



Review Article

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Biosimilars: A novel perspective in diabetes therapy

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ABSTRACT

Diabetes mellitus, an endocrine disorder, has a wider reach among most of the world population. The incidence of diabetes is high not only among adults but wider-age groups are also becoming susceptible to this disease because of modified food habits and lifestyle changes that are alien to the physiological system. The control of blood glucose level would be the prime focus of all the therapeutic targets, which is achieved through drugs, modified lifestyle, and paleo-based diets. To find a solution to these problems, earlier humans have revolutionized the science with the discovery of insulin from the porcine pancreatic crude extract. Later, developments have been made with artificial recombinant insulin and even insulin analogs that would mimic the physiological basal insulin in controlling the blood sugar levels. Various factors such as cost and logistics for quality delivery to the end-user at various corners of the world have impeded the reach of the original product. Hence, biosimilar insulins that are original insulin analogs were designed to execute similar physiological functions. In the current situation, the use of biosimilars has been approved in various clinical conditions that are very promising in its functions. In the present review, the various developmental phases of biosimilar preparations and the regulations enforced ensuring a quality product in the market through the Food and Drug Administration and the European Medicines Agency have been discussed.

KEYWORDS: Diabetes mellitus; Biosimilars; Insulin; Therapeutics

1. Introduction

Biosimilar insulins are based on the original recombinant DNA technology-based proteins which are used to treat diabetes in a

way similar to the original insulin products. Biosimilars or here biosimilar insulin is made by technology that has their patents expired and is not the same as the original product[1]. Biosimilars have the same amino acid sequence as the original recombinant technology product but differ from generic drugs in the type of biological system[2], different methods of the manufacturing process, and purification strategies[3,4]. Hence, biosimilars may not have the same 3-dimensional structure as the original product and also differ in the size and folding of the native protein produced. Some of the original insulin analogs are -insulin lispro [Humalog (Lilly)], insulin aspart (NovoLog, the brand name in the United States), NovoRapid (the brand name outside the United States; Novo Nordisk), and insulin glargine [Lantus (Sanofi)][5]. The patents of these insulin analogs may be impeding to replicating the exact sequence of the recombinant insulin.

According to the European Medicines Agency (EMA), biosimilars are copy versions of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety, and authorization is based on a comprehensive comparability exercise to the innovator product[6,7]. The manufacturing of recombinant drug products includes various strategies that may or may not influence the quality and efficacy of the product. Some of the factors that influence the end product include the expression system, purification processes, formation of

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protein aggregates, post-translational modifications[8,9], impurities in the growth media and stabilizers used[10] for the final pharmaceutical formulations. The extent of changes that occurred in the protein products to be used as drugs and the comprehensive information on the probable immunogenicity elicited by these drug products cannot be elucidated with the existing analytical methodologies[11]. Hence, sophisticated technologies and laboratory set up are required to study these functional aspects at the level of development and a standardization methodology to interpret the clinical study results is need of hour to evaluate the safety of biopharmaceuticals (Figure 1).

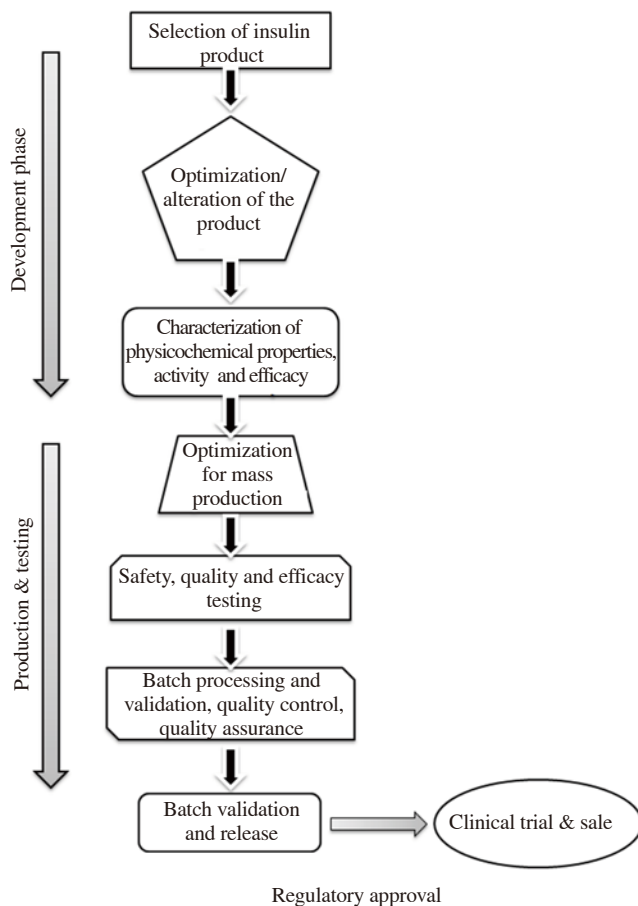


Figure 1. Biosimilars production.

