

Biosimilars of Biological Drug Therapies

Regulatory, Clinical and Commercial Considerations

George Dranitsaris,¹ Eitan Amir² and Kristine Dorward³

1 Augmentium Pharma Consulting, Toronto, ON, Canada

2 Department of Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada

3 School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK

Abstract

Biologicals are distinct from small molecule drugs in that they are larger, more structurally complex agents. While the overall risk is modest, the active protein structure characteristic of biologicals makes them more prone to induce an acute and/or chronic immune response. Biosimilars are a new class of drugs intended to offer comparable safety and efficacy to the reference, off-patent biological. They are not generic alternatives *per se* and are generally not interchangeable. Given their structural complexity, multifaceted manufacturing process and risk for immunogenicity, unique regulatory pathways are required for biosimilars. In this article, we review the clinical, safety and submission requirements for biosimilars in several major markets. We also highlight issues of ongoing debate amongst key stakeholders and examine some of the commercial challenges faced by developers of biosimilars. As the leader of biosimilars drug approval and product uptake, the EU is highlighted.

1. Introduction

Unlike traditional pharmaceuticals, biological drugs are derived from living organisms. Once the protein has been sequenced, recombinant DNA biotechnology has facilitated production on a large commercial scale. Approximately 90% of all biological products are produced from three sources: *Escherichia coli*, yeast or Chinese Hamster ovary cells.^[1,2] Biological drugs that have been produced and are commercially available include insulin, human growth hormone, erythropoietin, granulocyte colony-stimulating factor (G-CSF), interferon- α (IFN α) and monoclonal antibodies such as rituximab and trastuzumab, amongst others.^[2]

Two important differences between biological drugs and traditional pharmaceuticals are their respective molecular size and manufacturing processes. Biologicals are substantially larger; for

example, the anticancer agent paclitaxel has a size of 854 Daltons (Da), while the commercially available G-CSF (i.e. filgrastim), has a size of 18 000 Da.^[3] Monoclonal antibodies are even larger with sizes being in the range of 145 000–160 000 Da.^[3] The manufacturing process of biological drugs is also complex (figure 1). The protein production process begins with cloning of the relevant gene into a complementary DNA (cDNA) vector and transferring this into a host cell (such as *E. coli* or yeast). Once the protein is expressed, the appropriate cell line is selected and expanded in a fermentation medium where it produces the protein defined by the vector.^[2,3] A complex process of purification and validation is then required prior to obtaining the purified bulk drug. Quality control in the form of confirmation of the DNA sequence of the cloned gene by either southern blot analysis of total cellular DNA or sequence analysis of the messenger RNA (mRNA)

