

Biosimilars: Growing the Concept

The biosimilar concept has the potential to produce affordable new biotech medicines, but only if industry and regulators work together on a harmonised global approach, says *Cecil Nick*.

The prevailing view among regulators and industry is that, as proteins are much more complex than small molecule drugs, it is not possible to demonstrate the identical nature of two biological products arising from different manufacturing sources. Therefore, follow-on proteins produced by generic manufacturers cannot be approved as simple generics but need additional nonclinical and clinical data to demonstrate that they have an equivalent safety and efficacy profile to the originator product.

Experience with the approval of follow-on proteins varies across the world, but the European Union has led the way in establishing an approval process for biosimilars. EU legislation now differentiates between "generic medicinal products" and "similar biological medicinal products" (Directive 2004/27/EC¹) and outlines the approach to be followed to gain regulatory approval for a biosimilar medicinal product (Directive 2003/63/EC, Annex I, Part II, Section 4²). Both general³⁻⁵ and product-specific guidelines covering recombinant erythropoietin⁶, granulocyte colony-stimulating factor⁷, human somatropin⁸ and human insulin⁹ have been issued by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), as have further draft guidelines for interferon alpha¹⁰ and low molecular weight heparin¹¹. These guidelines all stipulate the need for at least some clinical data to support the approval of biosimilar medicinal products.

The EU to date has approved a number of biosimilars, including formulations of somatropin and epoetin¹²⁻¹⁵ and, most recently, filgrastim¹⁶. On the other hand, two products have failed the EU approval process – an interferon alpha and insulins¹⁷ – illustrating that demonstrating biosimilarity is not always plain sailing. In fact, even for some of the biosimilars that have been approved, the ride has not been smooth. For example, both approved epoetins were tested in more than 600 subjects, of whom more than 300 were exposed to the biosimilar epoetin for at least 24 weeks. Yet unlike the marketed products that have been approved for subcutaneous and intravenous use, both these biosimilar epoetins were approved only for intravenous use in the primary indication of chronic renal failure, allowing them access to just a small slice of the market.

The fact is that proving biosimilarity presents a web of complex challenges. Currently regulators and sponsors are learning with each submission. Those lessons will be applied and fed back into the guidelines within the EU, and picked up internationally.

Right now a number of new questions are looming. For example, how should follow-on monoclonals and other complex proteins be handled? Also, how much clinical data should be required, and is the prevailing view of biosimilarity too narrow? "Similar" does not mean "identical", and perhaps the concept could be applied more broadly, perhaps even to proteins with deliberately introduced differences, although this certainly would not be the EU regulatory view today. As more biologicals are approved and more come off patent, the questions will multiply and the debate will become more intensive.

In order to address these questions, there is the need to dispense with dogma and take a rational and scientific approach to the concept of biosimilarity and the extent to which clinical data is needed to demonstrate that one therapeutic protein is similar to another.

The impact of differences in structure and impurity profile

The introduction of new production processes, new formulations and even new containers and closures can affect protein structure and impurity profiles. These changes may not always be easy to detect but may impinge on the clinical effect in a number of ways. For example, changes in higher order structure or folding could impact receptor binding and hence potency and efficacy. Changes in glycosylation could also affect receptor binding, for example through steric factors, but the pharmacokinetic profile might also be impacted by glycosylation, for example due to differences in relative solubility changing the absorption profile and/or tissue distribution, or by changes in sensitivity to protease degradation or receptor interaction, which could affect clearance rates.

Immunogenicity is of particular concern for proteins since the immune system is geared to recognising and removing foreign proteins. Any change in protein structure, including post-

The EU has led the way in establishing an approval process for biosimilars...

...and has approved a number of biosimilar products, including epoetin and somatropin

New production processes, formulations or containers may affect protein structure...

