 17, Issue 7, pp. 510–526). Mary Ann Liebert Inc. https://doi.org/10.1089/dia.2014.0362

Home, P. (2015). Pharmacokinetics and pharmacodynamics of biosimilar insulins: Is clamp technology fit for purpose? In *Diabetes Care* (Vol. 38, Issue 12, pp. 2234–2236). American Diabetes Association Inc. https://doi.org/10.2337/dc15-1046

Hope Warshaw. (2014). *Rapid Acting / Fast Acting Insulin - How to Manage Your Diabetes | DSM*. https://www.diabetesselfmanagement.com/managing-diabetes/treatment-approaches/fast-acting-insulin/

Hu, J., Wang, M., & Zhao, Y. (2018a). SAR342434 - an insulin biosimilar for the treatment of type II diabetes. *Expert Opinion on Biological Therapy*, *18*(11), 1107–1112. https://doi.org/10.1080/14712598.2018.1533548

Hu, J., Wang, M., & Zhao, Y. (2018b). SAR342434 - an insulin biosimilar for the treatment of type II diabetes. *Expert Opinion on Biological Therapy*, *18*(11), 1107–1112.

https://doi.org/10.1080/14712598.2018.1533548

Hu, X., Zhang, L., Dong, C., Dong, Y., Jiang, J., & Gao, W. (2019). A Propensity Score Matched Comparison of Brand and Biosimilar Basal Insulin in Non-Critical Hospitalized Patients with Type 2 Diabetes Mellitus. *Advances in Therapy*, *36*(5). https://doi.org/10.1007/s12325-019-00922-9

Ilag, L. L., Deeg, M. A., Costigan, T., Hollander, P., Blevins, T. C., Edelman, S. V., Konrad, R. J., Ortmann, R. A., Pollom, R. K., Huster, W. J., Zielonka, J. S., & Prince, M. J. (2016). Evaluation of immunogenicity of <scp>LY2963016</scp> insulin glargine compared with <scp>L</scp> antus® insulin glargine in patients with type 1 or type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*, *18*(2), 159–168. https://doi.org/10.1111/dom.12584

James, J., Pollom, R. K., Hadjiyianni, I., Buchholz, G., & Reed, B. L. (2017). Biosimilar insulins: What do you need to know? *International Diabetes Nursing*, *14*(1), 32–35. https://doi.org/10.1080/20573316.2017.1340246

Jennifer Zahn. (2016). *Clinical Opportunities for Biosimilar Insulins*. http://www.diabetesincontrol.com/clinical-opportunities-for-biosimilar-insulins/

Joshua Cohen. (2020). *Will 2021 Be Another Break-Through Year For Biosimilars?* https://www.forbes.com/sites/joshuacohen/2020/12/03/will-2021-be-another-break-through-year-for-biosimilars/?sh=4482f69835d8

Kaduskar, P. (2016). Biosimilar insulins: An unavoidable option in South-East Asia. In *Indian Journal of Endocrinology and Metabolism* (Vol. 20, Issue 4, pp. 574–575).

Medknow Publications. https://doi.org/10.4103/2230-8210.183462

Kahn, C. R. (1985). The molecular mechanism of insulin action. In *Annual review of medicine* (Vol. 36, pp. 429–451). Annu Rev Med. https://doi.org/10.1146/annurev.me.36.020185.002241

Kalra, S., Azad Khan, A., Raza, S., Somasundaram, N., Shrestha, D., Latif, Z., Bajaj, S., Pathan, M. F., Sahay, R., & Mahtab, H. (2016). Biosimilar insulins: Informed choice for South Asia. In *Indian Journal of Endocrinology and Metabolism* (Vol. 20, Issue 1, pp. 5–8). Medknow Publications. https://doi.org/10.4103/2230-8210.164033

Kapitza, C., Nosek, L., Schmider, W., Teichert, L., Mukherjee, B., & Nowotny, I. (2020). A single-dose euglycaemic clamp study in two cohorts to compare the exposure of <scp>SAR341402</scp> (insulin aspart) Mix 70/30 with <scp>US</scp> - and <scp>European-</scp> approved versions of insulin aspart Mix 70/30 and <scp>SAR341402</scp> rapid-acting solution in subjects with type 1 diabetes. *Diabetes, Obesity and Metabolism*, dom.14260. https://doi.org/10.1111/dom.14260

Karena Yan, J. B. (2020). *Semglee, A Low-Cost Basal Insulin, Comes to the US | diaTribe*. https://diatribe.org/semglee-low-cost-basal-insulin-comes-us

