



HOW DISSIMILARLY SIMILAR ARE BIOSIMILARS?

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ABSTRACT

Recently Biopharmaceuticals are the new chemotherapeutic agents that are called as “Biosimilars” or “follow on protein products” by the European Medicines Agency (EMA) and the American regulatory agencies (Food and Drug Administration) respectively. Biosimilars are extremely similar to the reference molecule but not identical, however close their similarities may be. A regulatory framework is therefore in place to assess the application for marketing authorisation of biosimilars. When a biosimilar is similar to the reference biopharmaceutical in terms of safety, quality, and efficacy, it can be registered. It is important to document data from clinical trials with a view of similar safety and efficacy. If the development time for a generic medicine is around 3 years, a biosimilar takes about 6-9 years. Generic medicines need to demonstrate bioequivalence only unlike biosimilars that need to conduct phase I and Phase III clinical trials.

In this review, different biosimilars that are already being used successfully in the field on Oncology is discussed. Their similarity, differences and guidelines to be followed before a clinically informed decision to be taken, is discussed. More importantly the regulatory guidelines that are operational in India with a work flow of making a biosimilar with relevant dos and don't's are discussed.

For a large populous country like India, where with improved treatments in all sectors including oncology, our ageing population is increasing. For the health care of this sector, we need more newer, cheaper and effective biosimilars in the market. It becomes therefore important to understand the regulatory guidelines and steps to come up with more biosimilars for the existing population and also more information is mandatory for the practicing clinicians to translate these effectively into clinical practice.

Keywords: Biosimilar, Biopharmaceuticals, Biosimilar products, Biopharma products.

INTRODUCTION

Biosimilars are compounds that are similar but not identical to the reference biopharmaceutical. Biopharmaceutical medicines are the original medicinal products that serve as a reference and have been derived from biological systems (bacteria, yeast, or human cells) using biotechnology. Biological systems have been identified, sequenced and their DNA manipulated for producing the medicinal diagnostic and therapeutic products.

The class of biopharmaceuticals have been available for more than 20 years, blood coagulation modulators, Granulocyte colony stimulating factors (G-CSFs), enzymes, erythropoietin, gonadotrophins, human growth hormones, insulin, interferon, interleukins, monoclonal antibodies, vaccines, tissue plasminogen activators are few examples of biopharmaceuticals¹. These tend to be large in size and possess a complex structure and have a unique way of production from living cells. The unique line of living cells ensure identical copies unlike the chemical medicines having a smaller size and simple structure generated by a more predictable chemical process.

Whenever a new drug is first developed, it is patent protected for approximately 20 years. On an average the first 8-10 years are used during the trial phases and once the drug is marketed, the remaining 10-12 years of patent protection is ensured. When the patent expires, competitors are allowed to make medications with the same active ingredients and they are called generic versions. It is mandatory for the new generic product to meet the quality criteria and pharmacokinetic bioequivalence of the competing drug to enter the market. Thus numerous versions of small molecule variations have come into the market.

Recombinant DNA technology drugs are exceedingly more complex than small molecule medicines because, the innovators prefer to protect their trade secrets and do not make their production platforms available and so, these have

to be generated new by their competitor companies. Thus the resulting product may not be precisely identical on account of many steps involved in downstream isolation, purification and subsequent formulation of the product. These kind of similar compounds, not identical are called “Biosimilars” in Europe and “follow on biologic medicines” in the United States,” “Subsequent entry biologics” in Canada².

The major challenge for biosimilar manufacturers is demonstrating that their products have sufficient likeness to the originator product, in addition to showing consistency of quality between different production runs based on their original manufacturing ability^{3,4} as well as simultaneously maintaining the consistent product efficacy to avoid overdosing and concomitant risks of adverse events.

India has a robust biopharma sector actively engaged in production and marketing of the “non-innovator” or biosimilar products. With Indian population crossing 1.2 billion, only a small minority is insured or is economically capable of affording standard of medical care especially the high end biotherapeutics. Mass affordability is still a genuine problem in India and therefore regulatory processes seem to be a complex interplay of economics, science, public health and politics. We have over 100 companies actively engaged in development or production of biosimilars. This is because of lower development costs, lower risks and reduced expenditure on R&D, reduced time to market and expertise in reverse engineering drug development.

