**Biosimilar**

Philip Home

Insulin is a complex protein, manufactured to a high standard, and requiring special expertise. As modern insulins come off-patent, many companies are expected to try to enter the market with copies of current branded insulins, termed 'biosimilar insulins'. Philip Home discusses the issues in development and production of such biosimilars, and the regulatory hurdles and likely consequences for the insulin market.

**What is 'biosimilar insulin'?**  
Ordinary chemical medications used in diabetes, such as metformin or simvastatin, have a defined chemical structure. Once off-patent, these medications are available to any manufacturer to produce and market. The manufacturer needs only to show the drug regulators that the chemical they produce is the same as the original, is pure, can be manufactured consistently, and is formulated in a way that gives similar absorption from the gut. These things are relatively easy to do using modern techniques, and with a high degree of certainty.

Proteins like insulin are different. They are built from a small number of identical small molecules (amino acids), the same ones often being used many times over, but in a critically important order. The molecule then folds in complex ways which are necessary to its biological action. Showing that a protein molecule like insulin has the right number of amino acid components is easy, but showing that they are all in the right order, and that the molecule is folded correctly, is very difficult. Furthermore if a small amount of a manufactured protein is not perfect, then it may cause the production of antibodies with
insulins

repeated injection in patients, and demonstrating that such impurities do not exist in very small proportions is well nigh impossible.

For this reason the drug regulators do not refer to ‘generic insulin’ (as they do say for generic metformin) but have introduced the term ‘biosimilar insulin’. Presently (2011-2013) several important insulin analogues used in diabetes care are coming off-patent, including insulins aspart, glargine, and lispro. Manufacturers in America, China, India, Israel, and the UK are known to be interested in producing and marketing biosimilar insulins, insulin glargine being the principle target.

Why is biosimilar insulin difficult to produce?
The manufacturing process for a biopharmaceutical (defined as a biological medical product derived from cell culture and fermentation) is quite complex. In some ways the easy bit was the major technological advance, achieved around 1980, when bacteria and yeast were bioengineered with the genes that included the template for human insulin. The cell culture process then multiplies the bacteria/yeast while the genes are turned on to produce the insulin precursor. As can be imagined this results in a biological soup containing the precursor either in biological packets, the cells themselves, or the culture medium. From these the insulin must be extracted and purified to remove all the bacterial/yeast proteins and other biochemical molecules, before being processed to derive the insulin from the precursor protein.

The cells produce many other proteins, some similar to insulin, making purification difficult. The precursor must be cleaved to produce insulin by chemical and enzymatic methods, and this will create new impurities. In some processes the insulin must be persuaded to fold to produce the correct 3-dimensional structure, and failure to do so produces further impurities. Even purification itself can produce some further trace impurities, as can handling insulin, a delicate molecule, after production and in storage.

All this is important because impure proteins may be recognized by the body as foreign, and stimulate the generation of antibodies. These occasionally cause

---

**Schema of the manufacture of insulin by biological methods**

1. **Fermentation biomass**
2. **Cell harvesting/disruption/removal**
3. **Capture and purify insulin precursor**
4. **Enzymatic/chemical conversion of precursor**
5. **Purification of precursor**
6. **Folding and proinsulin conversion**
7. **Purification of protein product**
8. **Formulation of pharmaceutical product**
allergic reactions, and the allergy can become generalized to attack the body’s own insulin. Furthermore production of lots of antibodies can neutralize the effect of the insulin itself, which then loses efficacy. A new manufacturer of insulin, without a history of expertise in manufacturing it, therefore faces quite a barrier to getting a quality product to market.

Past problems with biosimilars

Insulin is not of course the only biopharmaceutical widely available. In endocrinology, another notable product is human growth hormone, and people with diabetes who develop renal failure will often be given recombinant erythropoietin (‘epo’) to help counter the development of anaemia. For rheumatoid arthritis a number of artificial antibodies directed against the substances which cause joint inflammation are available, and the drug trastuzumab (Herceptin) used in breast cancer is another familiar example.