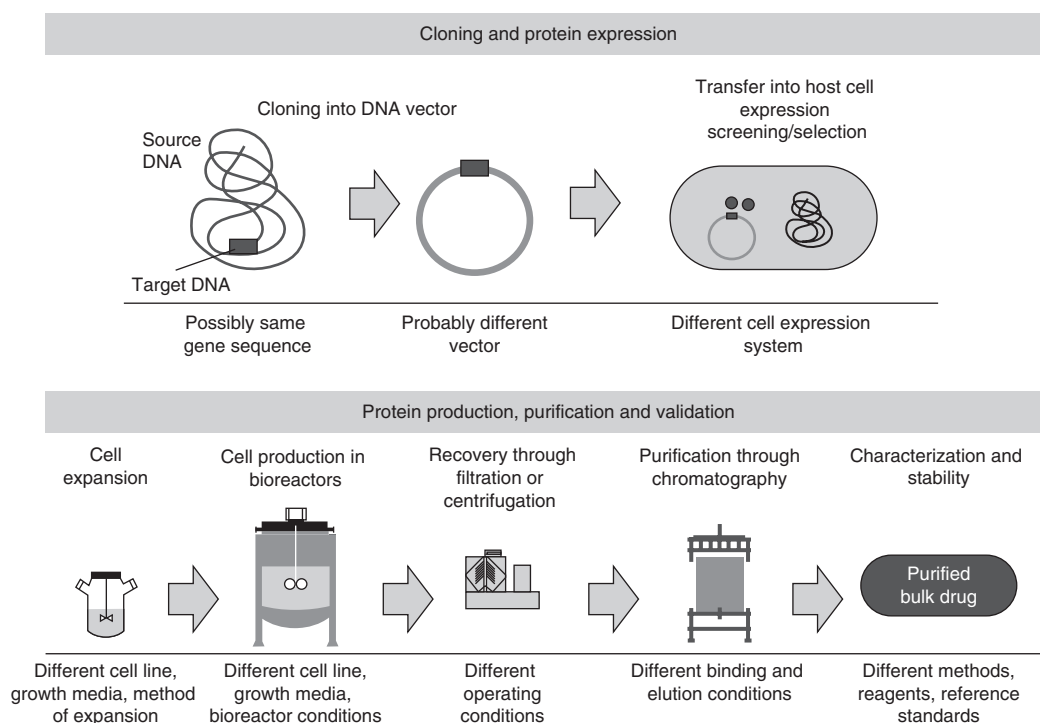


Fig. 1. The manufacturing process for biological drugs.

is usually conducted both before and after full-scale fermentation.^[2,3]

Over the past 10 years, there has been a rapid increase in the number of biological drugs that have received regulatory approval worldwide. As described in figure 2, fewer than 15 biological agents were approved by the US FDA in the early 1990s. By the middle of the last decade, the number of approved biological drugs surpassed that of small molecules (figure 2). By the end of 2009, biologicals in phase III clinical development made up 38% of all pipeline products for the pharmaceutical industry.^[4] These shifts in drug development and approval have subsequently been reflected in commercial adoption rates. In 2009, global sales of biological drugs reached \$US130 billion.^[5]

Most new drugs that receive regulatory approval are under patent protection. Patent life is typically 20 years from the time of filing a submission, which is usually done before clinical testing on humans begins. Since many of the first-

generation biologicals of erythropoietin and G-CSF were developed in the early 1990s, their patents have now expired. In addition, patents on the larger and more complex monoclonal antibodies such as rituximab and trastuzumab will also be expiring over the next 5 years. Commercially, this means that by 2016, approximately \$US64 billion worth of biological therapies will be going off patent and be open to generic competition.^[6] These developments have stimulated some manufacturers to invest substantial resources to develop a new class of drugs called biosimilars, which are described in this review.

2. Methods and Results of Literature Review

A literature search was conducted on PubMed, EMBASE and the Cochrane Database for the years January 2000 to June 2011. Search parameters included 'biosimilar' OR 'subsequent entry biologic' OR 'follow on biologic' AND

'regulatory pathway' OR 'approval'. The literature search was open to both clinical trials and review articles. Internet searches of Google Scholar and the various regulatory agencies (e.g. European Medicines Agency [EMA]) were also conducted to identify recent press releases, news items and guidelines related to biosimilars.

A total of 135 citations were identified and 39 were selected for a more extensive review. Reasons for citation rejection included type of study design (e.g. pharmacokinetic study), type of drug evaluated (e.g. low-molecular-weight heparin [LMWH] as opposed to a biological), evaluated physicochemical comparability between a biosimilars and a reference product, and the study focus was on stability/sterility issues of biosimilars.

3. The Emergence of Biosimilars

Unlike generic pharmaceuticals where only the chemical structure of the active drug needs to be reproduced, with biologicals both the protein structure and its folds need to be similar. Glycosylation is the enzymatic process that attaches polysaccharides to proteins, lipids or other organic molecules. Glycosylation patterns are important in the development of biopharmaceuticals because they can affect protein folds and overall stability, and may have a role in cell-cell adhe-

sion;^[3] they can be affected by the manufacturing process. Since biosimilar companies do not have access to proprietary manufacturing data from the brand company, developing an identical product with the same glycosylation pattern is very challenging. Given these considerations, the development of a biological drug that is fully interchangeable is virtually impossible given the technology that is available today. Therefore, the industry has focused on the development of biosimilars, agents that are biologically and clinically comparable to the innovator product but not exactly the same.^[2] The degree of comparability for a biosimilar is typically assessed on a product-by-product basis. In the US and Canada, biosimilars are called 'Follow on Biologics' and 'Subsequent Entry Biologics', respectively.^[7,8]

In developed markets, the official regulatory approval process for biosimilars is distinct from that outlined for generic formulations of small molecules. To receive regulatory approval, manufacturers of generic drugs only need to demonstrate pharmacokinetic comparability to the original product. Pharmacodynamic and clinical equivalence do not need to be shown. With pharmacokinetic comparability, generic drugs are deemed to be fully interchangeable with the innovator product and the same therapeutic effects are assumed. In contrast, biosimilars, even after regulatory

