

“SIMILAR BIOLOGICS REGULATION: CURRENT STATUS”**¹RAJNEESH KUMAR GAUR, ²KRISHAN K. TRIPATHI**Department of Biotechnology, Ministry of Science and Technology, CGO complex, Lodhi Road, New Delhi-110003
Email: meetgaur@gmail.com

Received: 25 Sep 2011, Revised and Accepted: 2 Mar 2012

ABSTRACT

The expiry of patents on innovator biologicals allures the interest of many companies to copy-cat their production as biosimilars. Regulatory agencies of various countries devised a mechanism to ensure their quality, safety and efficacy. India is in a process of developing the guidance document for copy-cat biotech products and adopted a term 'Similar Biologics' as substitute for biosimilar. Like EMA, the term covers only recombinant-DNA technology derived biotech products including recombinant vaccines and blood products. The aim of the article is to provide a brief overview of the scientific and regulatory challenges in developing and evaluating similar biologics products.

Keywords: Biosimilar, Similar Biologics, Regulation, RCGM, Challenges.**INTRODUCTION**

'Generics' are out-of-patent small molecular chemical drugs, while biological molecules manufactured similar to the innovator product after the expiry of the patent is popularly called as 'biosimilar'. The worldwide sale of biosimilars is expected to be ~US\$5 billion by 2015¹ and likely to capture 10-15% of the Indian biopharmaceutical market. In an era of process patent, flexible Indian regulatory system and reverse engineering skills of chemists pushed the Indian Pharma companies as successful players in the global generic drugs market. However, the global biosimilar market scenario is different from generic drugs in terms of manufacturing, cost and regulatory issues, therefore, repeating the level of success as generic drugs require strong commitment both from industry and governmental side.

Over the last few years, biotech products constituted the frontline products of pharmaceutical industries. These products named differently in different jurisdictions such as biopharmaceutical, biomedicine and biotherapeutics etc. With the expiry of patents on many innovators biological, the doors are open for companies around the world to manufacture and market them. In India, the companies are interested in marketing 'biosimilars' due to pre-1995 product patents exemption for number of molecules including some biologics under the Trade Related Intellectual Property Rights (TRIPS) agreement, and also biological based drugs are free from the government's price-control order, allowing independence in price setting.

In general, biologicals are complex molecules and susceptible towards manufacturing variation. The manufacturing heterogeneity demands a proper and defined regulatory procedure in order to ensure their quality, safety and efficacy. The regulatory agencies of many countries started and culminated the lengthy and time consuming process of compiling the opinion of experts, government and public stakeholders in formulating the statutory guidance documents. In 2008, Department of Biotechnology, Ministry of Science and Technology, India was entrusted for the formulation of guidelines up to pre-clinical studies for these copycat biotech products. The draft guidelines are expected to be completed and came into effect in 2012.

INDIAN REGULATORY FRAMEWORK

In India product manufactured or developed using recombinant-DNA technology require approval of various agencies. Currently, there are six competent authorities namely the Recombinant DNA Advisory Committee (RDAC), Institutional Biosafety Committees (IBSC), Review Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), State Biotechnology Coordination Committee (SBCC) and the District Level Committee (DLC), constituting the Indian biosafety regulatory framework. The framework regulates the manufacturing, use, import, export and storage of hazardous microorganisms/genetically

engineered/modified organisms (GMOs) or cells. The RCGM established under the Department of Biotechnology (DBT) supervises and accords approval for research activities including small-scale field trials/pre-clinical trials, whereas approval for large-scale releases and commercialization of GMOs are given by the GEAC, established under the Ministry of Environment and Forests. The SBCC's and DLC's have a major role in monitoring. IBSC oversee every institution engaged in GMO research and interface with RCGM².

