

Biosimilars: Opportunity or Cause for Concern?

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ABSTRACT

Biopharmaceuticals are drug products containing biotechnology-derived proteins as active substances, and have revolutionised the treatment of many diseases. A number of biopharmaceutical patents are due to expire in the next few years, or have already expired. The subsequent production of follow-on products, or 'biosimilars' has aroused interest within the pharmaceutical industry as biosimilar manufacturers strive to obtain part of an already large and rapidly-growing market. The potential opportunity for price reductions versus the originator biopharmaceuticals remains to be determined, as the advantage of a slightly cheaper price may be outweighed by the hypothetical increased risk of side-effects from biosimilar molecules that are not exact copies of their originators. This review focuses on the issues surrounding biosimilars, including manufacturing, quality control, clinical efficacy and side effects, and how government and industry regulations are evolving to deal with these topics.

BIOPHARMACEUTICALS AND BIOSIMILARS

According to the European Agency for the Evaluation of Medicinal Products (EMEA), "biological medicinal products" (referred to as biopharmaceuticals in this review) are medicinal products containing biotechnology-derived proteins as active substances (1). Sales of biopharmaceuticals currently amount to over \$30 billion in the United States alone (2). This figure is increasing as other complex biological medicines are being manufactured and marketed to help in the treatment of many diseases. A case in point is the

treatment of anaemia associated with chronic kidney disease. The advent of recombinant human erythropoietin (epoetin) has minimized the need for blood transfusions, revolutionizing the treatment and management of this chronic condition. The four main biopharmaceuticals accounting for the majority of sales are epoetin, insulin, growth hormone (GH), and granulocyte colony stimulating factor (G-CSF), but several other cytokines, antibodies and hormones are also available (3). Biopharmaceuticals make up a large proportion of new medicines and many are being developed using the same technology that is used to produce vaccines. Advances over the last quarter of a century in recombinant DNA technology have allowed the large-scale manufacture of biologically-engineered proteins within living cells (4). Many of the patents to these products are now close to expiring or have already expired (5), such as for Humulin®, Intron A®, Procrit®/Eprex®, and Neupogen®, and manufacturers of so-called copycat pharmaceuticals are attempting to expedite the production of follow-on biopharmaceuticals, termed biosimilars.

Biosimilars are fundamentally different from generic chemical drugs. Important differences include the size and complexity of the active substance, and the nature of the manufacturing process. Unlike classical generics, biosimilars are not identical to their originator products, and therefore should not be brought to market using the same procedure applied to generics. This is partly a reflection of the complexities of manufacturing, and safety and efficacy controls of biosimilars when compared to their small-molecule generic counterparts (6-8).

What are some of the issues that concern all stakeholders involved? Causes for concern include testing for similarity and comparability of the biosimilars with the originator products, as well as guidelines for long-term pharmacovigilance programmes and assessment of potential complications arising from both short and long-term use.

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Biopharmaceuticals are usually recombinant protein molecules manufactured in living cells (4, 9). Manufacturing processes for biopharmaceuticals are highly complex and require hundreds of specific isolation and purification steps (7). It is thus impossible to produce an exact copy of a biopharmaceutical, as changes to the structure of the molecule can occur with changes in the production process (10). A protein can be modified in many ways: side chains can be added, the product can have alterations to its tertiary or quaternary structure through protein misfolding; degradation by oxidation or deamidation can also occur. As manufacturing protocols are generally proprietary knowledge of the originator company, it is impossible for a biosimilar's manufacturer to duplicate the process. This makes the production of biosimilars extremely challenging as different manufacturing processes may invariably lead to structural differences in the final product. In turn, these differences may lead to differences in efficacy and, more importantly, in their ability to trigger damaging patient immune responses (11,12).

ASSESSING BIOSIMILARITY

Exact copies of synthetic, "small molecule" pharmaceuticals can be synthesized, and considered to be equivalent if they have the same chemical structure, composition, and pharmacokinetic profiles as the originator drugs (6,13). The case for biopharmaceuticals, however, is not as simple. Using an entirely different production process, biosimilar manufacturers can only produce a molecule that is "similar" but not identical to, the originator product. A challenge for biosimilar manufacturers is to demonstrate that their products have sufficient likeness to the originator product, in addition to showing consistency of quality between different production runs from their own manufacturing facilities (8,13,14). The maintenance of consistent product efficacy is also important in order to avoid product "overdosing" and the concomitant risks of incurring adverse events.