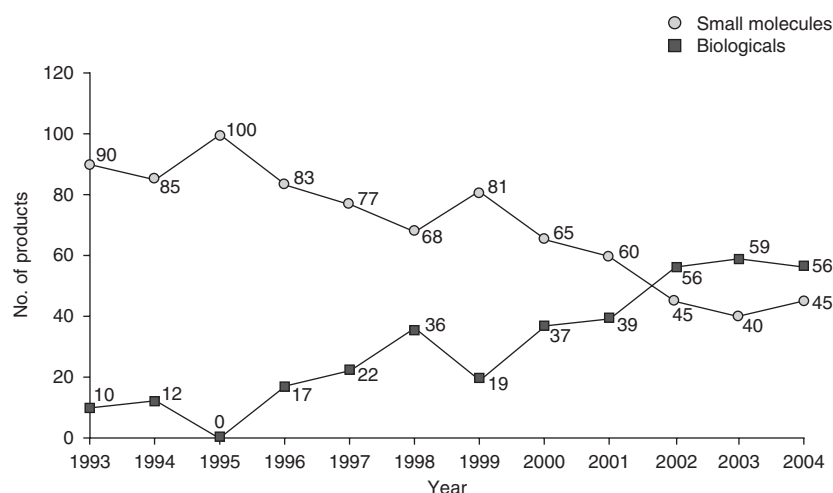


Fig. 2. Products receiving US FDA approval from 1993 to 2004.

approval, are currently not deemed interchangeable with the reference product.

The complexity and precision involved in the manufacturing processes of biological drugs should not be taken lightly. In the 1990s, cases of red cell aplasia (RCA) were reported in renal dialysis patients who were receiving treatment with subcutaneous epoetin alfa.^[2,9] After an intensive investigation, the most likely cause of the RCA was a formulation change, which led to antibody formation against all circulating erythropoietin. Removal of human serum albumin from the epoetin alfa formulation and its replacement with polysorbate 80 and glycine as stabilizers was suggested as the primary cause.^[9,10] This example illustrates how a small change in the development of a biological can lead to serious adverse events and patient complications.

Interchangeability with the reference product is a critical issue in the development and approval of biosimilars. The EMA does not have the authority to designate a biosimilar as interchangeable to the reference product. However, the new US Biologics Price Competition and Innovation Act does allow the US FDA to formally designate a biosimilar interchangeable.^[11] Under such a designation, a pharmacist would be able to substitute a biosimilar for the reference product without contacting the prescribing physician. One of the arguments against interchangeability stems from the fact that developers of biosimilars do not have access to data on quality and consistency from the brand product. However, it has been illustrated that branded biologicals also undergo changes over time, secondary to modifications in the manufacturing process or production carried out in multiple facilities.^[11] Therefore, it has been recommended that this variability be formally recognized by regulatory authorities and be used to create acceptability limits for evaluating biosimilars submissions.^[11]

4. How Similar is Similar Enough?

The EMA has developed a well defined process for the regulatory approval of biosimilar drugs. They have created guidelines customized and specific to particular classes of biosimilar agents related

to manufacturing quality, non-clinical pharmacology and toxicology, and pharmacokinetics and clinical considerations.^[7,9,10] Summaries of the EMA guidelines for biosimilar drug approval are presented in table I. The products where specific guidance has been issued include erythropoietin, G-CSF, insulin, growth hormone, LMWH and IFN α . The EMA also held workshops on biosimilars of monoclonal antibodies and made draft guidelines available on 26 November 2010 to stakeholders for a 6-month consultation period.^[12,13]

The major issues addressed by the EMA guidelines are safety, immunogenicity, clinical efficacy and extrapolation of indications. When the safety of biosimilars is being assessed, identical safety parameters that were used for the reference agent must be used in the development programme. There should also be a sufficient patient sample size in the clinical trial programme to quantify the adverse effect profile relative to the reference

Table I. Current European Medicines Agency (EMA) guidelines for the approval of biosimilars^[12]