The first step for approval of a biological product similar to an original innovator product, developed within India is the submission of upstream and downstream, analytical characterization, stability analysis and *in-vitro* efficacy study data along with pre-clinical toxicity (PCT) study protocol to RCGM for seeking permission to conduct PCT studies. The applicant also needs prior permission from RCGM and Directorate General of Foreign Trade (DGFT) for importing gene clone. All the protocols and data have to be reviewed and recommended by IBSC before submitting to RCGM. Approval from State Food and Drugs authority is also required for batch as well as large scale manufacturing of the product. After completion of PCT studies, a report has to submit to RCGM. Once the RCGM found PCT studies satisfactory, it recommends to the Drugs Controller General of India (DCGI). Then DCGI permit the applicant for conducting the clinical trials, which is abbreviated in case of biological products similar to original innovator products. Once DCGI satisfies with clinical trial studies, it authorizes the applicant for marketing the product. Currently, the biological products whether new or similar to the original innovator product (i.e. biosimilars) are approved as 'New Drug' under Schedule-Y of Drug and Cosmetics Act 1940. The schedule 'Y' has a provision of submission of phase-I data for the products discovered in countries other than India along with the application. Phase-III trials are required to be conducted in India before permission to market the drug in India. The provisions of schedule Y are not sufficient to maintain the quality, safety and efficacy of copy-cat biotech products, separate stringent regulation is desired.

GUIDELINES: A CHALLENGE**Global Overview**

In 1997, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) recommended the harmonized tripartite guidelines, for the preclinical safety evaluation of biotechnology-derived pharmaceuticals. ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and USA.

In 2006, European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) is the first and fastest to

formulate the guidelines for evaluation and approval of 'Similar Biological Medicinal Products' (SBMP). 'SBMP'/biosimilars applies to recombinant-DNA derived proteins (i.e. recombinant proteins and monoclonal antibodies) and cover proteins and peptides, their derivatives and products of which they are components (e.g. conjugates). The overall goal of the comparability exercise is to reduce the non-clinical and clinical data requirement³. EMA's clinical trial and pharmacovigilance data requirement makes the regulatory process rigorous. Currently, EMA is in the process of revising the guidelines (EMA, Ref. No. - CHMP/BWP/617111/2010).

In the USA, the generic chemical drugs are approved either under section 505 (b) of FD&C Act (1938) or ANDA (Abbreviated New Drug Application) of the Hatch-Waxman Act, 1984. A drug approved under 505(b) requires clinical trials to prove efficacy, while under ANDA drugs are approved after demonstration of bioequivalence with an innovator product. The US government recently cleared the regulatory pathway for biosimilar approval under 'biosimilar statute' i.e. Biologics Price Competition and Innovation Act (BPCI), 2009⁴.

WHO's term 'Similar Biotherapeutic Product' (SBP) applies only to recombinant-DNA derived proteins. Vaccines, plasma derived products, and their recombinant analogues are excluded. Similarity is defined as the absence of a relevant difference in the parameter of

interest. As per the guidelines, SBP will be licensed only on the basis of its demonstrated similarity with the reference biotherapeutic product (RBP) in terms of quality, non-clinical and clinical studies generated with the product itself. Demonstration of quality similarity is a pre-requisite for reduction of non-clinical and clinical development. If relevant differences are found in the quality, non-clinical or clinical studies, the product will not likely qualify as a SBP and a more extensive non-clinical and clinical data set will likely be required to support its application for licensure. Such a product should not qualify as a SBP as defined in this guideline⁵.

Indian Perspective

The number of factors such as the availability of good scientific work force, GMP certified manufacturing facilities and low cost of labor favoring marketing of copycat biologic/biosimilars probably at 20-30% lower price. For biosimilars, there is no access to original innovator manufacturing process; therefore, maintaining their quality similar to the original innovator product, in the absence of well-defined and strong regulatory procedure, is doubtful⁶. Therefore, the guideline formulation for biosimilars requires consideration of several scientific and technical parameters such as manufacturing, packaging, labeling, distribution and shelf-life of a product, which may directly involve in the head to head comparability exercise (Table-1).

Table 1: Proposed data requirements for a similar biologics application approval by RCGM. These requirements are not yet approved. Some of these requirements may be a part of the draft guidelines for similar biologics.