European Medicines Agency (EMA) has published guidelines for the development and marketing of Biosimilar products. These products undergo extensive head to head comparability testing with the reference biotherapeutic product to show their similarity in terms of quality, efficacy and safety. Strict guidelines that have been laid down by the Indian Regulatory bodies for the approval of Indian Biosimilars have been published and available in the website of Central Drug Standard Control Organisation and the

Schedule Y of drug and cosmetic rules. These guidelines are to some extent different from the European Medical Agency and also the recently published WHO guidelines. These guidelines are based on the recommendations of a Task Force on recombinant-pharmaceuticals accepted by the Govt of India in 2006⁵.

For any biosimilar, its biological reference should be authorised and should be in clinical use for several years and a large body of knowledge on its efficacy and safety should be available. It is intended to be used at the same dose, with dosing regimens similar to the reference product. The purpose of a biosimilar development is not to establish patient benefit since this would have already been achieved by the reference product.

The focus is to establish similarity with the reference product and convincingly give the basis of relying, based on efficacy and safety experience gained by the reference product. Various general and product class European guidelines define the non-clinical and clinical studies that need to be carried out to show that biosimilar medicine is safe and effective as the biological reference medicine⁶. Clinical Biosimilarity should be used to assess the potential differences between the biosimilar and the reference product.

BIOSIMILAR CONCERNS AND MARKET IN INDIA

The marketing opportunity for Biosimilars in India is huge. Approximately, more than 50 biologicals patented before 1995 are currently marketed in the country. There are 16 brands of Erythropoietin and 14 brands of granulocyte-Stimulating factor (G-CSF) available in India currently. Despite the concerns regarding the quality of available molecules and questions of their similarity to the innovator products, additional concern in India is the viability of the product when it reaches the consumer⁵ and maintenance of the cold chain at the stockist level.

BIOSIMILARS OF DRUGS USED IN TREATMENT OF CANCER

G-CSF

G-CSF supports proliferation, differentiation and activation of the committed progenitor granulocytes. The two currently available biosimilar G-CSF products in Europe are Filgrastim and lenograstim. They differ from the natural G-CSF and also significantly from one another with respect to biological characteristics and approved indications. Comparative studies have shown differences between their pharmacological properties and clinical outcomes and are therefore considered not interchangeable.

Studies have indicated that there are differences between Filgrastin and Lenograstim in terms of stem cell mobilisation, with Lenograstim showing 28% higher concentration of stem cell production compared to Filgrastim⁷. It has also been shown that there are significant differences between Lenograstim and Filgrastim in hematologic recovery following autologous peripheral blood progenitor cell transplant (PBPC) with high dose chemotherapy. Patients receiving Filgrastin had faster neutrophil, WBC, platelets recovery thus requiring fewer days of G-CSF administration and thus lesser days of hospitalisation compared to patients given Lenograstim⁸.

Interferons

The Interferon α indicated for treatment of patients with cancer include Interferon α 2A (Roferon – A) and Interferon α 2B (Intron A). These products are produced in similar expression systems and have similar molecular weights, but differing in one amino acid. Their differences are very meaningful clinically and are therefore considered not

interchangeable. The EMEA emphasises that 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. The EMEA's recent rejection of a biosimilar interferon product (Alpheon®; Biopartners) due to characterisation, manufacturing, and quality control issues underscores this fact that the pathway to approval for biosimilars is not as easy and straightforward. The studies showed a difference between products in the incidence of neutralising antibodies^{9,10}. Previous evidences have shown that risk of relapse is high in patients who developed neutralising antibodies¹¹.

Epoetins

Epoetins are used for patients receiving chemotherapy and for treating anaemia in patients with chronic kidney disease. All epoetin products in clinical use have the same amino acid sequence of endogenous erythropoietin but the sources have been different (CHO cells vs Human cells). The manufacturing processes have been different, glycosylation patterns, erythropoietin content, potency, dosage, routes of administration and indications have been different^{12,13}. While all epoetins have the similar molecular mechanism of action, there are differences in pharmacologic and clinical properties and therefore are capable of differential clinical responses. These products are therefore considered not interchangeable. The differences in glycosylation patterns are particularly important for pharmacokinetics of the product and may influence the efficacy, safety and most importantly immunogenicity.

An example illustrating the severe consequences of small manufacturing changes is that of Eprex® (epoetin alfa; Johnson and Johnson). Eprex has applications in 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^{14,15}. 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.¹⁶

This increased incidence of PRCA (pure red cell aplasia) coincided with the change in the product formulation of removal of human serum albumin from the European formulation of Eprex.^{14,17}

In addition, the issues of direct dosage conversions between epoetin products are also not available. This is particularly relevant in case of oncology setting where the dosage is 3-5 fold higher than patients with anemia of chronic kidney disease. Different dose response characteristics between agents are critical due to exaggerated pharmacodynamic response resulting in hypertension and thrombotic complications^{18,19}.