Criterion	Requirement for regulatory approval
Preclinical studies	Comparative non-clinical and toxicology studies (e.g. 28-day toxicity for G-CSF and epoetin)
Pharmacodynamics	Pharmacodynamic similarity markers should be based on clinical efficacy (e.g. for G-CSF, ANC and CD34 in human volunteers)
Pharmacokinetics	Single dose SC and IV in human volunteers. Criteria for acceptance based on clinical judgement
Clinical trials	At least one equivalence trial relative to the reference product is required or a three-arm trial relative to the reference product and placebo. If both the SC and IV route of administration are possible, then two separate clinical trials must be undertaken
Extrapolation to other disease sites	This may be permitted, but a final decision will usually be made on a case-by-case basis
Drug safety	Safety must be demonstrated in at least one equivalence trial with the reference product in the control arm
Immunogenicity	All clinical trials must include antibody testing
Post-approval requirements	Specific monitoring must be performed for efficacy in the extrapolated indications. A pharmacovigilance programme is required post-approval

ANC=absolute neutrophil count; **G-CSF**=granulocyte colony-stimulating factor; **IV**=intravenous; **SC**=subcutaneous.

product (table I). The EMA guidelines also put an emphasis on a well designed pharmacovigilance programme following approval in order to identify rare and potentially serious events.^[2,11,12]

4.1 Immunogenicity

Immunogenicity is a substantial safety concern for biopharmaceuticals.^[14,15] Biopharmaceuticals are biologically active molecules and have the propensity to induce an immune response. Several factors are known to affect a product's immunogenic potential. These can relate to the biopharmaceutical, the host or a combination thereof. Immunogenicity can be induced by the active-drug substance product, but more commonly results from manufacturing impurities originating from the producing cell line or media components. The presence of impurities in biological products, structural modifications as a result of the manufacturing process and/or sub-optimal storage conditions can increase the risk of immunogenicity.^[16] Patient factors such as age, human leukocyte antigen (HLA) expression, co-morbid conditions and previous exposure to biological agents are also related to immunogenicity.^[14] In addition, the route of administration of the biopharmaceutical can also affect immunogenicity. Generally, intravenous administration is less immunogenic than intramuscular or subcutaneous administration, as was the case with epoetin alfa and RCA.^[9,15]

While the likelihood of immunogenicity can be reduced through stringent testing of the biopharmaceutical during its development,^[17] many such tests are conducted in the preclinical setting and therefore do not predict well for immunogenic effects in individual patients. Therefore, the only robust means of establishing the safety of a biopharmaceutical is through clinical trials.

Minor formulation changes can result in severe consequences as described in section 3 for epoetin alfa.^[9,10] Biosimilar molecules are manufactured using independent processes compared with their reference products. The likely result is structural and biochemical differences in the actual molecule. Therefore, this raises concerns regarding the safety of biosimilar molecules. Given

these uncertainties in product safety, and the association of the underlying disease in the aetiology of immunogenicity, it is unlikely that clinical safety data can be extrapolated to other indications. As a result, the regulatory authorities of most countries require pharmacovigilance programmes for each drug following approval.

4.2 Clinical Efficacy

To demonstrate comparative safety and efficacy, the EMA has issued product class guidelines for biosimilar erythropoietin, G-CSF, insulin, human growth hormone, IFN α and LMWHs.^[7] In Europe, 14 biosimilars have been approved over the past 5 years (table II). The EMA documents provide biosimilar manufacturers with detailed guidance on pharmacokinetics, pharmacodynamics, toxicology and clinical studies that are required to receive drug approval. The goal of the clinical development programme for the biosimilar is to demonstrate no clinically meaningful difference relative to the innovator product. To do this, equivalence trials of adequate sample size must be conducted and should ideally be double-blinded. One of the first items required in designing an equivalence trial is to establish a 'minimally clinically important difference (MCID)' in the primary trial endpoint. The MCID is defined as the minimum difference in a meaningful clinical endpoint between two treatments beyond which regulatory bodies would consider the two drugs to be non-equivalent. From a trial design point of view, the smaller the MCID set during the design of an equivalence trial, the larger the final sample size.^[7]

The EMA guidelines for each product class are comprehensive, but they stop short of defining the MCID. Instead, the EMA prefers that the applicant define the primary endpoint in their trial protocol along with the MCID justified on clinical grounds. As an illustration, the MCID for the biosimilar IFN α -2a was response rate, which was set to $\pm 15\%$. For the biosimilar of filgrastim, the MCID was ± 1 day of severe neutropenia following myelosuppressive chemotherapy.^[7] In the oncology setting, the EMA guidelines for biosimilars of monoclonal antibodies require that equivalence be demonstrated in either disease-free,