Kim, A. P., & Bindler, R. J. (2016). The future of biosimilar insulins. In *Diabetes Spectrum* (Vol. 29, Issue 3, pp. 161–166). American Diabetes Association Inc. https://doi.org/10.2337/diaspect.29.3.161

Krentz, A. J., Weyer, C., & Hompesch, M. (2019). Pharmacokinetic and pharmacodynamic assessment of novel and biosimilar insulins. In *Translational Research Methods in*

Diabetes, Obesity, and Nonalcoholic Fatty Liver Disease: A Focus on Early Phase Clinical Drug Development (pp. 75–100). Springer International Publishing. https://doi.org/10.1007/978-3-030-11748-1_3

Kroon, L., Li, E., Segal, A., & Stevenson, J. (2015). Biosimilar insulins: Issues and considerations before clinical use. *ASHP Midyear Clinical Meeting and Exposition*.

Kuhlmann, M., & Schmidt, A. (2014). Production and manufacturing of biosimilar insulins: implications for patients, physicians, and health care systems. *Biosimilars*, *4*, 45. https://doi.org/10.2147/bs.s36043

Lamb, Y. N., & Syed, Y. Y. (2018). LY2963016 Insulin Glargine: A Review in Type 1 and 2 Diabetes. *BioDrugs*, *32*(1), 91–98. https://doi.org/10.1007/s40259-018-0259-4

Lecerf, J. M. (2016). Diabetes medication. *Pratiques En Nutrition*, *12*(45), 17–18. https://doi.org/10.1016/j.pranut.2015.12.005

LLano Andrea, Fisher Miles, M. G. (2017). *Biosimilar insulin: the current landscape - Practical DiabetesPractical Diabetes*. Practical Diabetes. https://www.practicaldiabetes.com/article/biosimilar-insulin-current-landscape/

LS Rotenstein, N. R. J. S. M. Y. K. C. (2012). Opportunities and Challenges for Biosimilars: what's on the horizon in the global insulin market? *Clin Diabetes*, *30*, 138–150.

Luis, Á., & De La Cuerda, R. (n.d.). *Biosimilares en España*.

Luis, Á., & De La Cuerda, R. (2016). *Biosimilares en España*.

M.D., S. G. (2019). *Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's steps*

on naming of biological medicines to balance competition and safety for patients receiving these products | FDA. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-steps-naming-biological-medicines-balance

Market, R. and. (2017). *Global Biosimilar Insulin Market Opportunity and Clinical Insight Outlook 2022*. https://www.researchandmarkets.com/reports/4077519/global-biosimilar-insulin-market-opportunity-and

Mayo Clinic. (2020). *Diabetes management: How lifestyle, daily routine affect blood sugar - Mayo Clinic*. https://www.mayoclinic.org/diseases-conditions/diabetes/in-depth/diabetes-management/art-20047963

Mayoclinic. (2019a). *Diabetes insipidus - Symptoms and causes - Mayo Clinic*. https://www.mayoclinic.org/diseases-conditions/diabetes-insipidus/symptoms-causes/syc-20351269

Mayoclinic. (2019b). *Insulin: Compare common options for insulin therapy - Mayo Clinic*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/diabetes/in-depth/insulin/art-20050970

McKinnon, R. A., Cook, M., Liauw, W., Marabani, M., Marschner, I. C., Packer, N. H., & Prins, J. B. (2018). Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review. In *BioDrugs* (Vol. 32, Issue 1, pp. 27–52). Springer International Publishing. https://doi.org/10.1007/s40259-017-0256-z

Momin, Z., Wijaya, C., Bernardo, P., & Newey, S. (2017). Biosimilars: Will Asia Go Big in

Adoption and Manufacturing? In *L.E.K. Consulting*. https://www.biosimilardevelopment.com/doc/will-asia-go-big-in-biosimilars-adoption-and-manufacturing-0001

Mönnig, V. E., Schloot, N., Hohberg, C., Wiesner, T., & Heinemann, L. (2016). Comparison of two insulin glargine formulations: Biosimilar vs. reference product. In *MMW-Fortschritte der Medizin* (Vol. 158, pp. 19–27). Springer Medizin. https://doi.org/10.1007/s15006-016-8609-y

Muthukumaran, K. (2019). *Medical Writing | Generics and biosimilars | Insulin biosimilars*. https://journal.emwa.org/generics-and-biosimilars/insulin-biosimilars/