Parameters	Requirements
General	A. Similar biologic can be substituted/Interchanged, when there are no clinical differences with innovator/reference product
	B. Mandatory clinical trials when a similar biologic shows significant quality and efficacy differences with a innovator/reference product
	C. Innovator/reference product approved in India must be kept same during all the studies
Quality control	A. Manufacturing process (Host cell type, Medium, fermentation parameters like yield, purification steps and overall yield, inclusion bodies)
	B. Characterization (Analytical techniques like NMR & Mass spectrometry, HPLC, Circular dichroism, Light scattering, Size exclusion chromatography, Sequence analysis, Endotoxin test, Restriction mapping and analysis)
	C. Biological function of an active substance (Biochemical, Elisa and Calorimetric assays)
	D. Stability studies (Regular as well as accelerated)
Pre-clinical	Drug product specifications
	A. Toxicity study (acute and repeat dose)
	B. Immunogenicity (both neutralizing & non-neutralizing antibodies, anti SS & DS DNA antibodies, T-cell proliferation and cytokine assays)
	C. Adjuvant's toxicology
	D. Route of administration
	E. Frequency & interval of doses
	F. Scientific basis of choosing animal model
	G. Histopathology
H. Genotoxicity, reproductive toxicity & carcinogenicity required only in case of observed organ and system's toxicity	
Clinical	A. Tolerability (Pharmacokinetic & Pharmacodynamic studies)
	B. Safety and determination of the dose of the drug

Some of the most challenging issues are discussed below to develop pragmatic and effective regulatory guidelines -

A. Terminology: The terminology adopted by different regulatory agencies for 'biosimilars' is different such as biopharmaceutical, biogeneric, bio-comparable, follow-on biologics, off-patent biologics, subsequent entry biologics⁷. In Europe, these copy-cat products are designated as 'Similar Biological Medicinal Product', popularly shortened as 'biosimilars' because it is impossible to show two biological products identical. Biosimilars is defined as any biological medicinal product whose similarity to innovator reference product is established through state of the art analytical procedures, the manufacturing processes employed, as well as clinical and regulatory experiences⁸.

In the USA, the term 'biosimilars' is recently accepted under 'Biological Price Control and Innovation Act' (BPCI), 2009. The BPCI act defines biosimilar as any biological product demonstrated to be highly similar and having no clinically meaningful differences

between a biological product and reference product in terms of the safety, purity, and potency of the product as demonstrated through clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics)⁹.

World Health Organization (WHO) designates biosimilars as 'Similar Biotherapeutic Product (SBP)'. SBP is any biotherapeutic product, which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. In addition to the quality data, SBP require non-clinical and clinical data generated by the product itself⁵.

All the above definitions are commonly emphasizing the similarity of a biological product in terms of quality, safety and efficacy against innovator product. Additionally, none of them includes complex biological products such as vaccines and blood products due to difficulty in their accurate physico-chemical characterization. In contrast, 'biosimilars' are designated differently by various regulatory agencies. It seems that either

the various regulatory authorities were keen to preserve their identity or there was sufficient confusion due to market pressure.

In India, since 2008, 'Review Committee on Genetic Manipulation (RCGM)', Department of Biotechnology was entrusted for development of regulatory guidelines for biosimilars. After several rounds of debate, the committee distilled the two terms i.e. Therapeutically Equivalent Biopharmaceuticals (TEB) and Similar Biologics. TEB inherently possesses pharmaceutical as well as bioequivalency (i.e. comparable pharmacokinetics). The compound is considered pharmaceutically equivalent when it is having same active ingredient, dosage form, route of administration and strength as of innovator product¹⁰. TEB covers both recombinant and non-recombinant biologicals. Later on, the term was dropped because of its demand for more stringent specifications such as full clinical trial etc. In March 2011, RCGM adopted 'Similar Biologics' as substitute of the term 'biosimilars'. Similar Biologics is defined as "any biological product/drug produced by genetic engineering technique and claimed to be "similar" in terms of quality, safety and efficacy to a reference innovator product/reference biologics, which has been granted a marketing authorization in India by a competent authority on the basis of a complete dossier, and with a history of safe use in India". The term also includes recombinant vaccines and blood products. In line with EMA, RCGM restricted 'Similar Biologics' to recombinant-DNA technology derived biological products.

B. Reference product selection: RCGM received a number of inputs from different stakeholders on the selection of an innovator reference product for comparability exercise. RCGM defined the reference product as any innovator product, which has been granted a marketing authorization in India by a competent authority on the basis of a complete dossier, and with a history of safe use in India. For the products where the reference innovator product is not authorized in India shall be considered on a case by case basis if such products have been granted marketing approval in countries with well-established regulatory systems such as US FDA, EMA etc. and have been in wide use for a minimum of four years. Another similar biologic cannot be considered as reference innovator product, as the reference innovator product should be the one that has been licensed based on a full quality, safety and efficacy data.