...while impurities may enhance immunogenicity against the therapeutic protein

translational modifications such as changes in glycosylation patterns, can impact immunogenicity. Impurities, too – including degradants, host cell proteins and leachates – may, apart from being immunogenic in their own right, act as an adjuvant to enhance immunogenicity against the therapeutic protein. Immunogenicity can lead to a spectrum of adverse effects including allergic reactions and infusion reactions, loss of efficacy or even autoimmunity due to neutralising antibodies cross-reacting with the natural protein. The issue of neutralising antibodies and autoimmunity was brought to the fore some years ago with the discovery that a formulation change to a brand of epoetin precipitated the formation of antibodies that neutralised the patient's own epoetin¹⁸. This resulted in a debilitating condition known as pure red cell aplasia, which caused patients to require frequent blood transfusions in order to survive. Neutralising antibodies are also a concern with other protein therapies and are a well-known problem associated with Factor VIII treatment¹⁹.

A first step in any biosimilarity exercise is to undertake a risk analysis to explore the potential impact of detected and potentially undetectable differences on the clinical efficacy and safety of the product. Issues that will need to be considered include:

- the ability to detect differences in structure and impurity profile using physico-chemical and biological methods, and the impact of any differences detected;
- the extent and relevance of nonclinical and clinical data required to support similarity; and
- the potential impact of immunogenicity – in some cases neutralising antibodies may have limited impact, as is the case with interferons, while on the other hand, as already described, neutralising antibodies against epoetin can have devastating implications (see CHMP guidelines on immunogenicity testing of biologicals²⁰).

The results of the risk analysis can be used to justify the level of clinical data that will be required. This approach requires an integration of knowledge from various disciplines including protein chemistry, analytics, immunology, pharmacology, pharmacokinetics and clinical science.

The importance and challenges of Phase I

Demonstrating biosimilarity at the clinical level must begin with Phase I studies

The process for demonstrating biosimilarity at the clinical level will need to begin with Phase I studies, which form a critical part of any biosimilar programme. Changes in pharmacokinetic profile are possible even with generic formulations of small molecules and could impact safety and efficacy. Pharmacokinetics is traditionally studied in Phase I healthy volunteer trials, and in most cases this is true for therapeutic proteins as well, although in the oncology setting, for example, these studies will likely need to be performed in patients.

Greater challenges are faced when dealing with therapeutic proteins. Batch-to-batch variability even with the reference compound can be far greater than for small molecules and this can complicate the interpretation of results. For example, while most small molecule active ingredients are controlled within the 95%-105% range in the finished product, the European Pharmacopoeia monograph for Erythropoietin Concentrated Solution allows a potency range of 80-125% (95% Confidence Intervals 64%-156%)²¹. Limits of detection and assay variability can also affect the design of the bioequivalence trial: for example, it may be necessary to dose at supranormal levels in order to enable reliable measurement of drug plasma levels, and this has been the approach with some studies on interferon beta, although today's methods allow lower limits of quantitation. The presence of endogenous protein might also interfere with the determination of drug plasma levels – such is the case with insulin – necessitating trials in patients or the use of special designs such as the glucose clamp that rely on pharmacodynamic measures.

Phase I also provides the opportunity to monitor pharmacodynamic endpoints. For some proteins such as epoetin, insulin and filgrastim, endpoints such as haemoglobin levels, glucose levels and absolute neutrophil count directly relate to the therapeutic effect and can be predictive of efficacy. On the other hand, for proteins such as somatropin and interferon beta, the correlation between pharmacodynamic endpoints and clinical effects is not as clearly definable. For some protein products, such as many monoclonals, a good pharmacodynamic marker may not exist at all.

Factors driving the need for clinical data

The therapy's pharmacological effect will influence how much supporting data is needed

The extent of supporting clinical data required will be influenced by a number of factors, such as whether the therapy replaces an endogenous protein, supplements an endogenous protein or has a novel pharmacological effect. It will also depend on how similar the reference product and the biosimilar are, and on the known impact of any differences in primary, post-translational and higher order structure or in impurities, and the degree to which similarity can be demonstrated using physico-chemical methods is clearly critical. Smaller nonglycosylated proteins such

as insulin, somatropin and filgrastim are relatively easy to fully characterise, while heavily glycosylated proteins such as epoetin or large proteins such as monoclonals and blood factors may not be fully characterisable.