NICE. (2020). *Diet and lifestyle | Information for the public | Type 2 diabetes in adults: management | Guidance | NICE*. https://www.nice.org.uk/guidance/ng28/ifp/chapter/diet-and-lifestyle

Nicole Corey. (2020). *Mylan and Biocon Announce U.S. Launch of Insulin Glargine Biosimilar - Big Molecule Watch*. https://www.bigmoleculewatch.com/2020/08/31/mylan-and-biocon-announce-us-launch-of-insulin-glargine-biosimilar/

Nicole Galan. (2021). *Diabetes statistics 2021 | The Checkup*. https://www.singlecare.com/blog/news/diabetes-statistics/

NIH. (2016). *Insulin, Medicines, & Other Diabetes Treatments*. National Institute of Diabetes and Deigestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/diabetes/overview/insulin-medicines-treatments

NIH. (2021). *Human Insulin Injection: MedlinePlus Drug Information*. https://medlineplus.gov/druginfo/meds/a682611.html

Of, H., Of, H., Information, P., & Information, P. (2008). Highlights of prescribing information. *Metabolism Clinical And Experimental*. www.fda.gov/medwatch.

Owens, D. R., & Bolli, G. B. (2008). Beyond the era of NPH insulin - Long-acting insulin analogs: Chemistry, comparative pharmacology, and clinical application. In *Diabetes Technology and Therapeutics* (Vol. 10, Issue 5, pp. 333–349). https://doi.org/10.1089/dia.2008.0023

Owens, David R., Landgraf, W., Schmidt, A., Bretzel, R. G., & Kuhlmann, M. K. (2012). The emergence of biosimilar insulin preparations-A cause for concern? In *Diabetes Technology and Therapeutics* (Vol. 14, Issue 11, pp. 989–996). Diabetes Technol Ther. https://doi.org/10.1089/dia.2012.0105

Perrin, C., Ewen, M., & Beran, D. (2017). The role of biosimilar manufacturers in improving access to insulin globally. In *The Lancet Diabetes and Endocrinology* (Vol. 5, Issue 8, p. 578). Lancet Publishing Group. https://doi.org/10.1016/S2213-8587(17)30218-8

pfizer. (2020). *What are Biosimilars and Biologics? | Pfizer Biosimilars*. https://www.pfizerbiosimilars.com/characteristics-of-biosimilars

Polimeni, G., Trifirò, G., Ingrasciotta, Y., & Caputi, A. P. (2015a). The advent of biosimilars for the treatment of diabetes: current status and future directions. *Acta Diabetologica*, *52*(3), 423–431. https://doi.org/10.1007/s00592-015-0771-7

Polimeni, G., Trifirò, G., Ingrasciotta, Y., & Caputi, A. P. (2015b). The advent of biosimilars

for the treatment of diabetes: current status and future directions. *Acta Diabetologica*, *52*(3), 423–431. https://doi.org/10.1007/s00592-015-0771-7

PubChem. (2021). *Insulin glargine | C267H404N72O78S6 - PubChem*. https://pubchem.ncbi.nlm.nih.gov/compound/Insulin-glargine#section=Entrez-Crosslinks

Raid M. Al-Ani. (2018). *Insulin plant (Costus igneus): Does it really work against diabetes? How it works?* https://www.researchgate.net/post/Insulin_plant_Costus_igneus_Does_it_really_work_against_diabetes_How_it_works

Rendell, M., Akturk, H. K., & Tella, S. H. (2013). Glargine safety, diabetes and cancer. *Expert Opinion on Drug Safety*, *12*(2), 247–263. https://doi.org/10.1517/14740338.2013.770469

Rosenstock, J., Hollander, P., Bhargava, A., Ilag, L. L., Pollom, R. K., Zielonka, J. S., Huster, W. J., & Prince, M. J. (2015). Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: A randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes, Obesity and Metabolism*, *17*(8), 734–741. https://doi.org/10.1111/dom.12482

Rotenstein, L. S., Ran, N., Shivers, J. P., Yarchoan, M., & Close, K. L. (2012). Opportunities and challenges for biosimilars: What's on the horizon in the global insulin market? *Clinical Diabetes*, *30*(4), 138–150. https://doi.org/10.2337/diaclin.30.4.138

Rubino, F., Moo, T. A., Rosen, D. J., Dakin, G. F., & Pomp, A. (2009). Diabetes surgery: a new approach to an old disease. In *Diabetes care: Vol. 32 Suppl 2* (Issue suppl 2, pp. S368–S372). American Diabetes Association. https://doi.org/10.2337/dc09-s341