Table II. Biosimilars approved in Europe

Biosimilar (manufacturer)	Reference product (manufacturer)	Date of approval
Human growth hormone		
Omnitrope® (Sandoz)	Genotropin (Pfizer)	April 2006
Valtropin® (Biopartners)	Humatrope (Ely Lilly)	April 2006
Epoetin		
Abseamed® (Medice Arzneimittel Pütter)	Eprex (Janssen-Cilag)	August 2007
Retacrit® (Hospira)		December 2007
Binocrit® (Sandoz)		August 2007
Epoetin alfa Hexal® (Hexal Biotech)		August 2007
Silapo® (STADA Arzneimittel)		December 2007
Granulocyte colony-stimulating factor		
Filgrastim Hexal® (Hexal Biotech)	Neupogen (Amgen)	February 2009
Biograstim® (CT Arzneimittel)		September 2008
Nivestim® (Hospira)		June 2010
Zarzio® (Sandoz)		February 2009
Ratiograstim® and Filgrastim Ratiopharm® (Ratiopharm)		September 2008
Tevagrastim® (Teva Pharma)		September 2008

progression-free or overall survival. Moving forward, selection of the final primary endpoint and the MCID will be based on a case-by-case basis in consultation with the EMA.

In the case of an adequately powered trial demonstrating equivalence in clinically meaningful efficacy and safety endpoints, an issue of unresolved debate pertains to extrapolation to other indications. The EMA guidelines, as well as those of some other countries, allow extrapolation to other indications, but this has to be assessed on a case-by-case basis because of the uncertainties (table III).

5. Regulatory Requirements Around the World

The three main components needed for a biosimilar to receive regulatory approval are degree of clinical and non-clinical similarity to the reference product, safety and immunogenicity, and the quality of the manufacturing process. Comprehensive guidance to biosimilars manufacturers has been provided by the EMA. In contrast, the situation in other countries is less transparent. In the US, the new Biologics Price Competitions and Innovation Act, approved in March 2010, now allows the FDA to approve biosimilars and to decide on interchangeability with the reference

product.^[11] However, unlike the situation in Europe, there is currently no legislated abbreviated pathway for the approval of biosimilars in the US.^[11] This is in contrast to the situation for generic drug approval where the Hatch-Waxman act creates a clear abbreviated pathway.

In November 2010, stakeholders met with the FDA to discuss the biosimilars act, which is part of the healthcare reform bill passed earlier in the year.^[6] The three main issues identified in the meeting were: (i) how interchangeability should be designated; (ii) the need for clinical trials; and (iii) the naming of biosimilar products. Even though the EMA has addressed many of these issues in their guidelines, limited reference was made to these during the 2-day meeting.^[6] As a result, it seems unlikely that the FDA will adopt the biosimilars guidelines developed by the EMA. Therefore, the situation with the FDA remains uncertain and biosimilar manufacturers for the time being will need to 'learn as they go', relying on prior experience. Formal biosimilars guidelines by the FDA are critical, since several monoclonal antibodies such as trastuzumab and adalimumab will be coming off patent over the next 5 years.

Other countries around the world such as Australia, Canada and Japan are following similar requirements as the EMA for an abbreviated

approval pathway (table III). Australia has adopted the EMA guidelines and each submission will be assessed on a case-by-case basis. Australian regulators are encouraging biosimilar manufacturers to seek pre-submission meetings in order to clarify the data required for drug approval.^[9] In Canada, the regulatory agency (Health Canada) has issued draft guidelines for subsequent entry biologicals after consultation with the key stakeholders.^[9,18] Health Canada plans to issue guidance for specific drug classes, similar to the European approach. In Japan, the ministry of health has also recently issued guidelines for the approval of biosimilars that are consistent with the EMA criteria.^[9] In countries such as China and India, the approval pathway for versions of biological drugs is not as comprehensive, and a wide range of agents have already been launched or are under development (table IV).^[19] However, such agents should not be considered as 'biosimilars' to reference products because they have not been adequately tested using rigorous criteria such as those developed by the EMA.

6. Patent and Data Protection Issues

The intent of patent protection is to provide the innovating company with an adequate time period in order to recoup their investment and make a profit. In addition to patenting the actual molecular structure of the product, the manufacturing process for the biopharmaceutical is also frequently patented. The innovating company is under no obligation to disclose this process to regulatory authorities evaluating biosimilar drug submissions. It is also possible that the therapeutic quality of the product may be linked to the manufacturing process. Therefore, this limits

the ability of government agencies to establish comparability and safety in manufacturing and quality control between the reference product and the biosimilar. Another major issue with the emergence of biosimilar versions of existing monoclonal antibodies will be data protection. It remains unclear whether manufacturers of biosimilars will be permitted to use the clinical data of the innovator product to promote use of the biosimilar in other indications that are still under patent protection. All of these issues will need to be addressed by the regulatory bodies, and it is foreseeable that many of them could end up in federal court.

