

CONCERNING ISSUES WITH BIOSIMILARS: AN OVERVIEW

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Summary

Biopharmaceuticals are biological medicinal products that have been developed through biotechnological practices, including recombinant human technology, gene technology or antibody methods. The imminent patent expiration of many biopharmaceutical products will produce the possibility for generic versions of these therapeutic agents (i.e. biosimilars). Biosimilars differ from generic low molecular weight chemical drugs in many important ways. These include the size and complexity of the active substance, which will affect the scientific requirement for testing; the nature of the starting materials (cell banks, tissues, and other biological products); the complexity of the manufacturing processes; and the limitations of state-of-the-art methods to characterize proteins and to detect all product variations that can influence clinical efficacy, side-effects like immunogenicity. Therefore, it was acknowledged that established legal and regulatory principles of 'essential similarity' that are applied to standard generics cannot be readily applied to biosimilars. Thus, verification of the similarity to or substitutability of biosimilars with reference innovator biopharmaceutical products will require much more than a demonstration of pharmacokinetic similarity, which is sufficient for

conventional, small molecule generic agents. This review deals with the issues surrounding biosimilars, including manufacturing, quality control, bioequivalence, clinical efficacy and side effects like immunogenicity, and how government and industry regulations are evolving to deal with these topics.

Key words: Biosimilars, Generics, Immunogenicity.

Introduction

Biopharmaceutical agents are medicinal products of biotechnological origin, which contain proteins derived from recombinant DNA technology and hybridoma techniques, and have revolutionized the treatment of many diseases, including anemia, diabetes, cancer, hepatitis and multiple sclerosis, etc [1]. Recombinant proteins are derived from cell lines that are maintained in long-term culture, including some that are derived from genetically engineered bacteria (e.g. *Escherichia coli*). Examples of biopharmaceuticals include biological proteins (e.g. cytokines, hormones and clotting factors), monoclonal antibodies (mAbs), vaccines and cell/tissue-based therapies [2]. The use of these agents has increased dramatically in recent years. Biological medical products that are biologically similar to registered innovator products are referred to as 'biosimilars' in Europe and South-East Asia and 'follow on biologicals' in the USA [3]. Biosimilars are defined as biological products similar, but not identical, to reference products that are submitted for separate marketing approval following patent expiration of the reference products [1]. Table shows standard definitions for conventional generic agents, biopharmaceuticals and biosimilars based on terminology used by the European Medicines Agency (EMA) [4].

Definitions of biological and chemical pharmaceuticals

Generic drug	Chemical and therapeutic equivalent of a low-molecular-weight drug whose patent has expired
Biopharmaceutical	‘A medicinal product developed by means of one or more of the following biotechnology practices: rDNA, controlled gene expression, antibody methods’
Biosimilar	‘A biological medicinal product referring to an existing one and submitted to regulatory authorities for marketing authorization by an independent application after the time of the protection of the data has expired for the original product’

The driving force behind biosimilars

With the ever-increasing cost of pharmaceuticals, both for small molecules and biosimilars, there is an impetus to reduce the fiscal cost of these interventions to increase patient access and limit the rapidly expanding health-care budget. The arrival of generic medicines and attempts by regulatory authorities to cap costs by imposing significant reductions in reimbursement or price is a worldwide phenomenon. A number of biopharmaceutical patents are due to expire in the next few years, or have already expired such as human insulin, human growth hormone and interferon alfa and beta. 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. Demand for biologics is also growing rapidly. According to a 2009 Federal Trade Commission report, in 2007 American consumers spent ~\$40 billion on biologics out of \$287 billion spent for prescription drugs overall [5].

Manufacturers, policymakers and regulatory authorities must ensure that the economic benefits that biosimilars promise are not endangered by unique safety risks that biosimilars can pose.

