Review Article

Biosimilar drugs: Current status

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Abstract

Biologic products are being developed over the past three decades. The expiry of patent protection for many biological medicines has led to the development of biosimilars in UK or follow on biologics in USA. This article reviews the literature on biosimilar drugs that covers the therapeutic status and regulatory guidelines. Appraisal of published articles from peer reviewed journals for English language publications, search from PubMed, and guidelines from European Medicines Agency, US Food Drug Administration (FDA) and India were used to identify data for review. Literature suggest that biosimilars are similar biological products, i.e., comparable but not identical to the reference product, are not generic version of innovator product and do not ensure therapeutic equivalence. Biosimilars present more challenges than conventional generics and marketing approval is also more complicated. To improve access, US Congress passed the Biologics Price Competition and Innovation act 2009 and US FDA allowed "abbreviated pathway" for their approval. U.S law has defined new standards and terms and EMA scientific guidelines have also set detailed approval standards. India being one of the most preferred manufacturing destinations of biosimilars, there is a need for stringent safety and regulatory guidelines. The New India Guidelines "Draft Guidelines on Similar Biologics were announced in June 2012, by Department of Biotechnology at Boston bio and available online.

Key words: Biologicals, biosimilars, European Medicines Agency, Food Drug Administration, guidelines, India

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Introduction

Biological or biopharmaceuticals are drugs produced from living cells through the biological process, and mimic natural biological substances such as hormones.[1-3] Biosimilars are copy drugs similar to biological drugs that has already been authorized (the biological reference medicine), hence similar but not identical.[4] Indian guidelines define a "similar biologics" as a biological product/drug produced by genetic engineering techniques and claimed to be "similar" in terms of safety, efficacy and quality to a reference biologics, which has been authorized by Drug Controller General of India (DCGI) for safe use in India.[5] The active substance of biosimilar medicine is similar to one of the biological reference medicine and used in general at the same dosage to treat the same disease.[6] Biosimilars are entity based (including product-process), regulatory based (under an abbreviated testing), and market based (same manufactures, different trade name).[7]

Biosimilars also known as similar biological products, follow-up biologics, subsequent entry biological, second entry biological, biogenerics, multisource products, and off-patent biotech products as synonyms.[8-10] General public and insurance companies prefer economic alternatives, the long-term economic consequence of using biosimilars have not been studied. The total cost of therapy with biosimilars may rise.[11,12]

Biosimilars are a new class of drugs intended to offer comparable safety and efficacy to the reference, off-patent biological. The active protein structure of biologicals makes them more prone to induce an acute and chronic immune response.[4] The overall risk is modest with biosimilars, but regulatory pathways are required because of structural complexity, manufacturing process and risk for immunogenicity.[13,14]

The problems/limitations with biosimilar are that, the two biosimilar have a different origin, the two biosimilars may

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have same therapeutic effect, may have different side-effects and hence require thorough testing.[15]

The main reason of biosimilar drug development is the expiry of patent protection for many biological medicines [Table 1].[8,9,16]

Biopharmaceuticals are different from the conventional small molecule drugs because of the size and complexity of the active substance and nature of the manufacturing process. Even minor change in the process can lead to the fatal outcome (process is product), safety, and efficacy issues.[1]

Biosimilars Episode

For Epoietin (Erythropoietin), minor change in the packaging process caused pure red cell aplasia. This prompted drug regulatory authorities to establish strict guidelines.[17-20]

European Medicines Agency (EMEA) and Committee for the Medicinal Product for Human use (CHMP) raised the objection that marvel insulin and reference human insulin were not comparable. Marvel Life Sciences Ltd., withdrew its application as they were unable to meet the standards set by CHMP,[21] but biosimilar insulin continues to flood Indian market. Hence, legal and regulatory principals applicable to generic drugs cannot be applied to biosimilars.

CHMP Guidelines Concerning Biosimilar Drugs

EMEA-CHMP has published product specific guidelines to establish the similarity in terms of safety, efficacy and quality of biosimilar product.[22-29] According to these guidelines the concept of similar biological products is applicable to any biological medicinal product. Moreover, in order to support pharmacovigilance monitoring, the specific product given to the patient should be clearly identified. The active substance of the biosimilar product must be similar in molecular and biological terms to the active substance of the reference medicinal product, and the same reference product throughout the comparability program. The pharmaceutical form, doses and route of administration of the biosimilar and the reference product should be the same. If the reference product has more than one indication, the safety and efficacy for all indications have to be justified or demonstrated for each indication separately.

The clinical safety must be monitored on an ongoing basis after marketing approval. The issue of immunogenicity should always be addressed, and its long-term monitoring is necessary.