7. Challenges for Commercial Success of Biosimilars

From a payer's perspective, the main driver behind the use of biosimilars is cost reduction. However, there are several legitimate concerns that physicians may have before using a biosimilar in place of an established biological. Physicians are unlikely to put cost savings ahead of a patient's well-being, especially when juxtaposed to a product with which they have had years of clinical experience and treatment success. Therefore, manufacturers of biosimilars products face several challenges following regulatory approval. These include the implementation of rigorous pharmacovigilance programmes, patient and physician acceptance, commercial scale-up, intensity of competition and level of price erosion.

Given the complexity and concerns associated with biosimilars, a comprehensive marketing programme is required to educate payers and physicians on the clinical utility of these agents. Manufacturing and development costs for some of the first-generation approved biosimilars has

Table III. Summary of regulations for biosimilars in selected countries^[2,7,9,11,18]

Requirement	Europe	Canada	Australia
Reference drug	Local	Local preferred	Local
Full quality dossier	Yes	Yes	Yes
Efficacy in one indication only	Acceptable	Possibly	Acceptable
Comparable safety	Yes	Yes	Yes
Extrapolation	Acceptable	Possibly	Acceptable
Pharmacovigilance programme	Yes	Yes	Yes

Table IV. Versions of biological drugs approved or currently in development in China and India^[11,18]

Approved	Under development
China	
Etanercept	Cetuximab
Muromonab	Basiliximab
	Teplizumab
	Daclizumab
	Rituximab
	Trastuzumab
	Infliximab
	Abatacept
India	
Rituximab	Etanercept
Insulin	Trastuzumab
G-CSF	Follicle-stimulating hormone
Erythropoietin	Bevacizumab
Interferons	
Insulin glargine	
Pegylated interferon	
Streptokinase	
Tissue plasminogen activator	
Pegylated G-CSF	
Human growth hormone	

G-CSF = granulocyte colony-stimulating factor.

been estimated to be \$US75 to \$US250 million.^[11,20] For more complex monoclonal antibodies, costs of up to \$US500 million have been projected.^[20] Given the aforementioned challenges and the high cost of product development, entry into the biosimilars arena presents a substantial degree of risk and uncertainty, and it may take years for a company to recoup its initial investment.

7.1 Recent Performance of Biosimilars

The EMA has set a precedent globally, with biosimilars being approved for somatropin, epoetin alfa, epoetin beta and filgrastim (table II). Biosimilars provide up to 30% savings relative to the list price of the original brand product, which could increase to a 50% savings as more agents receive approval.^[20] Despite this cost differential, the uptake of biosimilars in major European markets has been modest. Taking France and Germany as an example, the six biosimilars of filgrastim have only been able to capture <50% of the total mar-

ket share.^[20] We anticipate that this modest rate of adoption for biosimilars will characterize near-term market dynamics, which is in contrast to the rapid brand erosion typically seen with the launch of small molecule generics. Upon entry of a new competitive biosimilar to its market, an innovator company can compete on price, brand loyalty, uncertainty in safety and efficacy, and the development of next-generation products. As an illustration, Roche is currently developing next-generation products for rituximab, trastuzumab and bevacizumab.^[21] In addition, the EU, the US, Canada, Japan and Australia do not typically allow the automatic substitution of a biosimilar for the reference product because of safety and efficacy concerns, which mitigates one of the key drivers facilitating rapid penetration and market share uptake of generic small molecules.