A key question is the extent and relevance of the clinical data that might be required to confirm the equivalence of two therapeutic proteins and whether a good pharmacodynamic marker could supplant the need for comparative trials in patients. With filgrastim, for example, it is possible to generate a product that would be virtually indistinguishable from the innovator product. For such products, the structural activity relationship is well understood and there is a very close correlation between the results of biological assays, pharmacodynamic effects and clinical endpoints. Therefore, CHMP guidelines recognise that, if adequately justified, comparative pharmacodynamic studies in healthy volunteers could replace clinical equivalence trials. In these circumstances only limited data ought to be required to demonstrate biosimilarity, although some presubmission safety and immunogenicity data would still be required.

The size and duration of clinical trials will be affected by the availability of a clinical relevant endpoint. An endpoint that is easy to measure, displays low variability and is reached within a reasonable time period will facilitate small therapeutic equivalence trials of short duration. On the other hand, comparison of treatments, for example, in inflammatory disease and cancer, requires much larger clinical trials to demonstrate therapeutic equivalence.

Importance of formulation

The folded shape of proteins is determined by noncovalent interactions that are two or three orders of magnitude weaker than the peptide bonds that link the amino acids within the protein. These noncovalent bonds are easily disrupted by changes in the protein's environment. Therefore, it is not just changes in manufacturing but also changes in formulation that can affect the safety and efficacy of a protein. Indeed, the example of pure red cell aplasia cited previously was precipitated by a formulation change, ironically by the replacement of human serum albumin with polysorbate 80 to comply with a CHMP request to remove human serum albumin from the formulation. The theory is that the polysorbate 80 dissolved leachate from the rubber closure, which, in turn, enhanced immunogenicity. The problem appears to have been resolved by siliconisation of the rubber. This example displays the intricate interrelationship between protein, formulation and container^{22,23}.

In some cases formulation may be even more critical in terms of affecting safety and efficacy. Take insulin, for example, a well-known therapeutic protein that has been in use for almost a century (since 1923). Developing biosimilar insulin should be simple, because current physico-chemical and biological methodologies are more than capable of discerning any slight difference that could have an impact on safety and efficacy. Yet the only biosimilar insulin to be submitted to the CHMP received a negative opinion. Why? There were many factors, but one of the key points cited in the CHMP assessment report was that "the pharmacodynamic study did not demonstrate equivalent blood glucose lowering effect to that of the reference product". But if insulin can be fully characterised, how can this be? Although poor study design cannot be discounted, it could be that subtle differences in formulation are responsible. Insulin needs to be specially formulated in order to approximate the natural insulin release profile and if there are differences in release profile this could certainly impact glucose control and the approvability of a biosimilar insulin.

How similar is biosimilar?

What can and cannot be considered as a biosimilar is also not clear cut at present, and viewpoints vary. Some consider that only proteins that are fully characterisable, with no discernible differences in either the structure or the impurity profile, can be considered biosimilar. This is not precisely the view of the EU regulators, who allow a degree of difference provided this can be justified. For example, Valtropin (Biopartners' somatropin) is expressed from yeast whereas its reference product, Lilly's Humatrope, is expressed from *E coli*; this must mean differences in host cell impurities at the very least, yet the products have been shown to be biosimilar and accepted as such by the European Commission²⁴. Differences in glyco-profile have been seen between the reference product Eprex/Erypo (epoetin alpha; Janssen-Cilag) and the different presentations of epoetin zeta²⁵. These differences have been justified as being within the range of natural variants and clinical experience and the products have also been accepted as biosimilar.