2. Biosimilars: clinical and safety challenges

Till today, the existing biosimilars cannot completely copy the original processes of insulin analogs. Moreover, the difference in the amino acid composition may alter the product exposure to temperature and humidity during the production processes, which may influence the efficacy of the product in terms of physical stability. Thus the dosage of biosimilars to be administered may differ from that of the original analogs and hence the quantity gets compromised[11]. The amino acid composition of the biosimilars may alter the product exposure to temperature and humidity and

hence the quality and the quantity administered to the patients. This would affect the control of glucose levels in the body and would not have a uniform effect on the disease[8]. The routes of intake of such products and the type of administration devices into the body would also be factors to be considered in the designing of biosimilars. Most importantly, the presence of bacterial endotoxins from the bacterial expression systems, or the difference in the peptide sequence and the presence of denatured impurities while using other expression systems[12,13] would elicit an immune response in the patients[14].

Biosimilar insulins, for instance, glargine, produced using bacterial expression system, *Escherichia coli* having a difference in the codon usage produce inclusion bodies, which would be difficult to solubilize, and hence various additional steps were carried out to get the protein into solution. Similarly, in the case of usage of *Saccharomyces cerevisiae*, the post-translational modification-introduced proteins would release into the solution making it easier to purify[11]. Cleavage of pre-pro-insulin to active protein and the introduction of additional steps to join two different chain of insulin complicate the production steps. Hence, it was necessary to employ high-end equipment types of downstream processing steps such as ion exchange, reversed-phase and size-exclusion chromatography[15] to generate the biosimilar insulins.

The manufacture of insulin glargine from Lantus® (sanofi-aventis, Paris, France) as biosimilars by Biocon Ltd, Wockhardt Ltd in India and by Gan and Lee in China is a classic example of biosimilar insulin. Biocon Ltd. used *Pichia pastoris* expression system to manufacture insulin glargine as Basalog® whereas the Chinese used *Escherichia coli* to manufacture their product, Basalin®. All these products, including Glaritus® by Wockhardt Ltd., have insulin-related substances in them to the required maximum level of <1.5% as prescribed for the European market[16,17]. Concerning the pharmacovigilance in ensuring the safety of biosimilars, the generation of adverse events due to the insulin-related substances is under surveillance even in the post-marketing period. Such regulatory monitoring includes the tolerability of the product in the patients and if the casualty occurs as adverse events.

3. Regulatory aspects of biosimilars

Recombinant products to be considered as biosimilar have to follow all the guidelines outlined by EMA. For insulin biosimilars, the data concerning the immunogenicity of biosimilars generated during subcutaneous administration in clinical studies is required for 12 months before market authorization. Another clinical study to demonstrate compatibility has to be completed along with pharmacokinetic study by comparing it with an innovator product in case of type 1 diabetes mellitus. The study reported that a positive

time-response action profile of hypoglycemic response which was further supported by a double-blind, crossover, hyperinsulinemic, euglycemic clamp study[18]. When the pharmacokinetic data and pharmacodynamic data from the biosimilars are comparable with the innovator product, clinical trial efficiency studies for the biosimilars are not required[19,20].

The discovery that insulins from bovine and porcine pancreata can be used to treat diabetes has revolutionized the diabetes treatment[21]. But these insulins were obtained impure, allergic to the patients and were not efficient in maintaining the blood glucose levels due to unpredictable antibodies[22,23]. The dosage of such crude insulins varied and caused indeterminable effects. Since insulin secreted from the beta cells of the pancreas, the basal insulin, could not sustain the blood-glucose levels for various reasons like insufficient levels, unresponsive cells to glucose levels, scientists worked on creating long-acting insulin analog using recombinant DNA technology to cater the following criteria[21]: (a) 24 hour-long duration of insulin action; (b) A steady effect without extremities; (c) Relatively uniform dosage levels; (d) Effectively control the plasma glucose level; (e) To mimic the endogenous insulin in the release with the same safety levels and perform without having any acute side effects. Based on these criteria the following seven biosimilars examples are discussed.