Furthermore, in case the reference product formulation needs purification of the active substance for characterization, then what kind of approach an applicant must follow is still debatable. In general, studies must demonstrate that product heterogeneity and relevant attributes are not affected by the isolation process of the active moiety with scientific justification of the approach.

Manufacturing: Biological macromolecules are complex and their manufacturing is highly susceptible to heterogeneity due to the involvement of a number of steps from cloning to product formulation [Table-2].

Table 2: Selected major variables involved at different stages of bio- similar manufacturing

Stages	Sources of variation/heterogeneity
Active ingredient Manufacturing	Structure, Post-translational modifications (PTM's), Media and its component, Plasmid constructs, Plasmid stability, Host cells, Cell lines, Process variables, Glycosylation, Glycan content, Contamination, batch to batch yield variation
Purification	Contamination (protein and nucleic acids), number of purification steps, inclusion bodies, LPS and Endotoxin, disruption of disulfide bonds, aggregation, precipitation, linker cleavage,
Formulation	Sterilization, Viral decontamination, Pyrogen content, Intrinsic instability, additives like PEG, Preservatives, Adjuvant(s), Excipient(s)
Storage and handling	Cold chain interruption, colloid formation and degradation during transit, mixing of incompatible substances, Lack of proper knowledge about the product

A variety of undesired chemical alterations to the drug product can occur during this time including the oxidation or deamination. All these alterations might severely affect the safety and efficacy of the product e.g. the marked difference is observed between two laboratory preparations of human urinary erythropoietin and four preparations of EPO as a result of change in glycosylation pattern¹¹. Therefore, the stringent physico-chemical measures needs to be incorporated in the general guidelines and if possible certain product specific test may also be incorporated to ensure consistency in the production processes. RCGM is in discussion to incorporate a complete description for the manufacturing process from development and characterization of cell banks, stability of clone, cell culture/ fermentation, harvest, excipients, formulation, purification, primary packaging interactions etc and the consequences on product characteristics.

To improve the efficacy of a biological product, more often manufacturers modify the active substance absorption, delivery or therapeutic indication(s). Here the challenge is either to categorise the modified similar biologics as a 'New Drug' or license them as similar biologics with the support of supplementary data. In the later case, the requirement of the supplementary data needs to be defined.

C. Quality: The change of expression system and manufacturing process often leads to the presence of host cell proteins (HCP) as impurities in the product. Such impurities may lead to severe immunogenic reaction(s) e.g. almost 60% of patients treated with recombinant human Growth Hormone (rhGH) powder manufactured by API Covance (Somatropin Sandoz powder) developed anti-GH antibodies and all patients developed antibodies against *E.coli* proteins. In 'Genotropin' (Pfizer) case, only about 2%

and 0% of patients develop anti-GH and anti-HCP antibodies¹². In order to make 'Somatropin' comparable to 'Genotropin', an additional purification step was included to ensure the tolerability and efficacy of the product. Therefore, RCGM recently proposed that a 'Similar Biologic applicant must provide a full quality dossier for both active substances as well as the drug product including the physicochemical, biological, immunological characterization and stability analysis with respect to the innovator reference product [Table 1]. To ensure the statistical analysis, each quantitative experiment should be done at least three times and statistical significance of the data should be represented throughout the characterization data. Limitation of the assays used for quality assurance also needs careful consideration¹³.

D. Stability: Stability studies covering the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system) are essential to determine the shelf-life of a product during storage¹⁴. In general, EU and Japan follow the ICH guidelines for stability assessment. There may be two approaches for stability assurance from Indian regulatory perspective i.e. accelerated and stress stability studies to access the degradation profile, while real time stability tests may be useful to determine shelf life and storage conditions of a similar biologics.

E. Labelling: In general, different manufacturers market their products under different brand names. In India, chemical originated 'generics' are marketed with International Non-proprietary Names (INN) instead of brand names. INN automatically distinguishes a generic from the innovator product and directly provides price advantage to consumers. The adoption of a similar INN system would be advantageous for similar biologics.