In order for therapeutic proteins to be brought to the market more economically, it is critical to encourage the introduction of innovative and more efficient production technologies, including transgenic production, although these may introduce differences in impurities or post-translational modifications. It is hoped regulators will be sympathetic to this need and allow a biosimilar approach despite a degree of difference, provided of course that equivalent safety and efficacy

It is important to determine how much, if any, clinical data is needed to confirm equivalence

Changes in formulation are as likely to affect safety and efficacy as manufacturing changes

EU regulators allow a degree of difference when determining biosimilarity

to the reference product can be demonstrated. However, there is currently no precedent for this and such an approach would inevitably lead to regulatory scrutiny. Therefore, sponsors intending to adopt a biosimilar approach will have to rigorously justify their position to the regulators, particularly where potentially significant differences from the reference product are detected or are possible.

If differences in primary structure or profound post-translational modifications were detected, the prevailing view is that the product would need to be treated as a novel compound. However, perhaps such a black and white view is not entirely appropriate. Clearly a novel structure takes the product outside current clinical experience and, as such, the level of safety data will need to align with requirements for a novel protein. However, the fact is that clinical programmes for follow-on products will always need to differ from the innovator programme. For a start, the use of placebo will likely no longer be ethical. This will necessitate equivalence trials, which are more difficult to perform, require more patients and may not be practical at all. So it is necessary to consider whether it would be possible to extrapolate from one indication to other indications once therapeutic equivalence has been established, even for products displaying major structural differences. Clearly, extensive safety data would be required and there is no regulatory consensus for such an approach, which does not align with current thinking. However, in some cases there may be no practical option and such a hybrid approach is worthy of further consideration and discussion with the regulators.

Clinical programmes for follow-on products will always need to differ from innovators

Is the biosimilar approach applicable to more complex proteins?

The current EU approvals represent just the beginning of the biosimilar revolution. The existing product-specific guidelines will probably be re-evaluated in the light of experience. For example, the epoetin guideline is under revision²⁶. More importantly, a host of other products, including many subsequent-entry monoclonal antibodies, will probably be submitted to regulatory agencies in the coming years, spawning new controversies and new guidelines.

The question is, can the EU biosimilar concept be applied to more complex proteins? The Guideline on Similar Biological Medical Products (CPMP/BWP/437/04²⁷) states that in principle the concept of "similar biological medicinal product" applies to any biological medicine. However, the guideline goes on to state that in reality this will depend on a number of factors, including the ability to characterise the product, and it is more likely that highly purified and thoroughly characterised proteins will be accepted as biosimilars. The guideline states that the biosimilar route is more difficult to apply to ingredients extracted from biological sources. But even the more complex recombinant proteins may not qualify. The applicability of a biosimilar approach will depend on the effectiveness of available analytical procedures, the consistency of the manufacturing process and the regulatory and clinical experience to date.

The biosimilar route is more difficult to apply to ingredients from biological sources...

Blood products are singled out by guideline CHMP/437/04, which states:

In view of the complex and variable physico-chemical, biological and functional characteristics of blood factors it will not be acceptable to submit a reduced dossier when claiming similarity to an original reference product. Therefore CPMP Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX products (CPMP/BPWG/1561/99)^[28] published 19 October 2000 must be satisfied.

However, these Factor VIII and IX guidelines are fairly pragmatic and require a total database of fewer than 100 patients to demonstrate safety and efficacy; there is, therefore, not much scope for a truncated approach by adopting a biosimilar route.

The development programme for most subsequent-entry proteins will be more complex than for blood factors. Also, as already mentioned, the programme will, by necessity, differ from the innovator programme in that, critically, placebo trials will likely no longer be ethical. On the other hand, where there are no suitable endpoints, equivalence trials may be completely impractical and certainly it will not be reasonable to expect non-inferiority trials to be performed to support each indication, dosage regimen and population group. Thus, the development programme for a subsequent-entry protein must differ from the originator's programme and allowance needs to be made for this.

In fact, the biosimilar route may represent the only possible mechanism for approval for many subsequent-entry proteins and there seems no reason why most biologicals should not qualify for a biosimilar approval process. A biosimilar approach should only be inappropriate where it is impossible to extrapolate anything from the innovator's experience, and this is likely to be true for very few compounds. In most situations, much information will be available on the follow-on protein, and the relationship between pharmacodynamics, dose and therapeutic response will be better understood than was the case while the innovator product was under development. This information can be used to steer the development of a biosimilar and it would be inappropriate to ignore this valuable resource and to require, for example, repeat dose-ranging studies.