4. Biosimilar insulin

4.1. Glargine

Insulin glargine was designed using recombinant DNA technology[21] by altering the B-chain of native insulin sequence with the introduction of arginines and replacing the asparagine with glycine to make the glargine insulin molecule. This synthesized molecule is acidic in nature that results in precipitation at neutral pH at the subcutaneous site that ensures a sustained release of insulin for long-lasting action[24,25]. This molecule satisfied the criteria for longer action, less variability in the batches produced and no microvascular complications and diabetic retinopathy[26] that arises in crystalline neutral protamine Hagedorn insulin[27–30]. Some limitations about the functioning of insulin glargine have been observed with glycemic clamp technique[31]. It was found that the acidic nature of the molecule made it impossible to mix with other insulins. The action profile of glargine is less than 24 h and need an additional dosage in a day for type 1 diabetes mellitus patients[32]. Also, variability in its actions within individual patients was observed. Controversies are surrounding its usage on its role in causing cancer due to its mitogenic effects[33]. Insulin glargine binds to the insulin-like growth factor-1 receptor[34] and has upregulated the proliferation of both malignant and normal cell lines in addition

to upregulating the anti-apoptotic activities in such cell lines[35,36]. Ultimately, extensive clinical studies have concluded no implicating evidence against glargine in causing cancer[37–40].

4.2. Detemir

Insulin detemir was produced as an alternative to glargine with the threonine in B-chain of the molecule being replaced with a 14-carbon fatty acid-myristic acid to enhance the binding of insulin to albumin to extend the action of duration at all levels[41]. It is also stable for 24 h and has less individual variability compared to its glargine counterpart[42]. But the dosage levels deter its usage as an alternative to glargine insulin.

4.3. Insulin degludec

Degludec, the Novo Nordisk (Bagsværd, Denmark) has manufactured the long acting-insulin analog, wherein threonine at position 30 was replaced with 16-mer fatty acid and addition of lysine at position 29 of B-chain through a glutamic acid linker[43,44]. This molecule, when injected subcutaneously, gets converted into a multi-hexamer and its action was found increased for more than 24 h and stable with less variations observed between individuals. This molecule was tested for safety and passed through phase II of clinical studies in type 1 and 2 diabetes subjects with good control of glucose and less hypoglycemia[45,46]. Its use in Japan and Europe has been approved but is not approved in the US for its unsafe concern over cardiovascular complications[47].

4.4. LY2605541

Another insulin analog was developed by Eli Lilly to overcome the drawback of non-physiological glucose homeostasis. The modifications made by attaching a 20-kDa PEG to lysine 28 of insulin lispro (LY2605541) through its ϵ -amino acid and urethane bond[44]. Since PEG has a large hydrodynamic radius, its absorption is slow and hence greater duration of insulin action is ensured[44]. It was better than insulin glargine in its duration of action and has reduced patient variability[48,49]. Phase II clinical trials were promising with the parameters tested for its efficacy to be used as biosimilars in type 1 and 2 diabetes and their co-morbidities being explored.

4.5. SAR342432

SAR342432 is obtained from the reference insulin lispro, which is advocated for use in patients with type 1 and type 2 diabetes[50]. SAR342432 is under phase III clinical trials and

has shown satisfactory efficacy and long-term safety in terms of immunogenicity about its innovator product lispro[51]. Hence, it has the potential to reduce the treatment cost and would reach the patients widely. This biosimilar has been approved for its use in the European Union after confirming the similarity in pharmacodynamics and pharmacokinetics between SAR342434 and its reference lispro[10].

4.6. BIOD–basal insulin

The modified insulin glargine, BIOD-adjustable basal, and BIOD-smart basal which has insulin glargine along with glucose oxidase and peroxidase would convert glucose to gluconic acid that lowers pH to let insulin glargine available for circulation[21,52].

4.7. Smart insulin

As a futuristic approach, it was hypothesized that insulin would be modified to reversibly bound to glucose binding molecules. When the molecule encounters glucose, it releases the bound insulin and hence it would have a greater sense of insulin action proportional to the amount of glucose in the plasma thereby avoiding hypoglycemic conditions[53,54].

5. Delivery devices

Since the accuracy and dosage variability may influence the outcome of the biosimilar action, the devices delivering biosimilar insulin was partially replicated from the innovator products[55]. ClickSTAR®, SoloSTAR@[56] pens and Kwikpens@[57] are very well known in the biosimilar industry, and all of them have met DIN EN ISO 11608-1:2 000 requirements. These pen-type applicators have been tested for their coefficient of variation in the dosage levels and found to be better than the traditional insulin vials and syringes[58]. Patients in need of multiple insulin doses per day require a sophisticated set up for storage of insulin should also take into consideration. Moreover, the geographical location for temperature and storage, patients' financial conditions and occupation should also be under concern while improving the technology of biosimilar delivery devices.

6. Adverse events

The quality of biosimilars purified from recombinant DNA technology-based origins having bacterial or other microbial culture upstream would have some unwanted proteins as 'impurities'.