Biopharmaceuticals can be as large as hundreds of kilodaltons, and their molecular weights can vary by as much as 1000 daltons (14). Various *in vitro* tests are currently used to compare the structural aspects of biosimilars with their originator molecules, including assessments of the primary amino acid sequence, charge and

hydrophobic properties (7). Determination of higher-order structure is performed using nuclear magnetic resonance or mass spectroscopy, and predictions of immunoreactivity using assays based on conformational-dependent antibodies (7). However, *in vitro* tests cannot predict biological activity *in vivo*. Despite similarities in size and structure, there may be significant differences in biological activity. Furthermore, *in vivo* biological activity can also be affected by product formulation and packaging, in addition to cold chain handling, as these parameters can influence the presence of impurities and protein aggregates (4). In addition, biological activity is difficult to assess adequately as few (if any) animal models are able to provide data that can be extrapolated for an accurate prediction of biological activity in humans. Ultimately, controlled clinical trials remain the most reliable means of demonstrating similarity between a biosimilar molecule and the originator product in the clinic. However, even these trials may frequently be underpowered to detect infrequent iatrogenic complications. Detailed registry data may be a prerequisite.

THE PROBLEM OF IMMUNOGENICITY

The most critical safety concern relating to biopharmaceuticals is immunogenicity (9,13,15,16). All biopharmaceuticals are biologically active molecules derived from living cells, and have the potential to evoke an immune response. Although the immunogenic potential cannot be predicted through chemical or structural analyses of the biopharmaceutical (9), several factors are known to affect a product's immunogenic potential. The presence of impurities in the final product, structural modifications as a result of the manufacturing process and/or storage conditions can increase immunogenicity. Here, quality control procedures integrated into the manufacturing process are of paramount importance in ensuring the manufacture of safe products of consistent quality (15). The route of administration of the biopharmaceutical can also affect immunogenicity, with intravenous administration being less immunogenic than intramuscular or subcutaneous administration (15,16). Patient factors are also important, such as genetic background and HLA-

expression of the patient, what type of disease is being treated and the patient's immune status (12).

The risks of immunogenicity can be reduced through stringent testing of the biopharmaceutical during its development (17). Many of the tests used are performed *in vitro*, but some *in vivo* animal models are available and are employed under the caveat that many immunogenic reactions are species-specific. All of these tests can give an idea of the antigenic potential of a biopharmaceutical, but cannot predict its immunogenic effects in an individual patient. Because international standards are lacking and materials and methods differ between laboratories, a comparison of results is impossible. In order for a meaningful comparison of results, all assays used need to be standardised according to international guidelines and recommendations. The only means of establishing the safety of a biopharmaceutical is through the use of clinical trials. Long-term monitoring of the effects in patients must be undertaken in order to properly assess the immunogenic effects of any biopharmaceutical introduced to the market. Immunogenicity has already proved problematic for a number of biopharmaceuticals currently on the market. Inhibitory antibodies to interferon (IFN) beta, a product used in the treatment of multiple sclerosis, have already caused many patients to withdraw from treatment (18,19). The antibodies inhibit the bioavailability of the cytokine with subsequent decreased clinical effectiveness (20). Inhibitory antibodies to PEGylated-megakaryocyte growth and development factor (MDGF) led to the cessation of its clinical trials after 13 of 325 healthy volunteers developed treatment-associated thrombocytopenia (21,22).

An example illustrating the severe consequences of small manufacturing changes is that of Eprex® (epoetin alfa; Johnson and Johnson). One of its applications is for the treatment of patients with anaemia secondary to chronic kidney disease, as these individuals are unable to produce adequate amounts of endogenous erythropoietin. A minor change in the formulation of this epoetin alfa product resulted in the development of neutralising antibodies not only to the drug itself, but also to native erythropoietin in certain patients (23,24). A number of patients developed anti-epoetin antibodies that neutralised both endogenous erythropoietin and injected epoetin, rendering the

bone marrow aplastic for erythropoietic progenitor cells (25-27). Although the actual cause of this immunogenic reaction remains unknown, one hypothesis is that leachates resulting from interactions between uncoated rubber stoppers and a new stabiliser used in the product formulation could have induced antibody production in some patients (28-30). However, this hypothesis has been called into question as having limited biological plausibility; in addition, the published studies have been criticised for not being peer-reviewed or citing statistical analysis (31). Whatever the actual cause, this case highlights the potential catastrophic impact that even minor changes in manufacturing can cause, and the difficulties in production and formulation of biopharmaceuticals. It also raises concerns about the safety of biosimilar molecules. If biosimilar molecules are manufactured using a completely different process than their originator products (in all probability resulting in structural and biochemical differences in the actual molecule), how can their safety be guaranteed without extensive clinical testing?