...but it may represent the only approval route for many subsequent-entry proteins

Demonstrating biosimilarity means drawing on existing knowledge and bridging the gaps by conducting an appropriate development programme. It does not necessarily mean that the programme will be lighter than or even equivalent in size to the original programme. Its size and complexity will depend on the level of understanding of the structure, the impurity profile, and the biological, nonclinical and clinical data, and the way these factors interact. It will also depend on the relative complexity of demonstrating therapeutic equivalence to the satisfaction of the regulators. In some cases applying a biosimilar approach will require the study of more patients than were included in the innovator programme. The point is that in these circumstances disallowing a biosimilar approach would make development of the follow-on protein unrealistic because of the excessive number of patients required to trial the different indications and treatment scenarios.

The question of biosimilar monoclonals is not considered in CHMP guidelines, and just a few years ago some opinion leaders still questioned whether this would ever be feasible²⁹. Clearly, developing a biosimilar monoclonal is challenging and there are a number of key questions that need to be addressed, such as:

- can the innovator molecule be reproduced faithfully and can that be proved?;
- if differences exist or might exist, to what extent do these matter?;
- do suitable surrogate endpoints exist (as with G-CSF and EPO) to enable truncated clinical development?; and
- if equivalence trials require thousands of patients and placebo trials are unethical, how does one develop a biosimilar or even a stand-alone subsequent-entry monoclonal?

The answers to these questions need to be considered on a case-by-case basis. Certainly modern production methods and analytical techniques have evolved to a level that allows the production of highly similar monoclonals. However, demonstrating therapeutic equivalence in diseases such as rheumatoid arthritis and oncology will prove more challenging and will probably require large trials.

Globalisation of the biosimilar programme

An important factor for the success of a biosimilar programme is the ability to access global markets. Experience with biosimilars across the world varies. There has been extensive usage in Asia for many years, while in Europe biosimilars are just entering the market. Across the Atlantic, Health Canada has recently issued draft guidelines that in many ways reflect the EU position but also display differences in opinion. Japan too has issued draft guidelines, whereas in the US regulators are still grappling with how to establish a regulatory framework. The World Health Organization is trying to set a base standard and a conference was held in Seoul earlier this year.

The eventual regulatory approach for the approval of biosimilars in major markets, notably the US, will undoubtedly impact the future global strategy for biosimilars. These developments will set new precedents for the approval of subsequent-entry proteins and, coupled with other global trends and advancing technology, will likely influence EU processes.

A key challenge in formulating a global development programme is that there is no way of confirming that the reference product on sale in one region complies with the requirements in other regions. Until this problem is resolved, a truly global biosimilar programme is impossible. Currently, in the EU, it is a requirement that the reference product be sourced from within the EU. If a similar requirement is adopted by other major regions, then replicate programmes will need to be performed in each region, resulting in unnecessary effort and expenditure. Indeed, it would become impractical to repeat larger trial programmes with a reference product sourced from each geographic region.

There is, therefore, an urgent need to establish an international mechanism to allow mutual recognition of data lodged in marketing approvals. For instance, the US Food and Drug Administration, the EU or Japan could issue a certificate confirming that, according to the submission, postsubmission and pharmacovigilance data held on their files, the reference product had demonstrated a positive risk:benefit profile and that there were no outstanding safety issues. There is no need for mutual recognition of quality data since a full quality package on the follow-on protein would be available to all regional regulatory agencies.