FDA Approach Regarding the use of Biosimilar Drugs

FDA was given the authority to approve biosimilars, including interchangeable, to maintain safety, efficacy, and quality of biosimilar product.[30,31] Biologics Price Competition and Innovation Act of 2009 authorizes the FDA to oversee an "abbreviated pathway" for approval of biologics that are "biosimilar" to already approved products. The abbreviated pathway will eliminate unnecessary and unethical testing of biosimilars in animal and human. This will save the time, money and manpower. The Patient Protection and Affordable Care Act of 2010 (USA) also supports this. Introduction of biosimilars also requires a specifically designed pharmacovigilance plan.

Table 1: Patent expiration of biological/biopharmaceuticals*

Biopharmaceuticals	Products	Indication(s)	US patent status	EU patent status
Genentech	Nutropin™ (somatropin)	Growth disorders	Expired	Expired
Abbott	Abbokinase™ (eudurase urokunase)	Ischemic events	Expired	Expired
Eli Lilly	Humulin™ (recombinant insulin)	Diabetes	Expired	Expired
Genzyme	Ceredase™ (algucerase)	Gaucher disease	Expired	Expired
Astra Zeneca	Streptase™ (streptokinase)	Ischemic events	Expired	Expired
Biogen/Roche	Intron ATM (IFN-alfa-2b)	Hepatitis B and C	Expired	Expired
Serono	Serotim™ (somatropin)	AIDS wasting	Expired	NA
Eli Lilly	Humatrope™ (somatropin)	Growth disorders	Expired	NA
Amgen	Epogen™, Procrit™, Epres™ (erythropoietin)	Anemia	Expired	Expired
Roche	NeoRecormon™ (erythropoietin)	Anemia	NA	Expired
Genetech	TNKase™ (tenecteplase TNK-tPA)	Acute myocardial infarction	Expired	Expired
Inter Mune	Actimmune™ (IFN-gamma-Ib)	CGD, malignant obsteopetrosis	Expired	Expired
Genetech	Alteplase™ (tPA)	Acute myocardial infarction	Expired	Expired
Chiron	Proleukin™ (IL-2)	HIV	Expired	Expired
Amgen	Neupogen™ (filgrastim G-CSF)	Anemia, leukemia, neutropenia	Expired	Expired

*The main reason of biosimilars development is the expiry of patent protection for many biological medicines. CGD: Chronic granulomatous disease; G-CSF: Granulocyte colony stimulating factor; tPA: Tissue plasminogen activator; IL: Interleukin; IFN: Interferon

Indian Guidelines

The New India Guidelines "Draft Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India," were announced in June 2012, by Department of Biotechnology (DBT). The Indian guidelines on similar biologics address the pre-marketing and post-marketing regulatory requirement (i.e., "comparability exercise"), and also address the requirements related to manufacturing process and quality control. As such these Indian guidelines on similar biologics are comparable in many respects to biosimilar guidelines of USA and EU. India has adopted a "sequential approach" (like "stepwise approach" - US and EU) to market biosimilar products.[5,32]

The review committee on genetic manipulation of the Genetic Engineering Approval Committee (GEAC) with the permission of DCGI, approve clinical trials to be conducted in India related to biosimilar therapeutic products. The biosimilar has to demonstrate comparable data of non-clinical studies viz., pharmacokinetics and toxicology (safety pharmacology, reproduction toxicology, mutagenecity and carcinogenicity) and clinical studies (efficacy and tolerability for each indication) before it gets approval for all indication of the reference medicine.[33]

Biosimilars in India[34] consist primarily of vaccine, monoclonal antibodies, recombinant proteins and diagnostics, insulin (wosulin, insugen, recosulin), erythropoietin (hemax, epofer, wepox, ceriton, epofit), hepatitis B vaccine (Shanvac B, Revac B, Enivac B, Biovac B, Genevac B, Bevac), granulocyte colony stimulating factor (G-CSF–Grastim, Neukine), streptokinase (indikinase, shankinase, STPase), interferon alpha-2B (shanferon), Rituxinab (MAb), epidermal growth factor receptor (anti-EGFR) (MAb)–(reditux, bioMAB-EGFR). Status of similar biologics in India is elaborated in Table 2.[35-37]

There are about 100 biopharmaceutical companies actively involved in research and development, manufacturing and marketing of biosimilar therapeutic products in India. There were 14 therapeutic drugs (similar biologics) available in 50 brands in 2005; the number has increased to 20 therapeutic drugs in 250 brands in 2011. Biosimilar therapeutic products include insulin, erthropoietin, chorionic gonadotropin, streptokinase, interferon and heparin. The growing biosimilars market offers huge potential for companies involved in manufacturing, research and development.[12]

Pharmacovigilance and BiosimilarS

Pharmacovigilance is more important for biosimilar drugs because these are not reference medicine as such, and are from different manufacturer from the reference products. Many adverse effects may appear only after a biosimilar drug is used more extensively, for a longer period of time, in a greater number of patients. Both manufacturers and prescriber should be aware of the importance of post marketing vigilance, and careful on patients taking biosimilar.[38]