GUIDELINES AND REGULATION

The pharmaceutical industry together with drug regulatory bodies are wrestling with how stringently biosimilars should be regulated and how much needs to be known about a biosimilar for it to be deemed safe and effective. There are, of course, significant differences of opinion between manufacturers of originator products and potential manufacturers of biosimilars about how biosimilars should be regulated and monitored. Since biosimilars are not exact copies of their reference products, their safety, activity and efficacy need to be fully validated before their release on the market.

Creating guidelines that apply across all classes of biosimilars is difficult (32). The EMEA and the Committee for Human Medicinal Products (CHMP) have been working on guidelines that address non-clinical and clinical issues of biosimilars (32,33), including manufacturing processes, quality control (34) and guidelines specific to different classes of biosimilars such as recombinant human GH (35), insulin (36), erythropoietin (37) and G-CSF (38). The EMEA's recent rejection of a biosimilar interferon product (Alpheon®; Biopartners) because of characterisation, manufacturing, and quality control

issues underscores the fact that the pathway to approval for biosimilars is not as straightforward. The EMEA recognizes that the case for biosimilars differs from that of standard generics, and biosimilars manufacturers must fulfil quality, safety, and efficacy requirements. Testing of the biosimilar must be performed using an approved reference product as a control and include pre-clinical and clinical testing.

Pharmacovigilance monitoring is currently another grey area that awaits further definition. Although the EMEA stipulates that biosimilars manufacturers must have a plan for continuous post-marketing monitoring and pharmacovigilance, the definition of such post-marketing pharmacovigilance plans remains to be determined. Pharmacovigilance becomes an even more important factor in evaluating the safety of agents used to treat chronic disease (33). Current pharmacovigilance plans are based on individual adverse event reports, and it is often difficult to interpret data from individual adverse events across the general target population of a specific drug. In some cases (such as for vaccines), the size of pre-marketing clinical trials are often insufficient for the identification of rare adverse events, or those occurring after an extended period of time (34). That the clinical requirements for the approval of biosimilars are less than those for new chemical entities highlights the importance of rigorous pharmacovigilance monitoring to immediately identify any adverse events. A key issue for the success of any pharmacovigilance plan is proper product nomenclature. The current systems for naming of generic synthetic pharmaceutical products cannot be applied to biosimilars, as they are not identical to the originator product. Distinct International Nonproprietary Names (INNs) and trade names should be given to each biosimilar product, to optimise adverse events recording and product tractability. The use of distinct INNs ensures that adverse events are attributed to the correct product and prevents inadvertent substitution of products. A unique identification system would also ensure that patients are dispensed the exact medication prescribed by their physician.

The requirements outlined in the specific guidelines reflect the complexity of each class of biopharmaceutical. For example, it is not expected that clinical efficacy studies will be required for

insulin biosimilars, as these are relatively simple protein molecules. Pharmacodynamic and pharmacokinetic data may be sufficient to show equivalence in this case. Erythropoietin is a more complex molecule compared to either insulin or GH. The guidelines reflect this complexity and advocate at least two randomized controlled trials with safety data collected over at least 12 months from at least 300 patients in order to identify potential immunogenicity. Specific reference is made to include assessment of the incidence of PRCA within the pharmacovigilance plan for epoetin biosimilars (35). However, even with 300 patients, PRCA may not be detected due to the relatively small study size with respect to the rarity of this complication following previous alterations in manufacturing processes.

There is currently no set of guidelines for biosimilars in the United States. The FDA has recently approved Omnitrope® (Sandoz GmbH), a GH biosimilar, but this was done through the Abbreviated New Drug Applications (ANDA), which essentially defines them as drugs rather than biopharmaceuticals (3). However, this method of approval is rather an exception as currently no US regulatory guidelines for approval of biosimilars exist. Omnitrope is currently marketed at a price reduction of around 25%, but the market reaction to this drug remains to be seen. As several products are already available in the growth hormone market, the presence of Omnitrope may not have the same effect as would be the case if there was only one originator product. Approval of biosimilars in the US will likely be on a case-by-case basis and will depend on the complexity of the molecule and knowledge of its mode of action. New legislation may also be required to allow the marketing of biosimilars in the US, which could take a considerable length of time.

