Q&A
Biosimilar insulins

Citation: Gough S (2014) Q&A: Biosimilar insulins. *Diabetes & Primary Care* **16**: 290–2

Interview with Stephen Gough

In late June 2014, the European Medicines Agency Committee for Medicinal Products for Human Use recommended approval of a first biosimilar insulin (Medscape, 2014). With biosimilar insulins now thus on the cusp of being launched, we present a Q&A feature to cover the key facts on this emerging topic.

Questions asked by:
PB = Pam Brown, GP, Swansea
GH = Gwen Hall, Diabetes Specialist Nurse, Portsmouth

Q PB: What is a biosimilar insulin?

A biosimilar insulin is a copy version of an existing, fully licensed insulin, which has been demonstrated to have similar physiological characteristics, efficacy and safety, based upon a comprehensive development programme. Unlike simple chemical drugs, which are small, synthetically produced molecules, biosimilar insulins are large, complex proteins which, via recombinant DNA technology, are produced in living entities such as bacteria and yeast.

Q GH: I've heard two terms, biosimilar medications and biological medicine. What's the difference if any?

The two terms are the same and they refer to a copy of an original, existing insulin. Biosimilar indicates that the insulin is biologically similar and biological medicine refers to the process by which the product (or protein) is made (*see below*).

Q PB: What is the process for establishing that a new insulin is "biosimilar" to the "biological reference" or branded insulin?

The regulatory requirements for the approval of a biosimilar are more stringent than those for a simple chemical generic drug. In addition to demonstrating identical amounts of the same active ingredient in the same dosage form to the original formulation, biosimilar insulins will require a comprehensive analysis, including head-to-head comparisons of the new product's characteristics, pharmacology, clinical safety and efficacy outcomes.

Q GH: Can we be confident, then, that the quality will be similar too?

It is important to stress that a biosimilar insulin is, as its name suggests, similar and not identical to the insulin which is being "copied". There are well-defined regulatory requirements that a manufacturer will need to satisfy as outlined above, before a biosimilar insulin can be approved for prescribing. Both the European Medicines Agency (EMA) and the US regulators (the Food and Drug Administration [FDA]) have published guidelines on biosimilar insulins to try to guarantee similarity and also the quality of the product. First producing guidance in 2005 (EMA, 2005), the EMA has produced further advice on biosimilars (EMA, 2006; 2013a; 2013b), with this last being updated as a guideline specific to insulins in 2012 (EMA, 2012a). The EMA considers the "demonstration of similar pharmacokinetic and pharmacodynamic profiles as the mainstay of proof of similar efficacy of the biosimilar and the reference insulin" (EMA, 2012a).

Q GH: And can we be sure these medicines will act exactly the same way as current therapies in individuals? And if not, what would be the difference?

If they are approved by the EMA and FDA, they should work in a very similar manner to the original

Interviewee

Stephen Gough is a Professor of Diabetes and Consultant Physician, University of Oxford and Oxford University Hospitals NHS Trust, Oxford.

insulin. However, there may be differences, some of which, most importantly safety, may not have been identified at the time of launch, as is the case with any new product. Doses should be similar but may not be identical. Other potential differences may occur in terms of immunogenicity and allergic reactions as the biological copy is a protein that may be slightly different and with different excipients or additives in the solution.

Q PB: Will the biosimilar insulins be compatible with existing pens?

An important aspect of any new insulin development programme is the provision and evaluation of a delivery system capable of administering accurate and reproducible drug doses. We cannot assume that biosimilar insulins will be able to be used in the same pen device as the original insulin. They need to have had their own delivery system tested in a clinical trial programme.

Q PB: Even if guidance is provided of likely equivalences of dosing, profiles of glycaemic control are unlikely to be identical to those of the branded insulin, possibly leading to risk of hypoglycaemia and challenges to control. Was this a problem in the trials and do we have any estimate of the additional workload and whether this will occur in secondary or primary care?

This is an important question. It is not expected that the reference drug and the biosimilar drug will be identical, and the aim of the Chemistry, Manufacturing and Controls comparability exercise is to demonstrate that the degree of variability between the reference drug and the biosimilar drug is not significant.

Dosing becomes an important issue if there is switching between reference insulin products and biosimilars. Whilst comparative studies with the reference product may be sufficient to support switching, substitution of insulins at the pharmacy level will require more substantial clinical data. It is important to remember that the summary of product characteristics of many insulin products, includes the statement that "transferring a patient to another type or brand of insulin should be done under strict medical supervision" (EMA, 2009a; 2009b; 2009c). To prevent potential problems, prescribers may have an opportunity to prohibit pharmacy switching, by indicating "Dispense as Written" on prescriptions, although, even without this, pharmacists should not be able to instigate a switch at the point of dispensing. It is important that clear criteria need to be developed and adopted. Appropriate advice, information and education need to be made available to all healthcare professionals involved in the prescribing and administration of biosimilar insulin.

Q GH: What biosimilar insulins can we expect to see in the UK, and won't people with diabetes get confused?

It is most likely that the first biosimilar insulin that we will see in the UK will be an insulin glargine biosimilar. There are, however, others in development: not just long-acting insulins but also rapid-acting insulin analogue biosimilars. It is important that healthcare professionals and patients/carers alike receive appropriate education and support so that they do not become confused, as there is obviously the potential for this to happen.

