

Biosimilar insulin: the current landscape

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Abstract

The first insulin biosimilar, Abasaglar, is now available in the UK and several more are in development. Biosimilars are manufactured copies of previously approved biopharmaceuticals no longer under patent protection. They are not identical versions of their reference product due to the complexity of their production and resultant protein product.

The present article reviews the current biosimilar landscape including manufacture, regulatory requirements, safety and prescribing issues. Abasaglar is used to illustrate the process of biosimilar development and approval. Copyright © 2017 John Wiley & Sons.

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Key words

biosimilars; insulin glargine; regulatory requirements; diabetes

Introduction

Since insulin was isolated in 1922, its production has continued to evolve, more recently with the ‘incremental innovation’¹ of insulin analogues with improved pharmacodynamic and pharmacokinetic profiles. The approval of Abasaglar, biosimilar glargine insulin, marks the latest development in insulin therapy.²

Biosimilars are manufactured copies of previously approved biopharmaceuticals which are no longer under patent. They are produced in the same way, have similar actions to their reference product, but are not identical due to the complexity of the numerous steps in their production and of the resultant protein molecules.

There are several biosimilar products available across a number of clinical indications, including erythropoietin, somatotropin, infliximab, and filgrastim.

Abasaglar (insulin glargine) is the first biosimilar insulin to market, with others pending.

At present, the insulin market is dominated by a few pharmaceutical companies. While generic drugs offer bigger savings (approximately 80% reduction compared to the reference drug) biosimilars are estimated to cost 20–30% less than their originator drug.³ Therefore, they offer lower cost alternatives with the potential to expand market competition and increase access to treatment. A recent report estimated that health care systems in the United States (US) and the European Union (EU) could save up to \$110 billion by using biosimilars.⁴

Biosimilars vs generic drugs: why is there no generic insulin?

Most drugs are relatively small, simple chemical molecules. Biosimilars are larger complex molecules, with primary, secondary, tertiary and quaternary structures.

The chemical structure of inorganic drugs allows their production to be replicated to produce generic versions, which are identical copies of the reference drug with identical actions, and pharmacodynamic and pharmacokinetic profiles.

Biological drugs are a product of living systems. The inherent variability of biologics and relatively minor changes in the manufacturing methods, excipients or the presence of impurities can result in significant changes in the structure and biological action of the drug.⁵ As such, the final biological product will not be completely identical and is termed biosimilar.^{6,7}

Manufacture of insulin

The production of biological medicines utilises recombinant DNA technology. Pharmaceutical companies are not required to disclose full manufacturing details following patent expiry and so the methods used between companies are likely to differ with the resultant variability in the final product.

DNA is isolated from human cells and modified before insertion into an appropriate vector and expression system such as *Escherichia coli* or *Saccharomyces cerevisiae*. The expressed product is then recovered and refolded to form a pro-insulin-like molecule before C-peptide is

removed and the final product purified and processed for storage.⁸

There are many steps in the production process where impurities may be introduced and complex testing is required to assure purity and stability. The production process is very sensitive to physical conditions such as light and temperature and, as such, subtle changes in the manufacturing process can result in significant changes in the end product which can in turn affect its biological action.^{5,8}

Regulatory requirements

While the approval of a generic drug requires only demonstration of pharmaceutical and bio-equivalence, regulatory requirements for biosimilars are more complex. The main objective of the approval process is to establish comparability with its reference product in terms of safety, purity and potency. In 2005, the European Medicines Agency (EMA) became the first regulatory body to set out a framework for the approval of biosimilars and produced overarching guidelines^{9–11} as well as those specific to insulin biosimilars.¹² The US followed shortly after and released its final guidance on the development of biosimilars in 2015.^{13,14}

Applications for marketing authorisation of biosimilars can only be submitted once the exclusivity period for the reference medicine has expired. In the EU, the approval occurs via the centralised procedure¹⁵ and begins with full structural and functional characterisation of the biosimilar.^{10,12} Details of the manufacturing process and quality control must be provided. Thereafter, head-to-head comparability studies demonstrating comparable pharmacokinetic and pharmacodynamic profiles are required to show that any differences between biosimilars and the reference drug are not clinically significant.^{10,12} For insulins, the use of cross-over, preferably double-blind, insulin clamp studies is recommended by the EMA.¹²