WHAT ABOUT SUBSTITUTION?

Switching patients from one product to a similar but “not quite identical” product may have important consequences. When faced with the possibility of substituting an originator drug with a biosimilar product, it is important to carefully consider the potential risks to the patient, such as that of an immunogenic response to a different molecule.

Although some biosimilars may prove to be as safe as their originator products, any product

with less patient exposure should be handled with caution. Manufacturers and physicians are encouraged to provide information to all stakeholders (including patients, pharmacists, and other caregivers) providing a clear assessment of the risks involved in switching from an established product to its biosimilar equivalent. Risk tolerance will likely depend upon individual and socioeconomic factors, such as the severity of the disease in question and the local healthcare reimbursement policy. Drug price reductions may be an important factor to consider in developing countries, whereas patient safety and brand loyalty may be the main deciding factors in developed countries.

CONCLUSIONS

Unlike generic pharmaceuticals, biosimilars are not identical to their originator products. The highly unpredictable nature of immune responses against biopharmaceuticals urges the appropriate testing of biosimilars based on sound scientific rationale and rigorous experimental evidence. The extent of biosimilar entry into the healthcare market as alternative therapeutic options remains open to speculation. Physicians, pharmacists, health care fund holders and patients will need to balance possible cost savings of biosimilar medications verses the risk of iatrogenic complications.

REFERENCES

- [1]. Committee for medicinal products for human use. Guideline on Similar Biological Medicinal Products. CHMP/437/04 2005. 2005.
- [2]. C. S. Ben Maimon. Point: why biogenerics make sense. *Nat Biotechnol*, 24:268-269, 2006.
- [3]. M. J. Belsey, L. M. Harris, R. R. Das, and J. Chertkow. Biosimilars: initial excitement gives way to reality. *Nat Rev Drug Discov*, 5:535-536, 2006.
- [4]. M. Kuhlmann and A. Covic. The protein science of biosimilars. *Nephrol Dial Transplant*, 21 Suppl 5:v4-v8, 2006.
- [5]. H. Schellekens. Follow-on biologics: challenges of the "next generation". *Nephrol Dial Transplant*, 20 Suppl 4:iv31-iv36, 2005.
- [6]. H. Schellekens. How similar do 'biosimilars' need to be? *Nat Biotechnol*, 22:1357-1359, 2004.
- [7]. A. J. Chirino and A. Mire-Sluis. Characterizing biological products and assessing comparability following manufacturing changes. *Nat Biotechnol*, 22:1383-1391, 2004.
- [8]. D. Crommelin, T. Bermejo, M. Bissig, J. Damiaans, I. Kramer, P. Rambourg, G. Scroccaro, B. Strukelj, R. Tredree, and C. Ronco. Biosimilars, generic versions of the first generation of therapeutic proteins: do they exist? *Contrib Nephrol*, 149:287-294, 2005.
- [9]. H. Schellekens. Bioequivalence and the immunogenicity of biopharmaceuticals. *Nat Rev Drug Discov*, 1:457-462, 2002.
- [10]. J. S. Robertson. Changes in biological source material. *Biologicals*, 34:61-63, 2006.
- [11]. S. D. Roger. Biosimilars: how similar or dissimilar are they? *Nephrology* 11:341-346, 2006.
- [12]. H. Schellekens. Immunogenicity of therapeutic proteins: clinical implications and future prospects. *Clin Ther*, 24:1720-1740, 2002.
- [13]. H. Schellekens. Biosimilar therapeutic agents: issues with bioequivalence and immunogenicity. *Eur J Clin Invest*, 34:797-799, 2004.
- [14]. F. Locatelli and S. Roger. Comparative testing and pharmacovigilance of biosimilars. *Nephrol Dial Transplant*, 21 Suppl 5:v13-v16, 2006.
- [15]. M. Kessler, D. Goldsmith, and H. Schellekens. Immunogenicity of biopharmaceuticals. *Nephrol Dial Transplant*, 21 Suppl 5:v9-v12, 2006.
- [16]. H. Schellekens and N. Casadevall. Immunogenicity of recombinant human proteins: causes and consequences. *J Neurol*, 251 Suppl 2:II4-II9, 2004.
- [17]. A. J. Chirino, M. L. Ary, and S. A. Marshall. Minimizing the immunogenicity of protein therapeutics. *Drug Discov Today*, 9:82-90, 2004.
- [18]. H. P. Hartung, F. Munschauer, III, and H. Schellekens. Significance of neutralizing antibodies to interferon beta during treatment of multiple sclerosis: expert opinions based on the Proceedings of an International Consensus Conference. *Eur J Neurol*, 12:588-601, 2005.
- [19]. S. Malucchi, M. Capobianco, F. Gilli, F. Marnetto, M. Caldano, A. Sala, and A. Bertolotto. Fate of multiple sclerosis patients positive for neutralising antibodies towards interferon beta shifted to alternative treatments. *Neurol Sci*, 26 Suppl 4:S213-S214, 2005.
- [20]. F. Deisenhammer, H. Schellekens, and A. Bertolotto. Measurement of neutralizing antibodies to interferon beta in patients with multiple sclerosis. *J Neurol*, 251 Suppl 2:II31-II39, 2004.
- [21]. I. C. Haznedaroglu, H. Goker, M. Turgut, Y. Buyukasik, and M. Benekli. Thrombopoietin as a drug: biologic expectations, clinical realities, and