7.2 Future Outlook for Biosimilars and Next-Generation Biologicals

On a step-wise spectrum of all biological agents, monoclonal antibodies exhibit the most intricate and complex tertiary structures, and thus regulatory hurdles regarding immunogenicity and clinical efficacy parameters are most rigorous. Less regulated markets such as India and China have, however, seen the launch of several complex follow-on biologicals (table IV), since manufacturers of these agents circumvented the exhaustive regulatory hurdles and standards mandatory in developed markets. Dr Reddy's Laboratories garnered recognition for launching the very first follow-on monoclonal antibody globally, a version of Roche's blockbuster agent rituximab, which was commercialized in India in 2007 under the name RedituxTM. Dr Reddy's subsequently launched their own version of darbepoetin alfa called Cresp[®] in 2010. Grafeel[®], the company's haemopoietic growth factor that stimulates the proliferation of neutrophils, has a simple molecular structure relative to that of filgrastim and has been available in India since 2001.^[22]

With some markets exhibiting a rather acute demand for lower-cost biological alternatives, growth in the global biosimilars market may climb to an estimated \$US19.4 billion by 2014.^[23]

In order to capitalize on this opportunity, biotech and generics firms are partnering to optimize resources and gain access to expertise that may be lacking inhouse. Biotech start-up companies typically possess inhouse development and manufacturing capabilities, which are complimented by the distribution and marketing capabilities of the larger generics firms. For example, Teva Pharmaceutical Industries separately acquired IVAX and Sicor in order to gain technological expertise to characterize and purify recombinant proteins.^[23] They have also announced their plans to develop a biosimilar version of rituximab. Spectrum Pharmaceuticals and Viropro are among the most recent firms to announce their plans for a manufacturing and development alliance focused on biosimilars.^[24]

Approval of monoclonal antibodies is dependent on appreciably more efficacy and safety data, albeit to varying degrees depending on the agent under review. Generic manufacturing giant Sandoz has been able to capitalize on a market entry advantage in Europe owing to their comprehensive clinical development programme coupled with the EMA's regulatory requirements, which have impeded Indian manufacturers from gaining a foothold due to inferior clinical data packages. Sandoz has dominated the European biosimilars market since 2007 when it launched four of the first five commercialized biosimilars. Meanwhile, the EMA has not yet approved any regulatory application for a follow-on biological agent submitted by an Indian manufacturer. Such an extensive delay for Indian manufacturers to enter European markets provides Sandoz with substantial competitive advantage since the former may not be able to persuade physicians to switch products after they have gained considerable experience with Sandoz's biosimilars. Hence, Indian generics companies may target unregulated and semi-regulated markets in the near term.^[25] Given these types of distinct regional dynamics, disparity in clinical development investment and breadth of product portfolio, one may anticipate the emergence of corporate strongholds in select markets. While it may be some years before biosimilars of trastuzumab or adalimumab become widely prescribed by specialists in European and

North American markets, their acceptance upon launch will likely be influenced by the aforementioned factors and specifically by the manufacturer's corporate reputation.

Next-generation products are expected to provide incremental clinical advantages over currently approved biologicals, and may include new formulations with improved dosing regimens, improved efficacy and/or reduced immunogenicity. Innovators such as Amgen, Biogen Idec, Roche, Merck & Co. and Novo Nordisk have all announced plans to launch next-generation biologicals. Not surprisingly, Pfizer's research and development efforts have included the pursuit of an improved version of etanercept (Enbrel[®]), its blockbuster therapy for rheumatoid arthritis, due to face patent expiry in 2012.^[26]

8. Conclusions

Biosimilars or follow-on biologicals are a clinical reality, and over the next 10 years more agents with increased complexity will be entering global markets. They offer a potential for healthcare cost savings, but present some uncertainty related to safety and efficacy, particularly when the reference biological has multiple indications. This is highly relevant for the treatment of cancer, where patient and disease characteristics can affect drug activity. Health policy decision makers and clinicians need to be aware that these products are not generic versions of the original brand. Therefore, when a physician prescribes a biosimilar in place of the reference product, it should be seen as a new therapeutic intervention.^[2]

Since the manufacturing process for biosimilars is complex and involves living micro-organisms, both immediate and long-term immune reactions are a legitimate concern. Coupled with the abbreviated approval pathway requiring fewer patients than the reference product, pharmacovigilance programmes will also be required post-approval, to establish safety and efficacy across indications. However, on the positive side, biosimilars of somatropin, epoetin alfa and filgrastim have been used in Europe for at least 4 years and there have been no reports of serious adverse events submitted to the EMA. Nevertheless, as

part of the process to protect patients, regulators in other countries ought to consider emulating the European approach and engage with all key stakeholders in developing reasonable approval pathways. The ultimate success of biosimilars and their potential to save healthcare costs will depend on collecting information pre- and post-approval to address the many uncertainties.

Acknowledgements

No sources of funding were received for the preparation of this review. The authors have no conflicts that are directly related to the content of this review.