Differences between generics and biosimilars

Biosimilars are fundamentally different from generic chemical drugs [6]. Generic drugs represent chemical and therapeutic equivalence to the original drug whose patents have expired. Most chemical drugs are low molecular weight compounds that are made from standard chemicals and

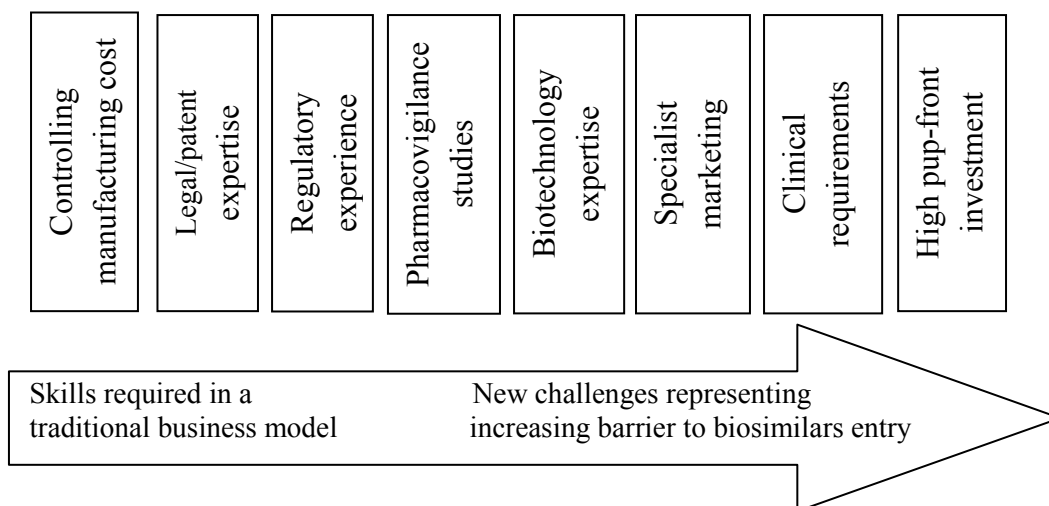
reagents, involving organic chemistry [3]. In contrast, biopharmaceuticals are high molecular weight compounds with complex three-dimensional structures and the production process is much more complicated.

Molecular weights of chemical drugs compared with biopharmaceuticals [6]:

	Drug name	Molecular weight (Da)
Chemical drugs	Paracetamol	151
	Rofecoxib	315
	Simvastatin	419
Biopharmaceuticals	Filgrastim	18 800
	Epoetin alfa	30 400
	Rituximab	145 000
	Factor VIII	264 000

It may be possible to mimic the initial amino acid sequence (primary structure), but further analysis of the biopharmaceutical's structure reveals both local folding (secondary structure) and subsequent global folding (tertiary structure), utilizing various hydrogen or disulphide bonds. Some biopharmaceuticals also exhibit quaternary structure, which is the stable association of two or more polypeptide chains into a multisubunit structure and this may further alter activity, duration of action and other properties [7]. The various cell lines often involving heterogeneous mammalian cell lines that are used to produce the proteins may have an impact on the overall structure of the protein, and may affect post-translational modifications such as the extent of glycosylation. Alteration of the degree of glycosylation of molecules may impact greatly on receptor binding, both in duration and efficacy, in addition to altering metabolic profiles. Further modification may occur outside of cell culture, with the addition of polyethylene glycol bridges (pegylation), to join proteins and further alter receptor binding and subsequent metabolic removal [8]. In fact there is a higher barrier to entry for the biosimilar market than for small-molecule generics which includes higher costs, greater risks, greater time and expertise in relation to the clinical development of these products. Furthermore, the marketing and launch of biosimilars requires a different strategy than small-molecule generics [9].

Skills and barriers required to develop biosimilars [9]:



Issues with manufacturing process for biosimilars:

As already mentioned, the manufacturing process of biopharmaceuticals is complex and risky. Compared to the manufacture of small molecular entities, the manufacture of biopharmaceuticals requires a greater number of batch records (>250 versus <10); more product quality tests (>2000 versus <100); more critical process steps (>5000 versus <100) and more process data entries (>60 000 versus <4000) [10]. The initial DNA sequence of the desired protein product must be determined and subsequently inserted into a suitable vector and then into the appropriate cell line. A bank of cells is derived and from that a master cell bank is defined. Cell culture of the master bank results in replication of cells and increased protein production. During extraction of particular protein, the supernatant (containing the protein) subsequently needs to be purified, which involves significant protein wastage to ensure adequate purity. No two master cell banks are the same and this account for the major dissimilarities between the innovator’s product and the biosimilars [3].

The total production process is prone to variability and it is probably justifiable to say that it will be impossible to produce an identical molecule. Slight changes in production conditions can result in subtle changes in the final product and hence it is argued that they can never be bio-identical. This may be a result of inter- and intra batch cell variability, different preservatives and unsecured cold chain handing. Moreover there

are major concerns over ensuring sterility and stability of the product delivered to market.