Safety studies focus on immunogenicity, an important safety concern in the use of biological drugs. Any biological product can induce the formation of antibodies following administration with subsequent

effects on glucose control and insulin dose as well as more serious adverse events such as allergic reactions. Antibody testing strategies should be described and the primary outcome measure should be the incidence of antibodies to the biosimilar and its reference product. If detected, the effects of such antibodies should also be investigated.¹²

Unexpected adverse events are more likely with biological drugs than with generic chemical drugs, making postmarketing surveillance crucial. Detailed plans for pharmacovigilance monitoring in the form of an EU risk management plan must be submitted.¹⁰

In the UK, newly licensed drugs must also be approved by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). NICE considers biosimilar medicines with their reference product in the form of a Multiple Technology Appraisal and produces an evidence summary where considered necessary.¹⁶

The SMC recently updated their policy for biosimilar medicines. Full submissions are not required if the reference product has previously been accepted for the same indication. However, if a product is expected to have an impact on NHS Scotland resources, a full submission may be requested.¹⁷

The US Food and Drug Administration (FDA) has several documents providing guidance for biosimilar submissions.^{13,14,18} As in the EU, biosimilarity must be demonstrated using analytical, animal and clinical studies. Safety studies focusing on immunogenicity are also needed.

For historical reasons, insulin analogues have been approved and regulated by the FDA as chemical drugs rather than a biological product.¹⁹ This means they are not approved by the Public Health Service (PHS) Act normally used for biological products, but via the New Drug Applications pathway under Section 505 of the Food, Drug and Cosmetic Act. Biosimilar products with reference products approved under 351(k) of the PHS Act are generally licensed under the Biosimilar Price Competition and

Innovation Act of 2009 (BPCI Act).^{18,20} However, since insulin is not considered to be a biological product, insulin biosimilars must be approved under the abbreviated new drug 505(b) (2) pathway.¹⁹ The FDA plans to eliminate this pathway in 2020 when all biosimilar drugs will be licensed under the BPCI Act.

Prescribing: interchangeability and substitution

Interchangeability is an important safety aspect as it can result in the automatic substitution of a prescribed biological with an equivalent biosimilar without the prescriber's knowledge. A drug can be considered as interchangeable with its reference medicine if biosimilarity has been demonstrated and the biosimilar produces the same clinical effect in any given patient. There should be no safety risk or diminished efficacy if the reference medicine is switched with the biosimilar.²¹

The EMA has left the decision to designate a biosimilar as interchangeable to individual countries.²² The MHRA advises against automatic substitution of a biosimilar for the original or reference product. Unlike chemical drugs which are commonly prescribed by generic name, biosimilars must be prescribed by brand name and batch numbers documented to facilitate pharmacovigilance.²³

In the US, further approval is needed in order to grant a biosimilar with interchangeable status. Several states have also introduced legislation to guide biosimilar substitution, allowing the prescriber to prevent substitution by documenting this decision on the prescription and requiring the pharmacist to inform the patient and prescriber of the substitution.²¹ As the FDA currently approves insulin biosimilars as new chemical entities rather than through the BPCI Act, the issues surrounding interchangeability in this group remain a grey area.

Biosimilar licensing in paediatrics

Prior to 2007, clinical trials were rarely done in children due to ethical and practical reasons. Since then, unless granted a deferral by the EMA, all new drug applications

are required to provide paediatric data to support their safety and efficacy in this population.²⁴

This is not the case in the biosimilar approval process where the underlying objective is to demonstrate comparability. The efficacy and safety of the reference product, Lantus, have been established in the paediatric population,²⁵ and therefore there are no published clinical studies comparing Abasaglar with Lantus in children and young people. In the US, paediatric assessment is not required if a biosimilar has been designated as interchangeable with its reference product.¹⁸

Insulin glargine biosimilar

Abasaglar (LY2963016) is an insulin glargine biosimilar with an identical amino acid sequence to its reference product, Lantus.⁸ It was granted marketing authorisation by the EMA through the biosimilar pathway in 2014 and launched in the UK in September 2015.²⁶ The situation was different in the US where LY2963016, known as Basaglar, was granted final approval in December 2015.²⁷ As Lantus was approved as a new chemical entity (NCE) in 2000 rather than a biological product, Abasaglar was licensed via the FDA's abbreviated new drug application pathway, 505(b) (2),¹⁹ and not the 351(k) biosimilar pathway. The US has additional legislation relating to biosimilar interchangeability, but it is not yet clear how this will relate to Abasaglar as it is not considered a biosimilar but a follow-on product.²⁷