Another hurdle to the adoption of a global data package is regulatory concerns about the impact of ethnicity. Regulators have been resistant to accepting data from populations where intrinsic or extrinsic ethnic differences might exist. However, it should be considered that for biosimilars, the sponsor is required to show therapeutic and safety equivalence to a reference product. This reference product will have already been approved and marketed in the target region and there would be no reason why a product shown to be similar would display a different spectrum of ethnicity. The fact is that a lack of ethnic effect should already be evident from studies on the reference product and further supported by considering factors such as whether similar doses are required in different regions and whether a similar adverse event profile is evident

CHMP guidelines do not consider the question of biosimilar monoclonals

Experience with biosimilars across the world varies...

...and there is an urgent need to establish an international mutual recognition mechanism

from postmarketing pharmacovigilance data. This information may not be readily available to the sponsor, so here again there is an opportunity for international co-operation and exchange of information between agencies in different regions.

Even if the above problems were to be resolved, regional differences in data requirements may still dictate the need for replicate programmes, which would need to be tailored to the requirements of specific regions. Global harmonisation of biosimilar guidelines, therefore, represents yet another area that would benefit from international collaborative efforts.

Definitions of biologicals and data requirements may vary in different regions

Even the delineation as to what is and what is not a biological may not be clear cut, and what is considered a biosimilar in one region may need to be handled as a novel biological in others. For example, monoclonal antibodies have been approved as biosimilars in India but it is not clear whether such products would qualify for a biosimilar approach in Europe or Canada.

Conclusion

Despite the progress in the EU, much uncertainty remains as to which products will qualify as biosimilars and the extent of similarity that is required to qualify for a biosimilar approach. Furthermore, the level of supporting clinical data that will be required is not easy to define. In fact, the problem is multidimensional and influenced by the complexity of the protein, the extent of difference between the reference product and the biosimilar and the ease of demonstrating therapeutic equivalence.

The extent of bridging clinical and nonclinical data needs to be based on risk analysis

Uncertainty and variability increase in line with complexity of structure. The extent of bridging clinical and nonclinical data needs to be based on risk analysis, with the amount of supporting data required being proportionate to the level of uncertainty and the level of risk. In fact, this concept of a risk-based approach drawing on available originator data could be applied even to deliberately modified proteins that displayed receptor interaction, pharmacokinetic and pharmacodynamic profiles similar to a reference drug. While such an approach does not fit within the current regulatory framework, if adopted in the future, it could serve to stimulate the introduction of innovation, including new production techniques, enabling the manufacture of more affordable medicines and encouraging better treatments through the development of novel formulations and modified therapeutic proteins.

Another important factor will be the ability for biosimilars to access global markets based on a single development programme that meets the requirements of all markets. The WHO is trying to set a base standard but the eventual regulatory framework for the approval of biosimilars in major markets relies on the generic and biotechnology industry galvanising international regulatory opinion into establishing a harmonised approach. The concept of biosimilarity is still in its infancy and industry and regulators alike hold the responsibility of nurturing the concept so that it becomes a powerful vehicle for bringing affordable and better medicines to the world.

References

1. Directive 2004/27/EC, *OJ*, 30 April 2004, **L136**, 34-57, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF>
2. Commission Directive 2003/63/EC, *OJ*, 27 June 2003, **L159**, 46-94, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:159:0046:0094:EN:PDF>
3. CPMP/437/04, Guideline on Similar Biological Medicinal Products, October 2005, www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf
4. CHMP/42832/05, Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance – Non Clinical and Clinical Issues, February 2006, www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf
5. CHMP/49348/05, Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues, February 2006, www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf
6. CHMP/94526/05, Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance – Non Clinical and Clinical Issues containing Recombinant Human Erythropoietin, March 2006, www.emea.europa.eu/pdfs/human/biosimilar/9452605en.pdf
7. CHMP/31329/05, Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance – Non Clinical and Clinical Issues containing Recombinant Granulocyte Colony-Stimulating Factor, February 2006, www.emea.europa.eu/pdfs/human/biosimilar/3132905en.pdf
8. CHMP/94528/05, Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance – Non Clinical and Clinical Issues containing Recombinant Human Growth Hormone, February 2006, www.emea.europa.eu/pdfs/human/biosimilar/9452805en.pdf
9. CPMP/32775/05, Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance – Non Clinical and Clinical Issues containing Recombinant Human Insulin, February 2006, www.egagenerics.com/doc/nick_biosim-development.pdf
10. CHMP/BMWP/118264/07, Similar biological medicinal products containing low-molecular-weight heparins, released for consultation in April 2008, www.emea.europa.eu/pdfs/human/biosimilar/11826407en.pdf