BIOSIMILAR GUIDELINES IN TERMS OF INDIAN REGULATORY SYSTEM

In India, there are several regulatory authorities involved in the approval of biotherapeutic products. The Review committee for Genetic Manipulation (RCGM) under Department of Biotechnology to monitor all research scale activity and approval for non-clinical studies, the Genetic Engineering advisory committee (GEAC) under Ministry of Environment for environment safety for large scale operations of live modified organism products (LMO)

products, Drug Controller General, under Ministry of Health, (DCGI) for product safety and efficacy and clinical trial approval for biotech drugs. Food and Drug control Administration (FDCA) from State Govt Body under Ministry of Health approves the plant products⁵.

Area of Biosimilar manufacture has to be a GMP (Good Manufacturing Process) facility. The Cell bank characterisation has to be as per the ICH (International Committee of Harmonisation) guidelines. A compatibility study as per the ICH Q5E and Post approval guidelines published by Drug Control General India, for the post approval changes are warranted. Extractable studies are necessary though the viral validation is not considered mandatory. The above mentioned guidelines are applicable for process. For the analytical purposes, detailed characterisation of the product including the post translational modifications, specifications needs to be justified and a central monitoring committee is required as per the DCGI guidelines. From the clinical perspective, the comparative pharmacokinetics/pharmacodynamics with the reference is not mandatory. Comparative clinical trials are not mandatory. A sound scientific advisory process is not indicated. However a post marketing surveillance for 4 years with a six monthly periodic safety reporting is essential.

SAFETY ASPECTS BEFORE CLINICAL USE OF BIOSIMILARS

The most critical safety concern relating to a biosimilar is its immunogenicity²⁰. All biosimilar products are biologically active molecules derived from living cells, and have the potential to evoke an immune response and 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. Quality control procedures integrated into the manufacturing processes, the route of administration, patient factors such as genetic background and HLA-expression of the patient etc need to be monitored.

Pharmacovigilance

It is important to collect post approval safety data for these biosimilars and have a clinical database. Since only a limited number of patients receive the product during the pre-approval period, the differences between the products of biosimilars in terms of efficacy, safety may not become apparent. The importance of post marketing pharmacovigilance has been highlighted by experience with epoetins and PRCA episodes in patients with chronic kidney disease. Therefore the pharmacovigilance programs need to monitor all biopharmaceuticals which includes both the innovator and biosimilar products, given the potential risks associated, particularly immunogenicity. The post marketing programs will need to be tailored to each biopharmaceutical category to address the product specific issues. One component of pharmacovigilance is spontaneous reports by healthcare professionals. Ideally, these reports should contain as much information as possible, including the type of adverse event and information on the drug (e.g. proprietary name, INN, dosage given and lot number).

There are well established pharmacovigilance programs from EMEA in Europe and the Food and Drug Administration (FDA) in the United States for the monitoring of adverse events to medicinal products. EudraVigilance is the EMEA network for reporting and evaluating suspected adverse reactions during development and following marketing authorization.^{21, 22}

Pharmacovigilance programs for biosimilars are required by the EMEA to provide a continuous method for the monitoring and evaluation of early detection of safety issues so that responses are rapid and accurate. Pharmacovigilance programs are also important for assessing the safety of products in specific patient populations. This is particularly important for the safe use of biosimilars in therapeutic indications for which the product may not have been formally evaluated (i.e. for an extrapolated indication).

Extend Innovation and Extrapolate

The approval process for growth hormone Omnitrope included a number of comparability studies to the reference product, Genotropin, including quality studies, pharmacokinetic and pharmacodynamic studies, clinical efficacy and safety studies, and immunogenicity studies.

The recent approval of two biosimilar growth hormones Omnitrope and Genotropin included extrapolation of clinical data for some indications. The rationale is that if the biosimilar shows adequate comparability to the innovator product for one indication, it may be reasonable to extend the approval of the biosimilar to all the indications of the innovator product. The EMEA has endorsed the concept of data extrapolation for biosimilars with the appropriate justification.

The efficacy and safety comparability studies between Omnitrope and its reference Genotropin has been conducted in children with growth disturbances. The labelling and dosage indication in adults was similar to that of reference. The reasons for this extrapolation between the reference growth hormone and the biosimilar were the long clinical history of safe use of growth hormone, the therapeutic window being wider, rare reports of neutralising antibodies, characterisation of the structure and biological activity by physicochemical and biological methods and also variety to assays available to characterise the active and product related substances²³.