However, biotechnology has advanced to such an extent that in some cases it may be relatively easy for potential biosimilar manufacturers to create accurate copies of an innovator's biologic, by using microbial cell production rather than mammalian cell lines [8].

The impact of differences:

The impact of even small structural differences on clinically relevant properties of proteins may be significant. Each of these processes differences can impact on the interaction between the biopharmaceutical and the cellular receptor. In turn, these differences may lead to differences in efficacy and more importantly, their ability to trigger and then damage patient immune responses [6]. For glycosylated proteins, differences in the glycopattern may significantly influence receptor binding, protein-protein interaction and pharmacokinetics of protein substances [11]. In case of immunoglobulins, small differences in core fucosylation can lead to big changes in Fcc receptor binding and consequently result in changes of immune effector functions such as antibody-dependent cellular cytotoxicity which is believed to be a major mechanism of action contributing to the potency of many monoclonal antibodies, particularly in oncological indications [12].

Safety issues-Immunogenicity

A key safety parameter in biopharmaceuticals is immunogenicity, i.e. the ability of a substance to trigger an immune response in the patient. Nearly all biopharmaceuticals induce antibodies, due to either the presence of foreign sequences or epitopes or the breaking of immune tolerance to self-antigens [13]. The latter mechanism which is not completely understood apparently does not only depend on patient characteristics, route of administration and disease-related factors but also on the quality of the protein product which includes the presence or absence of glycosylation, impurities as well as product handling issues have been associated with the induction of antibodies [14]. Therefore, products from different sources cannot be assumed to be equivalent concerning their immunogenic potential. There are various potential consequences of immunogenicity such as loss or enhancement of efficacy, neutralization of a native protein and general immune effects (allergy, anaphylaxis, serum sickness) [15]. There can be dramatic effects if a natural human protein with an essential activity is neutralized. Such cases had been described some years

ago for an erythropoietin product where a post-approval formulation change led to an increased number of cases of pure red cell aplasia (PRCA) this complication was manifested by severe epoetin-resistant anemia which required blood transfusions, immunosuppressive treatment and eventually kidney transplantation [15], as well as for megakaryocyte-derived growth factor where severe thrombocytopenia was induced in volunteers and cancer patients, and led to the termination of product development [16]. In 2006, the German pharmaceutical company TeGenero conducted a Phase I clinical trial to test the safety of an experimental immunomodulatory antibody developed to treat B-cell chronic lymphocyte leukemia and rheumatoid arthritis, known as TGN1412. In all participants, infusion with TGN1412 triggered the sudden release of proinflammatory cytokines, causing a condition known as system inflammatory response syndrome (SIRS) [17]. In a study of 174 biologics approved for use in the United States and Europe, postmarketing concerns were raised for nearly a quarter of those drugs. Safety-related regulatory actions were issued for 41 biologics, including “black box” warnings on 19 biosimilars [18]. Unfortunately, immunogenicity in humans is not predictable based on in-vitro or animal tests so that always data generated by clinical testing are required for assessment of immunogenicity and appropriate pharmacovigilance is mandatory.

Legal and regulatory issues with biosimilars:

The “process equals product” paradigm emphasizes the importance of process control, process validation and product testing to overcome the differences in the product attributes caused due to differential manufacturing processes as they cannot be solely assessed by analytical characterization as recognized by the regulatory authorities [19]. Hence, specific regulatory pathways for licensing biosimilar medicinal products have been adopted in some parts of the world, where “generic pathway” (used for conventional small molecules) is not applicable for biopharmaceuticals.

Preliminary guidelines from the European Agency for the Evaluation of Medicinal Products (EMA) states that the complexity of the product, the types of changes in the manufacturing process and differences in quality, safety and efficacy must be taken into account when evaluating biosimilars. For most products, results of clinical trials demonstrating safety and efficacy are likely to be required. Moreover, because of the

unpredictability of the onset and incidence of immunogenicity, extended post-marketing surveillance is also important.

According to EMEA, all applications should be made entirely in accordance with the Common Technical Document (CTD) presentation. The CTD is organized into five modules that require being adapted for biosimilars as explained in following table. The information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data) supplemented with bioequivalence and bioavailability data. As commented before, the type and amount of additional data needs to be determined on a case-by-case basis studying the relevant scientific guidelines [20].