- future directions. *Clin Appl Thromb Hemost*, 8:193-212, 2002.
- [22]. J. Li, C. Yang, Y. Xia, A. Bertino, J. Glaspy, M. Roberts, and D. J. Kuter. Thrombocytopenia caused by the development of antibodies to thrombopoietin. *Blood*, 98:3241-3248, 2001.
- [23]. H. Schellekens. Immunologic mechanisms of EPO-associated pure red cell aplasia. *Best Pract Res Clin Haematol*, 18:473-480, 2005.
- [24]. N. Casadevall. Antibodies against rHuEPO: native and recombinant. *Nephrol Dial Transplant*, 17 Suppl 5:42-47, 2002.
- [25]. N. Casadevall, J. Nataf, B. Viron, A. Kolta, J. J. Kiladjian, P. Martin-Dupont, P. Michaud, T. Papo, V. Ugo, I. Teysandier, B. Varet, and P. Mayeux. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med*, 346:469-475, 2002.
- [26]. N. Casadevall. Pure red cell aplasia and antierythropoietin antibodies in patients treated with epoetin. *Nephrol Dial Transplant*, 18 Suppl 8:viii37-viii41, 2003.
- [27]. H. Schellekens. Erythropoietic proteins and antibody-mediated pure red cell aplasia: a potential role for micelles. *Nephrol Dial Transplant*, 19:2422, 2004.
- [28]. K. Boven, J. Knight, F. Bader, J. Rossert, K. U. Eckardt, and N. Casadevall. Epoetin-associated pure red cell aplasia in patients with chronic kidney disease: solving the mystery. *Nephrol Dial Transplant*, 20 Suppl 3:iii33-iii40, 2005.
- [29]. K. Boven, S. Stryker, J. Knight, A. Thomas, M. van Regenmortel, D. M. Kemeny, D. Power, J. Rossert, and N. Casadevall. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney Int*, 67:2346-2353, 2005.
- [30]. A. Kromminga and H. Schellekens. Antibodies against erythropoietin and other protein-based therapeutics: an overview. *Ann N Y Acad Sci*, 1050:257-265, 2005.
- [31]. H. Schellekens and W. Jiskoot. Eprex-associated pure red cell aplasia and leachates. *Nat Biotechnol*, 24:613-614, 2006.
- [32]. A. Wiecek and A. Mikhail. European regulatory guidelines for biosimilars. *Nephrol Dial Transplant*, 21 Suppl 5:v17-v20, 2006.
- [33]. A. Kavanaugh and E. C. Keystone. The safety of biologic agents in early rheumatoid arthritis. *Clin Exp Rheumatol*, 21:S203-S208, 2003.
- [34]. E. Autret-Leca, L. Souda-Grimaldi, A. P. Jonville-Bera, and F. Beau-Salinas. Pharmacovigilance of vaccines. *Arch Pediatr*, 13:175-180, 2006.
- [35]. Committee for medicinal products for human use. Annex guideline on similar biological medicinal products containing biotechnology-Derived proteins as active substance: Non-clinical and clinical issues: Guidance on biosimilar medicinal products containing recombinant erythropoietins. European Medicines Agency. EMEA/CHMP/94526/2005 2005. 2005.
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