The biosimilar manufacturer would have to provide an adequate scientific explanation, and if the mechanism of action found to be different between indications, the biosimilar manufacturer should provide additional clinical data.

Substitution

Switching patients from one product to a similar but "not quite identical" product may have adverse 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 required to provide a clear assessment of the risks involved in switching from an established product to its biosimilar to all stakeholders (including patients, pharmacists, and other caregivers).

The severity of the disease in the individual and local healthcare re-imburements decides the aspects of risk tolerance. For a nation like India, drug price reductions may be an important factor to consider, but developed countries have patient safety and brand loyalty as the main deciding factors. Therefore automatic substitution is not considered appropriate for biopharmaceutical products.

Due to limited clinical experience with biosimilars at approval, small differences may affect clinical outcomes. This may become a confounding factor in the collection

for pharmacovigilance data as well. Therefore, in case of adverse events, without the documentation of product change, the event cannot be linked to a specific product during the pharmacovigilant assessment. Clinicians should therefore be aware of the exact biopharmaceutical product given to their patients. As a risk prevention measure, French legislators in early February 2007 approved a law that clearly distinguishes biosimilars from generics and prohibits automatic substitution with biosimilars.

Labeling biosimilars

It is important for the physicians, pharmacists and patients to distinguish between biopharmaceutical products for accurate pharmacovigilance. It is difficult to properly link adverse events to a specific product, When multiple products share one International Nonproprietary Name (INN) the pharmacovigilance reports may not contain additional identifying data for the specific product. Because biosimilars are not equivalent to reference products, their unique efficacy and safety data should be available with labeling. Furthermore, labeling should note those indications that are based on extrapolation of data.

Cost Effectiveness

An important benefit of biosimilars is that they are likely to be cost effective. However, the cost savings for biosimilars may not as significant as those seen with small-molecule generics due to substantial manufacturing costs for biosimilars and the additional costs of bringing the products to market. It also must be noted that drugs represent only a small fraction of the total cost of treatment for cancer patients. Nevertheless, cost savings with biosimilars will likely increase access to therapeutic proteins and stimulate innovative research.

Conclusions

Biosimilars will undoubtedly play an increasing role in disease management in future. A number of biosimilar products are either already approved (somatotropins, glucagons, hyaluronidase, calcitonin) or are under development (e.g. epoetins, G-CSFs). Biosimilars can provide a number of opportunities, but it is important that they be introduced in an appropriate manner.

There are potential concerns regarding the use of biosimilars in Cancer patients that warrant consideration when making a biopharmaceutical product choice. Clinicians need to have a thorough understanding of the issues associated with biosimilars so as to make informed decisions. Biosimilars are not generic versions of innovator products. Biosimilars may be approved as safe and efficacious agents by the EMEA, but they will be inherently different from innovator products. Therefore, switching or substitution between innovator products and biosimilars should be viewed as a change in clinical management.

Rigorous pharmacovigilance programs are needed to capture this data and to build a database to establish the clinical use of each biosimilar product. This is because of the limited clinical experience with biosimilars at the time of their approval, these potential clinical differences may not become apparent until after approval. Thus, to ensure that such pharmacovigilance programs establish an accurate database, automatic substitution should be prohibited, and the physicians need to effectively monitor patients receiving a biopharmaceutical.

Extrapolation of clinical data from one therapeutic indication to another for biosimilars also warrants concern for this data extrapolation entails a risk/benefit assessment.

The inherent differences between biopharmaceutical products may involve a greater risk-to-benefit ratio for certain patient populations (e.g. stem cell donors) than for others; extrapolation should be implemented on a case-by-case basis. If extrapolation of data is to be implemented, the package labeling should explicitly state this along with the clinical data used to support extrapolation.

In summary, relevant information is the key to address the potential concerns regarding the use of biosimilars, in particular, the differences between biosimilars and innovator biopharmaceuticals. Thus biosimilars are not very similar and physicians, pharmacists, health care fund holders and patients will need to balance possible cost savings of these biosimilar medications verses the risk of iatrogenic complications.