Format of the dossier - modules of the Common Technical Document [20]:

Module 1	Administrative information	Normal requirements
Module 2	Quality, non-clinical and clinical summaries and overview	Normal requirements
Module 3	Quality (chemical, pharmaceutical and biological information)	Full + <i>comparability exercise</i>
Module 4	Non-clinical study reports	Reduced+ <i>comparability exercise</i>
Module 5	Clinical study reports	Reduced+ <i>comparability exercise</i>

This Directive indicates that comparability studies between the biosimilar and the reference medicine have to be performed but it does not address the requirements for such tests. These studies should be conducted at different levels.

- Physico-chemical comparability.
- Biological comparability.
- Pre-clinical comparability.
- Clinical comparability.

The selected reference product will need to be the same throughout the comparability programme. Such comparability studies involve a thorough process starting by the comparison in terms of product quality and manufacturing process consistency as the safety and efficacy profile of the

product is closely linked to its manufacturing method. Currently, due to the state of the art in science it is almost impossible to prove that two biologic medicines have the same qualitative and quantitative composition. In order to prove that there are no relevant differences between both medicines, in most, if not all cases, comparison to the reference product has to be performed at non-clinical level. In all cases there should be PK/PD (Pharmacokinetic/Pharmacodynamic) comparison of a biosimilar and reference product and in some cases clinical therapeutic equivalence trials are requested to show similar efficacy and safety at least in one clinical situation.

The applicant has to justify with regard to safety and efficacy of the drug and may have consequences as to the amount of non-clinical and clinical data to be provided. For those product classes for which guideline annexes are available at present, relatively simple, easy-to-measure clinical endpoints or accepted surrogate endpoints are available which facilitate comparative trials. In future, with products requiring more complex clinical endpoints (e.g., monoclonal antibody products), the design of the comparative equivalence trials may become much more challenging. Furthermore, as the differences are not fully apparent at the time of approval, the guidelines request that for biosimilars (as for all biological medicinal products) pharmacovigilance monitoring has to be performed [21]. For this purpose, the specific product given to the patient should be clearly identified.

Using this regulatory framework, a number of biosimilar products already have been licensed in the European Union and are being marketed in several, but not yet in all, European countries. Details on the various guidelines on biosimilars and the product data which led CHMP to recommend their approval can be found in the European Public Assessment Reports accessible via the EMEA webpage [22]. At launch, these products were offered about 15–35% price discount vs. the list prices of the innovator products (depending on the product, country, and package size). On the other hand, one interferon alfa product has been rejected by CHMP [23] and the applications for three insulin products have been withdrawn [24] demonstrating that the European regulations, in order to ensure a high standard of quality, safety and efficacy represent significant hurdles as appropriate to prevent the market entry of sub-standard products.

In 2006, Australia's Therapeutic Goods Administration (TGA) adopted the European Union's guidelines on the approval of biosimilars. Since then, regulatory authorities for other countries including Argentina, India, Japan, Mexico and Turkey have also issued draft or final guidelines on the issue [25].

In 2009, the World Health Organization's Expert Committee on Biological Standardization issued its Guidelines on Evaluation of Similar Biotherapeutic Products, according to which the guidelines provide "globally acceptable principles" for the approval of biosimilar products and can be adopted or used by regulatory authorities around the world in establishing regulatory frameworks for the approval of these products [26].

In USA, Biologics Price Competition and Innovation Act of 2009 (BPCI Act) establishes an abbreviated approval pathway for biological products that are demonstrated to be 'highly similar' (biosimilar) to, or 'interchangeable' with, a FDA-licensed biological product. Under the BPCIA, a biosimilar product is "highly similar to the reference product not withstanding minor differences in clinically inactive components" with "no clinically meaningful differences" between the two products with respect to the "safety, purity, and potency of the product." The level of data required to demonstrate "highly similar," "minor differences" and "meaningful" may make all the difference and has yet to be determined [25].USFDA is planning to establish authoritarian guidelines for biosimilars in 2011.

Open issues with biosimilars:

Although regulatory frameworks for biosimilars have been adopted or are up coming, in many parts of the world, there are some open issues left which are presently under intense discussion.

Reference product

According to the EMEA guidelines, the reference product has to be authorized in the EU, based on a full dossier, and the same reference product has to be used throughout the comparative studies. Data generated from studies with medicinal products authorized outside the community may only provide supportive information [27]. However, innovator products authorized in different countries may differ concerning, e.g. production site, formulation and strength, so if the same demand would be made for all countries, a biosimilars manufacturer may be faced with the

need to do comparative studies separately for each country. Therefore, the option of national regulatory authorities to accept a reference product not licensed within their jurisdiction is under discussion but would call for information sharing between the regulatory authorities and/or additional data to be provided by the biosimilars manufacturers.