Table 2: Status of similar biologics in India

Company	Product name	Active substance	India launch year
Biocon	Basalog	Insulin glargine	2009
Wockhardt	Biovac-B	Hepatitis B vaccine	2000
Ranbaxy	Ceriton	Epoetin alfa	NR
Reliance Life Sciences	Choriorel	Chorionic gonadotrophin	NR
Dr. Reddy's Laboratories	Cresp	Darbopoetin alfa	August 2010
Emcure	Epofer	Epoetin alfa	NR
Intas Biopharmaceuticals	Erykine	Epoetin alfa	August 2005
Claris Life Sciences	Epotin	Epoetin alfa	NR
Biocon	Erypro	Epoetin alfa	NR
Claris Life Sciences	Fegrast	Filgrastim	NR
Reliance Life Sciences	FostiRel	Follitropin beta	August 2010
Wockhardt	Glaritus	Insulin glargine	March 2009
Dr. Reddy's Laboratories	Grafeel	Filgrastim	NR
Biocon	Insugen	Human insulin	NR
Intas Biopharmaceuticals	Intalfa	Interferon alpha-2b	April 2007
Reliance Life Sciences	Mirel	Reteplase	2009
Biocon	Myokinase	Streptokinase	NR
Intas Biopharmaceuticals	Neukine	Filgrastim	July 2004
Intas Biopharmaceuticals	Neupeg	Peg-filgrastim	August 2007
Biocon	Nufil	Filgrastim	NR
Dr. Reddy's Laboratories	Peg-grafeel	Peg-filgrastim	10 May 2011
Dr. Reddy's Laboratories	Reditux	Rituximab	30 April 2007
Reliance Life Sciences	Relibeta	Interferon beta-1a	NR
Reliance Life Sciences	Reliferon	Interferon α2b	2008
Reliance Life Sciences	Religrast	Filgrastim	2008
Reliance Life Sciences	Relipoietin	Epoetin alpha	2008
SB/Merieux Alliance	Shankinase	Streptokinase	June 2004
SB/Merieux Alliance	Shanferon	Interferon α2b	April 2002
SB/Merieux Alliance	Shanpoietin	Erythropoetin	January 2005
Wockhardt	Wepox	Epoetin alfa	March 2001
Wockhardt	Wosulin	Human insulin	13 August 2003

SB: Shantha biotechnics

Conclusion

Biosimilar are not generic; biologics are larger and more complicated than chemical drugs, due to the complexity of biological/biotechnology derived products the generic approach is scientifically not appropriate for biosimilar products. There is need to use well-designed clinical trials to establish biosimilarity. The challenge with biosimilars is to know the differences which matter clinically. The specific product given to the patient should be clearly identified.