For some of these agents, biosimilars have already been approved for human use, notably for epo. But the experience in this new area has not been without adverse experiences. It was a proprietary product and not a biosimilar which caused an unusual and fatal bone marrow problem with epo, a problem traced to the manufacturing process, but this is not an experience any biosimilar manufacturer (or its clients!) would wish to experience.

A biosimilar insulin has been submitted for approval to the European regulators (the European Medicines Agency, EMA) in recent years. As is usual for new drug submissions this went under detailed review, but in this case because of the novelty of the product the regulators were learning from the application. The insulin was a biosimilar of human insulin, and the clinical tests demanded by the regulators were judged not to demonstrate equivalence to the current human insulin products. The manufacturers withdrew the application.

Regulatory requirements for biosimilars

Because there is no way that a biosimilar insulin can be known to be identical to current preparations by chemical analysis, the drug regulators have drawn up guidelines requiring clinical laboratory studies and clinical trials as part of the approval process for new applications. Essentially the demand is to show by such studies in people with diabetes that the new product has the same clinical properties as the parent insulin already on the market, and additionally that it does not have any unexpected and new adverse effects.

The lead here has been given by the European regulators from 2004, and indeed their documentation has been used and built upon by drug regulators worldwide. EMA firstly issued general guidelines for approval of biosimilar medications, but later specific guidelines for different types of product including insulin. In contrast to much of the rest of the world, guidelines from the US regulators, the FDA, are still awaited at the time of writing.

The well-established method for showing that two insulins act similarly is known as the glucose clamp – this have the advantage that it can test the time course of action of an insulin (for example how quickly does it start acting, when is the peak action, how long does it last), and the total action (what is the total glucose lowering effect over its whole time of action). Accordingly this glucose clamp test has been a central part of EMA recommendations. Unfortunately the test is not easy to perform, particularly in the most important group of people as far as the profile of action is concerned, namely those with type 1 diabetes. As a result it is not very sensitive to differences between insulins, creating a real difficulty in showing similarity.

As a result EMA is reviewing its guidelines (this was always meant to be a learning process) and it is to be expected that more attention might be paid to clinical studies of duration of action particularly for longer-acting insulins, and to hypoglycaemia rates at different times of day. This would also fit in well with the antibody studies, which anyway have to

For biosimilar medications insulins the only way to exclude clinically meaningful differences in efficacy, safety and immunogenic potential – is from clinical data . . .

For insulin this suggests:

- pharmacokinetics studies → (the rate of absorption into the blood after injection)
- pharmacodynamics studies – a glucose clamp study → (the efficacy in lowering blood glucose levels)
be longer term (six to 12 months), and in larger numbers of people.

The biosimilar market place
As noted above a number of manufacturers are gearing up to produce biosimilar insulins. It may however be 3 years or so before a significant number of products are approved. Classically when generic drugs appear the price drops to around 10 % of the original patented medication, but as noted above for biosimilars the production process will remain complex and the regulatory studies will cost significant amounts of money.

Estimates then of price reductions from present levels range from 30 to 70 %, but even this would be welcome as insulin is relatively expensive. We can expect arguments to rage over whether a new biosimilar insulin is indeed identical in quality and performance to the original – there may even be claims it is better. Meanwhile the development of new insulins continues, so new premium priced products are already in advanced development from some insulin manufacturers, and no doubt the debate as to whether these will be worth the price premium over biosimilar insulins will be lively.

An important issue here will be whether a pharmacist, faced with a physician’s repeat prescription can, or can be required to, substitute a cheaper version of the same insulin for the branded insulin a person with diabetes has been using. This happens in many countries for generic drugs. At present reimbursement authorities are being conservative for biopharmaceuticals and recommending such changes should not be made except by agreement between the user and their physician. However such interchangeability decisions may come under review due to financial pressures in healthcare worldwide.

Philip Home
Professor Philip Home is a diabetologist, and Professor of Diabetes Medicine at Newcastle University in the UK. A past Vice-President of IDF, he has advised all major manufacturers of insulin over the past 30 years, and more recently some of those interested in producing biosimilar insulins.

Further reading