11. CHMP/BMWP/102046/06, Similar medicinal products containing recombinant interferon alpha, released for consultation in October 2007, www.emea.europa.eu/pdfs/human/biosimilar/10204606en.pdf
12. European Public Assessment Report for Omnitrope (somatotropin), Rev 4, 23 April 2008, www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en1.pdf
13. European Public Assessment Report for Valtropin (somatotropin), Rev 1, 29 August 2006, www.emea.europa.eu/humandocs/PDFs/EPAR/valtropin/H-602-en1.pdf
14. European Public Assessment Report for Binocrit (recombinant human erythropoietin alfa), Rev 2, 8 August 2008, www.emea.europa.eu/humandocs/PDFs/EPAR/binocrit/H-725-en1.pdf
15. European Public Assessment Report for Silapo (epoetin zeta), Rev 1, 11 August 2008, www.emea.europa.eu/humandocs/PDFs/EPAR/silapo/H-760-en1.pdf
16. Teva Pharmaceutical Industries press release, 16 September 2008, www.tevapharm.com/pr/2008/pr_786.asp
17. European Public Assessment Reports for withdrawal of Insulin Human Rapid Marvel, Insulin Human Long Marvel, Insulin Human 30/70 Mix Marvel, 21 February 2008, www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/31777807en.pdf
18. Casedevall N, "Pure Red Cell Aplasia and anti-erythropoietin antibodies in patients treated with epoetin", *Nephrol Dial Transplant*, November 2003, **18**, Suppl 8viii, 37-41
19. CPMP/BPWG/1561/99rev1, Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX Products, 19 July 2007, www.emea.europa.eu/pdfs/human/bpwg/156199endraft.pdf
20. CHMP/BMWP/14327/06, Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins, January 2008, www.emea.europa.eu/pdfs/human/biosimilar/1432706enfin.pdf
21. European Pharmacopoeia 6.0 01/2008 1316, Erythropoietin Concentrated Solution (pg 1813)
22. Boven K et al, "The Increased Incidence of Pure Red Cell Aplasia with an Eprex Formulation in uncoated stopper syringes," *Kidney Int*, June 2005, **67** (6), 2346-53
23. Boven K et al, "Epoetin-Associated Pure Red Cell Aplasia in Patients with Chronic Kidney Disease: Solving the Mystery", *Nephrol Dial Transplant*, May 2005, **20**, Suppl 3iii, 33-40
24. See Reference 13
25. See Reference 15
26. EMEA/CHMP/BMWP/170734/08, Revision of the guidance on similar medicinal products containing recombinant erythropoietins, released for consultation July 2008, www.emea.europa.eu/pdfs/human/biosimilar/17073408en.pdf
27. See Reference 3
28. See Reference 19
29. Schellekens H, *Nature Reviews*, June 2002, **Vol 1**

Professional
PIL
Production



Luto Research Ltd
103 Clarendon Road
Leeds LS2 9DF



We speak the right language. In anybody's language.

Clear, concise and straight to the point. As European & UK market leaders in the creation, editing and user testing of patient information, we believe that clear communication provides better comprehension – in any language.

- ▶ Bridging analysis & strategy
- ▶ User testing of package leaflets for branded, generic & biotech medicines for CP, DCP or national submissions
- ▶ PIL writing services from SmPC
- ▶ PIL design & layout service
- ▶ Faithful translations and linguistic validation
- ▶ Readability testing of Risk Management Plan patient education materials



Bringing clarity and understanding to patient information across the EU

For further information
please contact
Professor Theo Raynor

+44 (0)870 126 3202

solutions@luto.co.uk
www.luto.co.uk