Hence, it induces adverse events in patients who have shifted from the original innovator insulin to biosimilars. One such adverse effect has been reported with complaints of difficulty in breathing, wheezing, congestion in the chest, headache and palpitations. Detailed investigations reported the shift from insulin glargine to its biosimilars and hence there were such effects. Besides, the abnormal basophil degranulation at the site of injection using one particular vial of the biosimilar in the same batch used has been identified as the root cause of the problem. Moreover, the batch-to-batch variability observed here has some contaminating agents that have triggered the hypersensitivity reaction. Although such adversities have been observed, those reports did not reveal the details of the biosimilars or antibodies against this insulin were observed. Such generalization to implicate biosimilars would impede the progression in the biosimilars arena but would give sufficient guidance, caution, and responsibility to give a better product[23,59].

7. The regulatory pathway for biosimilar development and approval according to the Food and Drug Administration (FDA) and EMA guidelines

FDA and EMA have regulated criteria for approval of biosimilars. FDA mandates 505(b)(2) pathway based on physicochemical characterization[60], PKPD (pharmacokinetics and pharmacodynamics) clamp studies and efficacy of the drugs based on HbA1c standard and safety with regards to immunogenicity. EMA requires the product to be extensively *in vitro* characterized by clamp studies and immunogenicity tested for 12 months. To determine a product to be biosimilar, it must demonstrate the following in comparison with the innovator product.

The biosimilar must have similar primary, secondary, tertiary and quaternary structure, post-translational modifications and biological activity alike the innovator product. The linkers or biological inactive components added as a part of the biosimilar must prove inert. Structurally, the biosimilars must be similar to the original product and must be tested in different lots to test the batch-to-batch variability during the manufacturing of the biosimilars. The *in vitro* release of insulin and the stability of the product tested must be compared with the reference product[61].

In vitro studies such as affinity and insulin- and IGF-1 binding assays need to be performed in terms of the concentration-response relationship. The sensitivity, specificity and minor differences arising out of the testing must be taken into consideration during animal studies[60]. When the structural, functional and animal toxicity studies were comparable with the innovator product, nonclinical safety pharmacological studies for reproductive, toxicity and carcinogenic studies are not warranted[62].

The gold standard[63] for testing the insulin action measurement is euglycemic or iso glycaemic hyperinsulinaemic clamp technique. This technique involves the constant insulin infusion above the physiological level, while the glucose infused to maintain a euglycemic range as 90 mg/dL. The effects of exogenous insulin were obtained by measuring the glucose infusion rate versus time curve area[61]. It was suggested that the experiment has been repeated for various doses of insulin before the final report has been submitted for approval.

The potential of the biosimilars tested for its efficacy in reducing the HbA1c has also been considered as the control of glycaemia[64]. FDA does require this and consider the product is acting similar to its reference product. These tests must be performed with other drugs for comparison, and such test results must obtain similar or comparatively better glycemic control. However, EMA does not require this test and rely on the clamp studies for the approval of the product. It requires only the biosimilars to demonstrate similar PK and PD profiles and the tests must be repeated at an interval of days or weeks.

EMA mandates the presence of patients with type 1 diabetes for this study and must be performed in subjects for at least 12 months, along with a 6-month comparative phase[65]. The study outcome must detail the incidence of antibodies to the test product in comparison with the reference product. If the presence of antibodies to the product in the test is more, then the impact on glycemic control, insulin dosage required after being neutralized by the antibodies, safety and other hypersensitivity reaction must be investigated. In addition, the post-marketing survey of the immunogenicity has also been suggested for the safety of the patients.

8. Perspectives

The perspective of patients falling in the categories of type 1 and type 2 diabetes differ when considering replacing the original insulin product to the recently developed insulin biosimilar[65]. The cost of the insulin analogs developed as biosimilars would be cheaper compared with the original insulin. Still, the usage of biosimilars has some undesired immunogenicity that affects the quality of the product and the trust of the patients. These facts concerned fear surrounding such products would affect the usability in the case of patients with type 1 diabetes. On the contrary, patients with type 2 diabetes would consider using biosimilar insulin as they are concerned about the cost of insulin as one of the factors in controlling their medical expenditure apart from the medications involved for other comorbidities. Hence, developing the biosimilars for insulin would largely depend on the type of end-user having diabetes which would be a factor in controlling the disease.

Conflicts of interest statement

The authors declare there is no conflict of interest.

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Authors' contributions

U.S, B.V, P.T and M.T conceived the review idea and focus, drafted the article, critically revised the article. I.M was involved in the references collection, drafting the article. All authors have contributed to the final manuscript revision.

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