Five phase I studies and two phase III studies were undertaken to demonstrate biosimilarity at several dose levels.⁸ Three phase I studies using healthy volunteers and patients with type 1 diabetes demonstrated comparable bioavailability, pharmacokinetic and pharmacodynamic properties for Abasaglar and Lantus.^{28–30}

ELEMENT 1 and ELEMENT 2 were randomised controlled phase III trials used to demonstrate the comparably efficacy and safety of LY2963016 with Lantus in patients with type 1 and type 2 diabetes.^{31,32} The primary endpoint in each was the HbA_{1c} change from baseline to 24 weeks following treatment with

Date	Event
2000	Approval of Lantus by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA)
2011–2015	Phase I–III trials of LY2963016 to demonstrate safety and comparability with Lantus
2014	Marketing authorisation granted from the EMA. Tentative FDA approval pending resolution of patent infringement lawsuit between Sanofi and Eli Lilly
2015	Lantus patent expiry. FDA approval following settlement of lawsuit. Absaglar launched in the European Union
2016	Abasaglar launch expected in the United States

Table 1. Timescale of events in the approval of Abasaglar

LY2963016 or Lantus. Non-inferiority of LY2963016 with Lantus was demonstrated with both treatment groups having similar decreases in HbA_{1c} at 24 weeks (ELEMENT 1: -0.35 vs -0.46% [95% confidence interval -0.002 to 0.219], $p > 0.05$; and ELEMENT 2: -1.29 vs -1.34% [95% confidence interval -0.070 to 0.175], $p > 0.05$).^{31,32} Both LY2963016 and Lantus had similar safety and immunogenicity profiles.⁸

Abasaglar is available in the same strength as Lantus (100 units/ml) and at the time of writing is priced at £35.28 for five cartridges vs £41.50.³³ The annual cost for the use of 20 units per day of Abasaglar or Lantus is estimated to be £343.39 and £403.93 respectively,³³ representing a cost saving of 15%.

Current advice states that Abasaglar should only be initiated in patients new to insulin glargine or in those who require a review of their therapy due to poor control; those who are stable on Lantus should not be switched to Abasaglar as their effects may not be identical.³⁴

(The timescale of events in the approval of Abasaglar is outlined in Table 1.)

Upcoming biosimilars

There are several biosimilar insulins currently under development.

MK-1293 is another insulin glargine biosimilar from Merck which was recently demonstrated to be non-inferior to Lantus in phase III trials in patients with type 1 and type 2 diabetes mellitus,³⁵ and which

has been filed for approval with the FDA.

SAR34234 is an insulin lispro biosimilar from Sanofi currently in phase III trials.³⁶

Basalog, Biocon's insulin glargine biosimilar, has recently been approved in Japan and there are plans to apply to the FDA for approval.³⁷

Conclusion

In recent years, regulatory authorities have finalised guidance for the regulatory approval of biosimilars following the approval of the first insulin glargine biosimilar in 2015. It is expected that several more insulin biosimilars will make their way to market in the future.

Although development and regulatory costs are higher than for generic drugs, they represent a less expensive option for therapy and are seen as an opportunity to create competition with further potential for cost savings and access to treatment for more patients.

However, their acceptability and use by clinicians and patients may be limited by lack of experience and concerns about long-term safety. This confusion is likely to be compounded with the availability of other biosimilars in the coming years and in the presence of an ever-increasing choice of insulins now available to prescribers.

NICE has clarified the role of biosimilars in the treatment of diabetes and many health providers have drawn up biosimilar prescribing guidance in order to address the uncertainty regarding their use

Key points

- Biosimilars are manufactured copies of previously approved biopharmaceuticals with similar actions, more expensive than generics but cheaper than their reference product thus offering a lower cost alternative
- Abasaglar is the first insulin biosimilar to be approved in the EU and is promoted as an insulin glargine alternative
- There remains uncertainty about the role of insulin biosimilars and concerns about interchangeability and substitution with the potential to impact on patient safety

and avoid the inappropriate transfer of patients onto biosimilars.

The economic and clinical impact of biosimilar insulins over the coming years therefore remains to be seen.

Declaration of interests

Dr Llano has no conflicts of interest.

Professor Fisher has received payment for lecturing and advisory boards from Eli Lilly, MSD, Novo Nordisk, and Sanofi.

Professor McKay has received payment for lecturing and advisory boards from Eli Lilly, MSD, Novo Nordisk and Sanofi.

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