References

1. Dranitsaris G, Amir E, Dorward K. Biosimilars of biological drug therapies: Regulatory, clinical and commercial considerations. Drugs 2011;71:1527-36.
2. Crommelin DJ, Storm G, Verrijk R, de Leede L, Jiskoot W, Hennink WE. Shifting paradigms: Biopharmaceuticals versus low molecular weight drugs. Int J Pharm 2003;266:3-16.
3. Brockmeyer C, Seidl A. Binocrit: assessment of quality, safety and efficacy of biopharmaceuticals. Eur J Hosp Pharm Pract 2009;15:34-40.
4. Schellekens H, Casadevall N. Immunogenicity of recombinant human proteins: Causes and consequences. J Neurol 2004;251 Suppl 2:II4-9.
5. The New India Guidelines on Similar Biologics, Oct 2012. Available from: http://www.biospectrumasia.com/biospectrum/analysis/3021/biosimilars-guidelines-a-step-direction-india#.UehBf6DRiSo. [Last accessed on 2013 Jul 16].
6. Roger SD. Biosimilars: How similar or dissimilar are they? Nephrology (Carlton) 2006;11:341-6.
7. Duerden M. Prescribing advice needed for new biosimilar biological drugs. Prescriber 2007;18:1-2.
8. Schellekens H, Ryff JC. 'Biogenerics': The off-patent biotech products. Trends Pharmacol Sci 2002;23:119-21.
9. Joshi SR. Biosimilar insulins: Are they really 'similar'? J Assoc Physicians India 2009;57:38-41.
10. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, *et al*. Biosimilars-why terminology matters. Nat Biotechnol 2011;29:690-3.
11. Malhotra H. Biosimilars and non-innovator biotherapeutics in India: An overview of the current situation. Biologicals 2011;39:321-4.
12. Rathore A. Development and commercialization of biosimilars in India. BioPharm Int 2011;24:36-40.
13. Haselbeck A. Epoetins: Differences and their relevance to immunogenicity. Curr Med Res Opin 2003;19:430-2.
14. Wadhwa M, Thorpe R. The challenges of immunogenicity in developing biosimilar products. IDrugs 2009;12:440-4.
15. Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, *et al*. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood 2001;98:3241-8.
16. Thomas TK. Patent for biosimilar drugs may be made mandatory. The Hindu Business Line. Available from: http://www.thehindubusinessline.in/2008/05/06/stories/2008050651531000.htm. [Last accessed on 2013 Jul 15; Published on 2008 May 06].
17. Locatelli F, Del Vecchio L, Pozzoni P. Pure red-cell aplasia "epidemic" – Mystery completely revealed? Perit Dial Int 2007;27 Suppl 2:S303-7.
18. Schellekens H. Biosimilar epoetins: How similar are they? Eur J Hosp Pharm 2004;3:243-7.
19. Keithi-Reddy SR, Kandasamy S, Singh AK. Pure red cell aplasia due to follow-on epoetin. Kidney Int 2008;74:1617-22.
20. Yang J, Joo KW, Kim YS, Ahn C, Han JS, Kim S, *et al*. Two cases of pure red-cell aplasia due to anti-erythropoietin antibodies. J Nephrol 2005;18:102-5.
21. European Medicines Agency. Marvel Lifesciences Ltd. withdraws its marketing authorization applications for insulin human rapid marvel, insulin human long marvel and insulin human 30/70 mix marvel. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015335.pdf. [Last accessed on 2013 Jul 15].
22. Guideline on Similar Biological Medicinal Products. London: CHMP/437/04; 2005. Available from: http://www.ema.Europa.eu/human/biosimilar/0437004en.pdf. [Last accessed on 2013 Jul 15].
23. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance; Quality Issues. London: EMEA/CHMP/BWP/49348/2005; 2006. Available from: http://www.ema.europa.eu/odfs/human/biosimilar/4934805en.pdf. [Last accessed on 2013 Jul 15].
24. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: non Clinical Issues. London: EMEA/CHMP/BMWP/42832/2005; 2006. Available from: http://www.ema.europa.eu/odfs/human/biosimilar/4283205en.pdf. [Last accessed on 2013 Jul 15].
25. European Medicines Agency. Committee for medicinal products for human use. Guideline on similar biological medicinal products. Available from: http://www.ema.europa.eu/pdfs/human/biosimilar/043704en.pdf. [Last accessed on 2013 Jul 15].
26. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). 2012 May 24. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05/WC500127960.pdf. [Last accessed on 2013 Jul 15].
27. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; 2006. Available from: http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf. [Last accessed on 2013 Jul 15].
28. European Medicines Agency. Guidance on similar medicinal products containing recombinant erythropoietins; 2006. Available from: http://www.emea.europa.eu/pdfs/human/biosimilar/9452605en.pdf. [Last accessed on 2013 Jul 15].
29. Pavlovic M, Girardin E, Kapetanovic L, Ho K, Trouvin JH. Similar biological medicinal products containing recombinant human growth hormone: European regulation. Horm Res 2008;69:14-21.
30. Hodgson J. WHO guidelines presage US biosimilars legislation? Nat Biotechnol 2009;27:963-5.
31. World Health Organisation. Expert Committee on Biological Standardization. Guidelines on evaluation of similar biotherapeutic products (SBPs). 2009 Oct 19-23. Available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22 APRIL2010.pdf. [Last accessed on 2013 Jul 16].
32. GaBI Online-Generics and Biosimilars Initiative. India releases draft 'similar biologic' guidelines [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International. Available from: http://www.gabionline.net/Guidelines/India-releases-draft-similar-biologic-guidelines. [Last accessed on 2013 Jul 16].
33. Declerck P. Biologicals and biosimilars: a review of the science and its implications. Generics Biosimilars Initiative J (GaBI J) 2012;1:13-6.
34. OPPI position paper on 'biosimilar' in India. Available from: http://www.indiaoppi.com/oppibiosimilars.pdf. [Last accessed on 2013 Jul 16].
35. Jayaraman K. India's Cipla sets sights on Avastin, Herceptin and Enbrel. Nat Biotechnol 2010;28:883-4.
36. Mody R, Goradia V, Gupta D. How similar are biosimilars in India? Pharmafocus Asia. Ochre media. Available from: http://www.pharmafocusasia.com/research_development/blind-comparative-study.html. [Last accessed on 2013 Jul 18].
37. Som N. India on biologics trail. Biospectrum 2012. Available from http://www.biospectrumindia.com/biospecindia/news/155886/india-biologics-trail. [Last accessed on 2013 Jul 20].
38. Joshi SR. Biosimilar peptides: Need for pharmacovigilance. J Assoc Physicians India 2011;59 Suppl: 44-7.

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