F. Pre-clinical evaluations: In general, a drug's short and long term toxic effects are assessed by doing *in-vitro* and *in-vivo* animal toxicity studies. Depending on the nature of the drug, its intended use, route of administration, and the extent of the proposed clinical trials, a toxicity testing program may consist of acute/subacute or subchronic/chronic toxicity studies, carcinogenicity studies, reproductive toxicity studies, genotoxicity studies, and toxicokinetic studies. Safety pharmacology, reproduction toxicity, mutagenicity and carcinogenicity studies may not be required for similar biologics unless indicated from the results of repeat dose studies.

Generally, the animal toxicological test does not work well in case of biological products because protein drugs do not cross the nuclear membrane and interact with DNA. Also many biologics do not show activity in rodents (i.e. rat and mice) as drug receptors found in lower species are different from humans. To overcome this drawback, primate models may be used. Unfortunately, many countries banned the use of primate models for preclinical studies¹⁵. A well-defined animal model study can provide greater confidence about the drug's potential equivalence and assist in the design of the pharmacokinetic component of the Phase I clinical trial. The ICH (International Conference on Harmonisation) guidance (ICH S6) for preclinical development of biopharmaceuticals states that safety evaluation should normally include two relevant species (ie, two species in which the drug is pharmacologically active). However, when only one relevant species identified or when the biological activity of the biopharmaceutical is well understood, it is acceptable to do toxicity testing in only one species¹⁶. There is a debate over the selection of the appropriate animal model/species for toxicological studies. The models should be selected in such a manner where the efficacy is demonstrable. If no relevant species are available, the applicant has been demonstrated, the applicant may use the appropriate transgenic animal model(s).

Currently EMA guidelines require one study for a single indication of a biosimilar to demonstrate comparable quality, efficacy and safety against innovator product. These results may be extrapolated to all other therapeutic indications of a product. Extrapolation of the data for indications other than the approved ones is doubtful and risky e.g. Recombinant human growth hormone (rhGH) replacement doses are generally sufficient in GH deficient patients, while in non-GH deficient patients, higher doses are required, which might not be tolerated by the patient¹². Therefore, all the therapeutic indications for which a 'Similar Biologics' is seeking approval should be included in the comparability exercise. In addition, it is also important to decide how many efficacy and safety trials are sufficient for approval.

G. Clinical evaluation: In general, biological activity of a biopharmaceutical is assessed *in-vitro* using cell-based assays and *in-vivo* using animal models but these methods do not provide data that can accurately predict biological activity in humans¹⁷. Therefore, EMA incorporated controlled clinical trials in the regulatory approval of a biosimilar. The clinical data requirement depends on the existing knowledge about the innovator reference product and the claimed therapeutic indication(s).

Immunogenicity methods should be able to characterize type, concentration and titer of antibodies. When neutralizing antibodies are detected, the impact on PK/PD parameters and overall efficacy and safety should be analyzed well. This is particularly true for proteins with post-translational modifications such as glycosylation where small differences in the glycosylation pattern may result in significantly different immunogenicity profile¹⁸.

H. Pharmacovigilance: The minor differences between a similar biologic and innovator product is not always detectable with quality control studies. For example, In Korea, three biosimilars of epoetin alfa i.e. 'Eporon' (Dong-A Pharmaceutical Company Ltd), 'Espogen' (LG Life Sciences), 'Epokine' (CJ Corporation) have been shown to differ in the activity, concentration, isoforms, structural stability from the reference product 'Epogen' (Amgen, USA)¹⁹⁻²⁰. Unfortunately for intensive post-marketing monitoring, currently India does not have a very well established pharmacovigilance

system. Recently, Central Drugs Standard Control Organization (CDSCO) has taken an initiative to establish a Pharmacovigilance Programme of India (PvPI), which is expected to be fully operational by 2015²¹. In India, implementation of a strong Pharmacovigilance plan will certainly escalate the overall cost of a similar biologic and hit the consumers directly; therefore, the duration of the post-marketing surveillance is an extremely important factor from an industrial point of view.