Q GH: Will NICE provide guidance before biosimilar products become available?

The Association of the British Pharmaceutical Industry has said that all biosimilars should be assessed by NICE, and its counterparts such as the SMC, in the same way as their originator products.

Q PB: Are biosimilar insulins manufactured in other countries likely to be licensed in the UK market, and will we be forced to use them in preference to those manufactured by UK or US companies if they are cheaper? Will all have to meet EMEA regulations?

A number of biosimilar insulins have been developed in other countries and have been through varying standards of local approval. Any biosimilar prescribed in the UK must go through the EMA submission and approval process.

"An important aspect of any new insulin development programme is the provision and evaluation of a delivery system capable of administering accurate and reproducible drug doses. It cannot be assumed that biosimilar insulins will be able to be used in the same pen device as the original insulin. They need to have had their own delivery system tested in a clinical trial programme."

"It will be crucial that the manufacturer of the biological drug is able to show that there is no significant batch–batch variability and that it meets accepted quality standards."

Q PB: Do we know what the possible clinical impact of differing protein folding and structure created by the different production process may be in the long term, when compared with the traditional "reference" insulin? Is there any evidence of antibody production in the studies?

Biosimilar insulins will be based upon the original formulation of the reference product and obviously that of insulin itself. Insulin is a non-glycosylated, disulphide-bonded heterodimeric molecule, made up from 51 amino acids, of which 21 are in the A chain and 30 in the B chain. It has a well-defined primary, secondary and tertiary structure, all of which are crucial for its biological action. At the present time, with current technology, the only approach to manufacturing is the use of genetically modified organisms. This process, including biological incubation, is complex, and it could lead to differences in protein folding. The use of different additives or excipients and potential day-to-day variations in production could all contribute to differences with respect to immunogenicity and immune reactions in patients. It will be crucial, therefore, that the manufacturer of the biological drug is able to show that there is no significant batch–batch variability and that it meets accepted quality standards. It is also important, as with any "biologic", that immunogenicity is evaluated in clinical trial and post-authorisation programmes.

Q PB: Why did Marvel's insulins fail to achieve a licence with the EMA? Was this due to problems with the marketing submission, manufacturing concerns or the quality of the product?

In 2007, Marvel Life Sciences Private Ltd (Mumbai, India) submitted biosimilar insulin applications, which were subsequently withdrawn. The Committee for Medicinal Products for Human Use had raised concerns, including inadequate product submissions and failure to demonstrate biosimilarity to the original insulin (EMA, 2008a; 2008b; 2008c). In 2012, Marvel Life sciences withdrew additional applications, which had been submitted to the agency, indicating that they needed more time to repeat pharmacokinetic and pharmacodynamics studies, in order to comply with the biosimilar insulin guideline (EMA, 2012b). ■

Further reading

Information from Diabetes UK on biosimilar insulins can be found at:

www.diabetes.org.uk/Biosimilar-insulins

European Medicines Agency (2005) *Committee for Medicinal Products for Human Use. Biosimilar Guidelines*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf (accessed 25.11.14)

European Medicines Agency (2006) *Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant human soluble insulin*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003957.pdf (accessed 25.11.14)

European Medicines Agency (2008a) *Pre-authorisation evaluation of medicines for human use: withdrawal assessment report for insulin human Rapid Marvel* (EMEA/CHMP/317778/2007). EMA, London. Available at: www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067086.pdf (accessed 25.11.14)

European Medicines Agency (2008b) *Pre-authorisation evaluation of medicines for human use: withdrawal assessment report for insulin human 30/70 Mix Marvel* (EMEA/CHMP/70179/2008). EMA, London. Available at: www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067169.pdf (accessed 25.11.14)

European Medicines Agency (2008c) *Pre-authorisation evaluation of medicines for human use: withdrawal assessment report for insulin human Long Marvel* (EMEA/CHMP/70349/2008). EMA, London. Available at: www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067170.pdf (accessed 25.11.14)

European Medicines Agency (2009a) *Humalog: EPAR – Product Information*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000088/WC500050332.pdf (accessed 25.11.14)

European Medicines Agency (2009b) *Lantus: EPAR – Product Information*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000284/WC500036082.pdf (accessed 25.11.14)

European Medicines Agency (2009c) *NovoRapid: EPAR – Product Information*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000258/WC500030372.pdf (accessed 25.11.14)

European Medicines Agency (2012a) *Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136392.pdf (accessed 25.11.14)

European Medicines Agency Press Release (2012b) *Marvel LifeSciences Ltd withdraws its marketing-authorisation applications for Solumarv, Isomarv medium and Combimarv (human insulin)*. EMA, London. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001665.jsp&mid=WC0b01ac058004d5c1 (accessed 25.11.14)

European Medicines Agency (2013a) *Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf (accessed 25.11.14)

European Medicines Agency (2013b) *Committee for Medicinal Products for Human Use. Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues*. EMA, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf (accessed 25.11.14)

Medscape (2014) *EMA Advisory Panel Recommends First Biosimilar Insulin*. Available at: http://www.medscape.com/viewarticle/827497 (accessed 25.11.14)