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., & Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, *157*. https://doi.org/10.1016/j.diabres.2019.107843

Sataloff, R. T., Johns, M. M., & Kost, K. M. (2016). *Biosimilar insulin: the current landscape*. https://wileymicrositebuilder.com/practicaldiabetes/wp-content/uploads/sites/29/2017/03/Rev-Llano-lsw.pdf

Schaffer, R. (2020). *FDA publishes final guidance to streamline biosimilar insulin development*. https://www.healio.com/news/endocrinology/20200220/fda-publishes-final-guidance-to-streamline-biosimilar-insulin-development

Sean Mc Gowan. (2021). *The US biosimilar market: Predictions for 2021* -. https://pharmaphorum.com/views-and-analysis/biosimilar-market-predictions-2021/

Sinha, M. S. (2020). *Metformin: Side Effects, Dosage & Uses - Drugs.com*. https://www.drugs.com/metformin.html

Stanton Mehr. (2020). *Lannett Seeks to Enter Biosimilar Insulin Market, File 351(k) Application in 2022* |. https://biosimilarsrr.com/2020/06/15/new-entrant-into-insulin-

market-wants-to-file-as-biosimilar-in-2022/

State, D., & Organisations, T. (2012). *Insulin & Diabetes*. *24*, 1–6. https://www.diabetes.co.uk/body/insulin.html

The Wellness Network. (2019). *Lifestyle Management for Diabetes Patients - The Wellness Network*. https://www.thewellnessnetwork.net/health-news-and-insights/blog/lifestyle-management-diabetes/

Thiruvengadam, M., Venkidasamy, B., Chung, I.-M., Thirupathi, P., & Subramanian, U. (2020). Biosimilars: A novel perspective in diabetes therapy. *Asian Pacific Journal of Tropical Medicine*, *13*(7), 288. https://doi.org/10.4103/1995-7645.285827

Tsuruta, L. R., Lopes dos Santos, M., & Moro, A. M. (2015). Biosimilars advancements: Moving on to the future. *Biotechnology Progress*, *31*(5), 1139–1149. https://doi.org/10.1002/btpr.2066

UIC. (2018). *Insulin glargine: Side Effects, Dosage, Uses, and More*. Healthline. https://www.healthline.com/health/insulin-glargine-injectable-solution#about

US. Food & Drug Administration. (2020). *Insulin Gains New Pathway to Increased Competition | FDA*. FDA. https://www.fda.gov/news-events/press-announcements/insulin-gains-new-pathway-increased-competition

Watson, S. (2016). *Long-Acting Insulin: How it Works*. Healthline. https://www.healthline.com/health/diabetes/long-acting-insulin

WebMD. (2019). *Diabetes Treatments and How it is Diagnosed*. WebMD. https://www.webmd.com/diabetes/guide/understanding-diabetes-detection-treatment

WebMD. (2021a). *Insulin Glargine Subcutaneous: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD*. https://www.webmd.com/drugs/2/drug-20805/insulin-glargine-subcutaneous/details

WebMD. (2021b). *Pioglitazone Oral: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD*. https://www.webmd.com/drugs/2/drug-17406/pioglitazone-oral/details

White, J., & Goldman, J. (2019). Biosimilar and Follow-on Insulin: The Ins, Outs, and Interchangeability. In *Journal of Pharmacy Technology* (Vol. 35, Issue 1, pp. 25–35). SAGE Publications Inc. https://doi.org/10.1177/8755122518802268

Windisch, J. (2015). Biosimilars versus Erstanbieterbiologika: Gemeinsamkeiten und Unterschiede von der Entwicklung bis zur Zulassung. *Zeitschrift Fur Rheumatologie*, *74*(8), 672–681. https://doi.org/10.1007/s00393-014-1486-9

Winston & strawn. (2021). *What Is the Patent Dance? | Winston & Strawn Law Glossary*. https://www.winston.com/en/legal-glossary/patent-dance.html

Wire, F. (2021). *Pandemic Fallout to Delay US Drug Price Reform, Biosimilars Uptake*. https://www.fitchratings.com/research/corporate-finance/pandemic-fallout-to-delay-us-drug-price-reform-biosimilars-uptake-18-02-2021

Yamada, T., Kamata, R., Ishinohachi, K., Shojima, N., Ananiadou, S., Nom, H., Yamauchi, T., & Kadowaki, T. (2018). Biosimilar vs originator insulins: Systematic review and meta-analysis. *Diabetes, Obesity and Metabolism*, *20*(7), 1787–1792. https://doi.org/10.1111/dom.13291