Labeling

Labelling for biosimilars is not an easy process when compared to generic small molecule drugs because they are not identical, but only similar to their reference products and are licensed on the basis of their own development, including clinical data. Therefore, the labelling should differentiate clinical safety and efficacy data which have been obtained with the biosimilar product itself from reference product, particularly in extrapolated indications where no studies have been done with the biosimilars at all [28]. Furthermore unique safety data should be included and substitution advice should be provided.

Pharmacovigilance

In case of biosimilars, an appropriate system of pharmacovigilance is needed to assure responsibility for their products on the market and to ensure that appropriate action is taken if necessary [29] because the pre-authorization safety database will be relatively small due to the abridged clinical development program. Pharmacovigilance is of special importance in case of rare serious adverse events which might not be evident at approval due to the limited data package available at this time. Pharmacovigilance systems based on spontaneous reporting will be limited by under-reporting as well as by data quality, which is often insufficient to allow a meaningful assessment [30]. Therefore, a more proactive approach may be required.

Naming

In order to support post-approval monitoring, the specific medicinal product given to the patient must be clearly identified [19]. International non-proprietary names (INNs) are assigned to drug substances by the WHO INN Programme. The INN is the 'technical' name for medicinal products. The generic versions of chemical medicines are assigned the same name, as they are identical copies of the reference product [15]. WHO does not intend to introduce a specific process for naming biosimilars [31], and the INN as a cataloging system for drug substances can neither be relied upon as an appropriate means to ensure identification

and traceability of biological, including biosimilar products nor as the sole indicator of product interchangeability. Therefore, it will be necessary that biosimilar products are marketed using brand names.

Interchangeability and Substitution

Small molecular generics can be interchangeable while biosimilars are not: here interchangeability should be demonstrated by scientific data proving that two products can be safely substituted for one another and do not create adverse health outcomes, e.g. generating a pathologic immune response after repeated switching. In the absence of such data patients and physicians should be aware that protein products with similar molecular composition may indeed not be interchangeable [32]. EMEA recommends that the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional [33].

Conclusion

The market for biotechnology-derived medicinal products is evolving rapidly with the imminent entry of biosimilars. Product quality, safety and efficacy of biopharmaceuticals are highly reliant on the process of production, purification and formulation and subtle differences are often observed between the innovator's product and biosimilars. Therefore, it is important to show that biosimilar drugs are comparable in structure and function to that of the innovator and any differences have to be supported with data showing no influence on these parameters. The only way to ascertain the safety and efficacy of a biosimilar will be to conduct pre-clinical tests and clinical trials and implement tailored pharmacovigilance plans. Awareness of the differences between original biotechnological medicines and biosimilars is essential for the safety of the patients.

References

1. Schellekens H. Biosimilar therapeutics-what do we need to consider?. *Nephrology Dialysis Transplantation Plus* 2009; 2 (Suppl 1): i27–i36.
2. Schellekens H. Follow-on biologics: challenges of the 'next generation'. *Nephrol Dial Transplant* 2005; 20 (Suppl 4): iv31–iv36.
3. Roger SD. Biosimilars: How similar or dissimilar are they? *Nephrology* 2006; 11:341–346.

