Biosimilar insulins: opportunities and challenges

Stephen Gough

Following the isolation of insulin in 1922 and the commercial production of animal insulins, a number of key developments have taken place over the last 90 years, including the publication of the amino acid sequence of insulin in 1951 by Frederick Sanger and the subsequent publication of its three-dimensional structure in 1969 by Dorothy Hodgkin. These undoubtedly paved the way for the development and application of recombinant DNA technology for the production of human and then analogue insulins, such that we now have a range of short-acting, long-acting and mixture insulins for our patients with diabetes. During this time, the scientific progress of researchers in developing ever more effective and convenient insulins has been adequately matched by the implementation of high standards of quality control and a rigorous process of regulatory review. In the same way that technological advances in insulin production will allow the production of biosimilar insulins, it is crucial that these medicines are subject to the same standards of approval, to ensure that they exhibit similar efficacy and safety profiles to those of the original insulin product.

As the expiry date for the patent of a number of insulins rapidly approaches – including, for example, insulin glargine (November 2014 in Europe and February 2015 in the USA) – much interest is emerging around the development of second generation copies of the original therapeutic. The expectation, by many, is that an opportunity exists to produce a similar product at a lower price which will introduce greater competition in the market place, and which ultimately will be of benefit to health care providers, the payers and of course our patients. While to some extent this may be the case, it is important to consider not only the opportunities but also the challenges and dangers that we may face, when companies attempt to produce and market a ‘copy-cat’ biological product, or biosimilar insulin.

What is a biosimilar insulin?

A biosimilar has been defined as a copy version of an already authorised biological medicinal product with demonstrated similarity in physiological characteristics, efficacy and safety, based upon a comprehensive comparability exercise. In contrast to the smaller molecule, chemical generics, biosimilars are large complex proteins. In terms of biosimilar insulins, they are based upon an original formulation of the insulin molecule which is a non-glycosylated, disulphide-bonded heterodimer, made up from 51 amino acids of which 21 amino acids are in the A chain and 30 in the B chain. When looking to manufacture human insulin or one of its analogues, it is important to remember that insulin has a well-defined primary, secondary and tertiary structure, all of which are crucial for its biological action. Because of its complex structure and the limits of current technologies, production at the present time is via the biotechnological approach using genetically modified bacteria and yeast. This is in contrast to medicines with the more simple chemical structures which can be produced by chemical synthesis and, in terms of a copy version, results in the production of a ‘generic’.

Challenges in producing a biosimilar

The major challenges arise from the method of production. Biological conditions, including, for example, the incubation conditions in different laboratories using slightly different strains of bacteria and yeast, will lead to the production of similar but not identical insulins, which could have highly significant different clinical effects. Even very small differences in the copy version could have a significant impact on efficacy and safety with respect to bioavailability, receptor binding, duration of action and unwanted effects – including, for example, those related to differences in the immune response, antigenicity and antibody formation to an exogenous protein. The use of different excipients between manufacturers, which will almost certainly be the case, and manufacturing related impurities may also have a clinically relevant impact. A further important consideration is the potential variability in quality of the insulin. In contrast to chemical synthesis, the production of biopharmaceutical products takes place in batches on different days, not as part of a continuous production line. This will require not just a robust process of production but also high standards of quality control, both of which come at a cost. Finally, an important practical issue surrounding insulin development, approval and marketing is the provision of the delivery system. Any company producing a new insulin cannot expect that their insulin will automatically be suitable for another company’s pen device.

Regulatory review of biosimilar insulins in Europe

The differences in manufacture between small molecule generic drugs and the more complex protein based biosimilars, and the potential consequences of the production process, highlight the need for appropriate regulatory review of biosimilar insulin. While it may not seem sensible to waste time and resources evaluating a biosimilar in exactly the same way as the original insulin formulation, it is vital that all biosimilars are subject to the same level of pre-clinical and clinical evaluation that clearly demonstrates equivalence with respect to efficacy and safety.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) produced the first overarching guideline, ‘Guideline on similar biomedical medicinal products’ in 2005, insisting upon a clear demonstration of biosimilarity between the original and biosimilar product through stringent and robust pre-clinical and clinical data with the further emphasis that biosimilars are not generic products. They also produced a product-specific guideline entitled ‘Guideline on non-clinical and clinical development of
similar biological medicinal products containing recombinant human insulin and insulin analogues in 2005, and a concept paper on the revision of the guideline which was agreed by the Biosimilar Medicinal Products Working Party (BMWP) in 2011 and adopted by the CHMP for release for consultation, the deadline of which for final comments is June 2013.7 Within the paper, the non-clinical section addresses pharmacokinetic, pharmacodynamic and safety studies as well as the risk management plan.