References

- Woodcock J, Griffin J, Behrman R, et al. The FDA's assessment of follow on protein products: a historical perspective. *Nat Rev Drug Discovery* 2007; 6: 437-42
- Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol* 2008; 19: 411-9
- Beck A. European medicines workshop on biosimilars monoclonal antibodies: perspective from the EU. *MAbs* 2009; 1: 406-10
- Data on file, IMS, 2009
- Kueppers E. Follow on biologics: how to develop a competitive advantage. *Bus Dev Licens J* 2010; 12: 17-8
- Bruce F. FDA should look to the EU for guidance on biosimilars, November 5, 2010 [online]. Available from URL: <http://www.scripintelligence.com/home/FDA> [Accessed 2010 Nov 6]
- Fox A. Biosimilar medicines: new challenges for a new class of medicine. *J Biopharm Stat* 2010; 20: 3-9
- Gottlieb S. Biosimilars: policy, clinical, and regulatory considerations. *Am J Health Syst Pharm* 2008; 65 (14 Suppl. 6): S2-8
- Roger SD. Biosimilars: current status and future directions. *Expert Opin Biol Ther* 2010; 10: 1011-8
- Minghetti P, Rocco P, Del Vecchio L, et al. Biosimilars and regulatory authorities. *Nephron Clin Pract* 2010; 117: c1-7
- McCamish M, Woollett G. Worldwide experience with biosimilars development. *MAbs* 2011; 3: 209-17
- Reichert JM, Beck A. European medicines workshop on biosimilars monoclonal antibodies. *MAbs* 2009; 1: 394-405
- Draft guideline on biosimilar medicines containing monoclonal antibodies released for consultation, November 26, 2011 [online]. Available from URL: <http://www.ema.europa.eu/ema/index> [Accessed 2011 Nov 26]
- Schellekens H. Bioequivalence and the immunogenicity of biopharmaceuticals. *Nat Rev Drug Discov* 2002; 1: 457-62
- Schellekens H. Biosimilar therapeutic agents: issues with bioequivalence and immunogenicity. *Eur J Clin Invest* 2004; 34: 797-9
- Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern? *J Pharm Sci* 2007; 10: 405-10
- Chirino AJ, Ary ML, Marshall SA. Minimizing the immunogenicity of protein therapeutics. *Drug Discov Today* 2004; 9: 82-90
- Health Canada. Draft guidance for sponsors: information and submission requirements for subsequent entry biologics [online]. Available from URL: <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/consultation/seb-pbu/2008-tc-tm-eng.php> [Accessed 2010 Nov 26]
- Iyer H. European medicines workshop on biosimilars monoclonal antibodies: perspectives from India. *MAbs* 2009; 1: 411-3
- Merrill J. Opening a door to biosimilars in the US, October 2, 2010 [online]. Available from URL: <http://www.windhover.com/windhover/content/home.aspx> [Accessed 2010 Nov 26]
- Whalen J. Roche CEO girds for first biotech fight. *New York (NY): Wall Street Journal*, 2010 Nov 2
- Rajan S. Dr Reddy's launches darbepoetin alpha in India under the brand name Cresp [online]. Available from URL: http://www.fiercepharma.com/press_releases/dr-reddys-launches-darbepoetin-alfa-india-under-brand-name-cresp [Accessed 2011 Jan 5]
- Crandall MA. World markets for biogenerics. *New York (NY): Kalorama Information*, 2008: 79-80
- Razvan R. Rituximab biosimilar to be developed by Spectrum Pharmaceuticals and Viropro [online]. Available from URL: <http://www.genengnews.com/gen-news-highlights/rituximab-biosimilar-to-be-developed-by-spectrum-and-viropro/81244470> [Accessed 2011 Jan 5]
- Ariyanchira S. The opportunity for India in the global biosimilars market [online]. Available from URL: <http://www.pharmaphorum.com/2010/06/21/the-opportunity-for-india-in-the-global-biosimilars-market> [Accessed 2011 Jan 5]
- Rockoff JD, Loftus P. Pfizer pushes on new biotech drugs. *New York (NY): Wall Street Journal*, 2010 Apr 28 [online]. Available from URL: <http://online.wsj.com/article/SB10001424052748704464704575208580328253618.html> [Accessed 2011 Jan 8]

Correspondence: Dr George Dranitsaris, 283 Danforth Ave, Suite 448, Toronto, ON, M4K 1N2, Canada.
E-mail: george@augmentium.com