4. Crommelin DJ, Bermejo T, Bissig M. Pharmaceutical evaluation of biosimilars: important differences from generic low-molecular weight pharm. *Eur J Hosp Pharm Sci* 2005; 1: 11-17.
5. Federal Trade Commission (FTC). Emerging Health Care Issues: Follow-On Biologic Drug Competition: A Federal Trade Commission Report. Washington, DC, 2009.
6. Roger SD, Ashraf M. Biosimilars: Opportunity or Cause for Concern?. *J Pharm Pharmaceut Sci* 2007 May 18;10 (3): 405-410.
7. Horton HR, Moran LA, Ochs RS, Rawn DJ, Scrimgeour KG. Principles of Biochemistry. 3rd ed. New Jersey: Prentice Hall/Pearson Education; 2002.
8. Wildt S, Gerngross T. The humanization of N-glycosylation pathways in yeast. *Microbiol* 2005; 3: 119–28.
9. Mark JB, Laura M. Harris, Romita RD, Chertkow J. Biosimilars: initial excitement gives way to reality. *From the analyst's couch* 2006 July;5: 535-536.
10. Schellekens H. Manufacture and quality control of biopharmaceuticals. *Revista Española de Economía de la Salud* 2008; 6: 340–344.
11. Lis H, Sharon N. Protein glycosylation-structural and functional aspects, *Eur. J. Biochem.* 1993; 218:1–27.
12. Arnold JA, Wormald MR, Sim RB, Rudd PM, Dwek RA, The impact of glycosylation on the biological function and structure of human immunoglobulins, *Annu. Rev. Immunol.* 2007;252: 1-50.
13. Kresse GB. Biosimilars-Science, status, and strategic perspective. *European Journal of Pharmaceutics and Biopharmaceutics* 2009;72: 479–486.
14. Mukovousov I, Sabljic T, Hortelano G, Ofosu FA, Factors that contribute to the immunogenicity of therapeutic proteins, *Thromb. Haemost.* 2008;99: 874-882.
15. Nowicki M. Basic facts about biosimilars. *Kidney Blood Press Res* 2007 July 4; 30:267–272.
16. Basser RL, O'Flaherty E, Green M, Edmonds M, Nichol J, Menchaca DM, Cohen B, Begley CG. Development of pancytopenia with neutralizing antibodies to thrombopoietin after multicycle chemotherapy supported by megakaryocyte growth and development factor, *Blood* 2002; 99: 2599-2602.

17. Suntharalingam G. Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412. *New Engl. J. Med.* 2006; 355(10): 1018–1028.
18. Giezen TJ. Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union. *JAMA* 2008; 300(16):1887–1896.
19. Andrzej W, Ashraf M. European regulatory guidelines for biosimilars. *Nephrol Dial Transplant* 2006; 21 (Supp 5): v17–v20.
20. Leyre Z, Begoña C. Biosimilars approval process. *Regulatory Toxicology and Pharmacology* 2010;56: 374-377.
21. EMEA, Guideline on similar medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/ 42832/2005, 2006. Available from: <<http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf>>.
22. EMEA, EPARs for authorised medicinal products for human use. Available from: <<http://www.emea.europa.eu/htms/human/epar/eparintro.htm>>.
23. EMEA, Refusal assessment report for Alpheon, EMEA/H/C/000585, 2006. Available from: <<http://www.emea.europa.eu/humandocs/PDFs/EPAR/alpheon/H-585-RAR-en.pdf>>.
24. EMEA, Withdrawal assessment report for Insulin Human Rapid Marvel, EMEA/H/C/845, 2008. Available from: <<http://www.emea.europa.eu/humandocs/PDFs/EPAR/insulinhumanrapidmarvel/31777807en.pdf>>.
25. Madeleine M, Jennifer Stonecipher H. Learning from our neighbors about regulation of biosimilar drugs. *The national law journal, food and drug practice a special report* 2011 Mar 14.
26. Barbara Mounho. Global Regulatory Standards for the Approval of Biosimilars. *65 Food & Drug L.J.* 2010; 819.
27. EMEA, Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues/Guidance on similar medicinal products containing recombinant erythropoietins, EMEA/CHMP/BMWP/94526/2005, 2006. Available from: <<http://www.emea.europa.eu/pdfs/human/biosimilar/9452605en.pdf>>.

28. European Commission, Notice to applicants: a guideline on summary of product characteristics, 2005. Available from: <<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/spcguidrev1-oct2005.pdf>>.
29. EMEA, CPMP Position Paper on Compliance with Pharmacovigilance Regulatory Obligations, CPMP/PhVWP/1618/01, 2001. Available from <<http://www.emea.europa.eu/pdfs/human/phvwp/161801en.pdf>>.
30. EMEA, Executive Summary Report on EMEA Meeting with interested parties and research centers on ENCEPP, EMEA/601107/2007, 2007. Available from: <<http://www.emea.europa.eu/pdfs/human/phv/60110707en.pdf>>.
31. WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products, Geneva, 4–5 September 2006. Available from: <http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf>.
32. EMEA, Guideline on similar medicinal products containing biotechnology derived proteins as active substance: quality issues, EMEA/CHMP/BWP/49348/2005, 2006. Available from: <<http://www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf>>.
33. EMEA, Questions and Answers on biosimilar medicines (similar biological medicinal products), EMEA/74562/2006, 2007. Available from: <<http://www.emea.europa.eu/pdfs/human/pcwp/7456206en.pdf>>.