Table 1

Some Biosimilars available in Indian Market

PRODUCT	Number of company launches in India
G-CSF	14
EPO	16
Peg EPO	1
Peg G-CSF	2
Alpha interferon	1
Rituximab	1
EGFR1 Mab	1

Table 2

Biosimilars related to oncology under development in India

Product	Diseases involved
Peg IFN α	Hepatitis, Hematological Cancers
IFN - β	Multiple Sclerosis
Infliximab	TNF fusion protein
Trastuzumab	Breast Cancer that express Her2
Bevacizumab	Colorectal, breast, NSCLC cancers

Figure 1

Work Flow of a Biosimilar Production and necessary Approvals



REFERENCES

1. Pere Gasgon. Presently available biosimilars in hematology-oncology: G-CSF, Target Oncology, 2012 ; 7 : 29-34.
2. Arnold G Vulto and Stacy A Crow. Risk Management in oncology: each medicine is work in progress, Target Oncology 2012; 7 : 43-49.
3. Crommelin D, Bermejo T, Bissig M, Damiaans J, Kramer I, Rambourg P, et al., Biosimilars, generic versions of the first generation of therapeutic proteins : do they exist? Contrib Nephrol 2005; 149 : 287-294.
4. F. Locatelli and S. Roger. Comparative testing and pharmacovigilance of biosimilars. Nephrol Dial Transplant 2006 ; 21 : v13-v16.
5. Hemant Malhotra, Biosimilars and non-innovator biotherapeutics in India: An overview of the current situation, Biologicals 2011; 39: 321-4.
6. European Medicines Agency. 2006. Guidance on similar medicinal products containing recombinant erythropoietins. Available at: <http://www.emea.eu.int/pdfs/human/biosimilar/9452605en.pdf>

7. Watts MJ, Addison I, Long SG, Hartley S, Warrington S, Boyce M, et al. Crossover study of the haematological effects and pharmacokinetics of glycosylated and non-glycosylated G-CSF in healthy volunteers. *Br J Haematol* 1997; 98: 474-79.
8. Kim IH, Park SK, Suh OK, Oh JM. Comparison of lenograstim and filgrastim on haematological effects after autologous peripheral blood stem cell transplantation with high-dose chemotherapy. *Curr Med Res Opin* 2003;19:753-759.
9. Oberg K, Alm G. The incidence and clinical significance of antibodies to interferon- α in patients with solid tumors. *Biotherapy* 1997;10:1-5.
10. Antonelli G, Currenti M, Turriziani O, Dianzani F. Neutralizing antibodies to interferon- α : relative frequency in patients treated with different interferon preparations. *J Infect Dis* 1991;163:882-885.
11. McKenna RM, Oberg KE. Antibodies to interferon- α in treated cancer patients: incidence and significance. *J Interferon Cytokine Res* 1997;17:141-143.
12. Deicher R, Horl WH. Differentiating factors between erythropoiesis-stimulating agents: a guide to selection for anaemia of chronic kidney disease. *Drugs* 2004;64:499-509.
13. H. Schellekens. Erythropoietic proteins and antibody-mediated pure red cell aplasia: a potential role for micelles. *Nephrol Dial Transplant*, 2004; 19 : 2422.
14. Bennett CL, Luminari S, Nissenson AR, Tallman MS, Klinge SA, McWilliams JD et al. Pure red-cell aplasia and epoetin therapy. *N Engl J Med* 2004; 351: 1403-1408.
15. Casadevall N, Nataf J, Viron B, AKolta, JJ. Kiladjian, PMartin-Dupont, et al., Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med*, 2002, 346: 469-475
16. Casadevall N. Pure red cell aplasia and anti-erythropoietin antibodies in patients treated with epoetin. *Nephrol Dial Transplant*, 2003; 18 : viii37-viii41
17. Schellekens H and Jiskoot W. Eprex-associated pure red cell aplasia and leachates. *Nat Biotechnol* 2006; 24: 613-614.
18. Maschio G. Erythropoietin and systemic hypertension. *Nephrol Dial Transplant* 1995;10 :74-79.
19. Levin N. Management of blood pressure changes during recombinant human erythropoietin therapy. *Semin Nephrol* 1989 ;9 :16-20.
20. Kessler M, Goldsmith D, and Schellekens H. Immunogenicity of biopharmaceuticals. *Nephrol Dial Transplant*, 2006 ; 21 : v9-v12.
21. European Medicines Agency. 2004. Pharmacovigilance—Medicinal Products for Human Use and Veterinary Medicinal Products. Available at: <http://eudravigilance.emea.eu.int/human/docs/Vol9en.pdf>
22. US Food and Drug Administration. 2005. Guidance for Industry—Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Available at: <http://www.fda.gov/Cder/guidance/6359OCC.htm>
23. European Medicines Agency. 2004. Similar biological medicinal products containing recombinant human growth hormone. Available at: <http://www.emea.eu.int/pdfs/human/biosimilar/14648904en.pdf>

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