Although the pace of the establishment of an appropriate regulatory review process seems slow, since the original guideline came into effect in 2006, no biosimilar insulin has been licensed in the EU; indeed, only three products, by the same applicant, were submitted and all were withdrawn prior to opinion. More recently, however, advice has been sought on the development of several biosimilar insulins, particularly insulin analogues, which are currently not adequately covered by the original guideline.

**What is happening outside Europe?**

The World Health Organization produced a guideline in 2010, very much along the lines of the EU guidelines in the hope that it would provide some help to those countries lacking any form of regulation.8 There are, unfortunately, numerous examples of marketed biosimilar insulins that have not been subject to internationally accepted pre-clinical and clinical trial evaluation and regulatory approval.7 With respect to insulin glargine biosimilars these include, for example, Bonglixan (Mexico) for which no trial information is available, and Glaritus (India) for which there appears to be limited phase 1, phase 2 and phase 3 trial data. Basal insulin marketed in China, with little in terms of robust clinical trial data has been rejected in Colombia, apparently because of no immunogenicity data. There are also other examples, globally, of marketed biosimilar recombinant human insulins copying both prandial and mixture insulins.7

The situation in the USA is also quite different from that in Europe. After much discussion, the Food and Drug Administration (FDA) has recently published a guideline for biosimilars as part of the Biologics Price Competition and Innovation Act (BPCI Act) in 2010.8 While a programme of evaluation is expected and will be reviewed, it is not as robust as that which is required for a new ‘innovators product’. Of some surprise, however, is that the BPCI considers that insulin is not a biosimilar, but a generic and is not covered by this guideline!

**Substitution of an original insulin by a copy insulin**

In addition to the provision of guidance on the evaluation and regulation of biosimilar insulins there is also, in many countries, advice on the interchangeability and substitution by biosimilar insulins.9 In the EU, substitution is not permitted in most countries, including the UK, although advice to physicians can vary from active prohibition, to advice on only prescribing brand names or those insulins on official published lists. The position in the USA again is different, and the issue of interchangeability and what constitutes a biologic that can be used as a switch from the reference product is currently being considered by the FDA.9

**A biosimilar or a new insulin?**

Although some rapid-acting insulin analogues including, for example, insulin aspart (2012) and insulin lispro (2013), lost their patent protection before insulin glargine, it is this basal analogue that appears to be attracting the greatest degree of biosimilar interest. In addition to the developments outside Europe and the USA, detailed above, Lilly and Boehringer Ingelheim are developing a new version of insulin glargine, LY2963016. This insulin product is reassuringly currently undergoing a comprehensive phase 3 evaluation. At the present time it is not clear how similar LY2963016 will be to insulin glargine and what, if any, differences we are likely to see in terms of its efficacy and safety. Interestingly, the company is suggesting that this is actually a new insulin and not a biosimilar. Either way, the evaluation of LY2963016 appears robust and the developers and, indeed, our patients should benefit from the confidence that this insulin will be subject to a similar standard of regulatory review as other new insulins.

**Conclusions**

Over the last 90 years we have seen the development of many different insulins including animal, human and analogue products, all of which have been subject to robust and ever improving methods of evaluation and regulation; a process crucial to ensure that these lifesaving medicines are both efficacious and safe when given to people with diabetes. The costs involved in bringing new insulins to market for use by health care professionals can be significant. As patents start to expire on these medicines, an opportunity arises for alternative manufacturers to produce copy insulins, at a lower cost. While at first glance it is easy to see the attraction of additional versions of an existing insulin and the competitive market forces that this could bring, there are also many challenges and potential dangers in trying to produce copies using current biotechnological approaches without an appropriate internationally agreed process of regulation. However, once we take into account the full costs associated with the production of high quality proteins and the completion of appropriate pre-clinical and clinical evaluation programmes, to ensure acceptable levels of efficacy and safety for our patients, the savings may not be quite so great.

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**Declaration of interests**

The author has received honoraria for lectures and advisory board attendance from Novo Nordisk, Eli Lilly, Sanofi, GSK, Takeda and BMS.

**References**

References are available in Practical Diabetes online at www.practicaldiabetes.com.
References