Streamlining the regulatory procedure

The major drawback of the existing approval process is the involvement of a number of drug regulatory authorities, which makes the overall process time consuming and unnecessarily lengthy. To streamline the approval process, Department of Biotechnology (DBT) has drafted a bill for the development of the Biotechnology Regulatory Authority of India (BRAI), which is waiting for introduction in the parliament. BRAI will be an "autonomous and professionally led body to provide a single window mechanism for the biosafety clearance of genetically modified products and processes." In other words, BRAI will replace much added bureaucracy. BRAI will also include a training centre for its biotech regulators to build and maintain their professional competence²².

Conflict of Interest Declaration

The authors declare that there is no financial or non-financial competing interest related to the manuscript.

Disclaimer

The authors alone are responsible for the views expressed in this publication and have NO relation with the official position in the Department of Biotechnology, Ministry of Science & Technology, New Delhi, India.

REFERENCES

1. http://www.prweb.com/releases/biosimilars/human_growth_hormone/prweb8131268.htm (accessed July 20, 2011).
2. <http://www.envfor.nic.in/divisions/csurv/geac/groundrules.pdf> (accessed August 19, 2011).
3. Guidelines on Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance-quality issues. London, UK, European Medicines Agency, 2006; CHMP/BWP/42832/05.
4. Bonilla JW, Beaver N. The new US biosimilar legislation-one year later. *BioProcess Int* 2011;9(5):22-30.
5. http://www.who.int/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_22APRIL2010.pdf (accessed August 19, 2011).
6. Joshi SR. Biosimilar Insulins: are they really 'similar'? *JAPI* 2009;57:338-41.
7. Rader RA. What is a Generic biopharmaceutical? Biogeneric? Follow on Protein? Follow on biologics? Biosimilar? *BioProcess International* 2007;5(3):28-38.
8. Guidelines on Similar Biological Medicinal Products, London, UK, European Medicines Agency. 2005. CHMP/437/04.
9. US Code, Title 42, The Public Health and Welfare, Chap. 6A, Public Health Service, Subchapter II, General Powers and Duties, Part F, Licensing of Biological Products and Clinical Laboratories, Subpart 1, Biological Products, Sec.262, Regulation of Biological Products, (i)(2)(A).
10. <http://www.fda.gov/Drugs/informationondrugs/ucm079436.htm> (accessed August 20, 2011).
11. Yuen CT, Storrington PL, Tiplady RJ, Izquierdo M, Wait R, Gee CK et al. Relationships between the N-glycan structures and biological activities of recombinant human erythropoietins produced using different culture conditions and purification procedures. *Br J Haematol* 2003;121:511-526.
12. Declerk PJ, Darendeliler F, Goth M, Kolouskova S, Micle I, Noordam C et al. Biosimilars: controversies as illustrated by rhGH. *Current Med Res & Opin* 2010;26:1219-29.
13. Chirino AJ, Mire-Sluis A. Characterizing biological products and assessing comparability following manufacturing changes. *Nat Biotechnol* 2004; 22:1383-91.

14. Srinivasan A, Iser R, Devinder SG. Common Deficiencies in Abbreviated New Drug Applications: Part 3-Control of the Drug Product and Stability. *Pharmaceut Tech* 2011;35:58-67.
15. Langley G. Next of Kin: A report on the use of Primates in Experiments, British Union for the Abolition of Vivisection; 12.
16. ICH S6 Guidance: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. <http://www.fda.gov> (accessed June 14, 2011).
17. Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern? *J Pharm Pharmaceut Sci.* 2007;10:405-10.
18. Schellekens H. Biosimilar therapeutics—what do we need to consider? *NDT Plus* 2009;2 (suppl 1): i27–i36.
19. Park S, Patel K, Ko J, Meriage D, Chen L, Crouse J et al. Analytical comparisons of erythropoietin products from Korea and Amgen's EpogenR (epoetin alfa). *Nephrol Dial Transplant* 2006;21:iv14.
20. Deechongkit S, Aoki KH, Park SS, Kerwin BA. Biophysical comparability of the same protein from different manufacturers: a case study using Epoetin alfa from Epogen and Eprex. *J Pharm Sci* 2006;95:1931-43.
21. <http://cdsco.nic.in/pharmacovigilance.htm> (accessed August 10, 2011).
22. http://dbtindia.nic.in/Draft%20NBR%20Act_%2028may2008.pdf (accessed August 02, 2011).