Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

REGULATORY PERSPECTIVE OF BIOSIMILARS IN INDIA

Katla. Sirisha*, T. M. Pramod Kumar, V. Yugender Reddy , Akhilesh. P

Pharmaceutical Regulatory Affairs group, Dept. of Pharmaceutics

J.S.S College of Pharmacy, S.S Nagar, Mysore-570015, India.

ABSTRACT

Biosimilar drugs are follow-on versions of original biopharmaceutical medicines. They are independently developed after the patent protecting the original product has expired. Biosimilars are designed to target specific components of immune system as these drugs are capable of targeting proteins in a more specific fashion, yet have lower risks of systemic side-effects; they have considerable advantages over the older Immunomodulators. As these products are more effective Indian *bio-Pharma companies carry the advantages of low cost manufacturing and a highly skilled workforce with global expertise. Biosimilar medicines are intended to have the same mechanism of action for the same diseases as the original biopharmaceutical drug. The regulatory pathway for biosimilars in India was developed jointly by Central drug standard control organisation (CDSCO) & Department of Biotechnology (DBT) through Review Committee on Genetic Manipulation (RCGM).*

Keywords: *Biosimilars, patent, CDSCO, Biopharmaceutical companies, RCGM*

INTRODUCTION

Biosimilar 'denotes a biological medicine which is highly similar to an already authorized reference biological medicine and also referred to as Bio therapeutic products, Follow on biologics, Subsequent entry biologics, with respect to different Ministry of health. A biologic medicine is a large molecule typically derived from living cells and used in the treatment, diagnosis or prevention of disease.

Biologic medicines include therapeutic proteins, DNA vaccines, monoclonal antibodies and fusion proteins. Biologic medicines are often 200 to 1,000 times the size of a small molecule drug and are far more complex structurally. They are also highly sensitive, making them more difficult to characterize and produce[1].

**Correspondent Author:*
Katla. Sirisha
JSS College of pharmacy
Ph. No: 8553403358
Email: sirikatla138@gmail.com

In India, apart from Central Drugs Standard Control Organization (CDSCO), the office of Drug Controller General of India (DCGI) the apex regulatory body under Government of India (GoI), two other competent authorities are involved in the approval process of biosimilars or Similar Biologics products (SBPs) [2, 3]

These include: Review Committee on Genetic Manipulation (RCGM), which works under Department of Biotechnology (DBT), Ministry of Science and Technology. RCGM regulates import, export, carrying out research, preclinical permission, No objection certificate for clinical trial (CT) and other related activities involving genetically modified organism (GMO), as per the DBT guidelines.

Genetic Engineering Approval Committee (GEAC), which functions under the Department of Environment (DoE) as a statutory body for review and approval of activities involving large scale use of genetically engineered organisms (Living Modified Organism - LMO) and their products in research and development,

industrial production, environmental release and field applications. Unlike pharma generics, biosimilars/SBPs have to go through a series of regulatory approvals/permissions, right from the research and development (R&D) before they can be commercialized in India. While there are many companies who are commercially importing biosimilars into India and marketing, there are others who are buying the biosimilars from local manufacturers and selling under their brand name on a principle to principle (P2P) basis.

STRENGTH OF LOCAL COMPANIES IN INDIA

- Overall, the Indian biopharmaceutical industry comprises 350 biopharmaceutical companies, of which 50% are involved in product development, 20% are involved in clinical development, 15% provide research services, and 5% focus on platform technologies. Companies such as Biocon, Serum Institute, Bharat Biotech, and Panaceam, are some of the key players in the Indian biopharmaceutical sector.
- Currently, local Indian companies have the expertise to develop and manufacture several recombinant biotech products sold on the domestic market[4]. The recombinant DNA pharmaceuticals approved for marketing in India include insulin, Granulocyte macrophage colony-stimulating factor (GM-CSF), Granulocyte colony stimulating factor (G-CSF), interferon alpha, interferon gamma, interleukin, blood factor VIII, streptokinase, HBsAg vaccine, human growth hormone, Tissue plasminogen activator (t-pa), erythropoietin, follicle stimulating hormone, and human protein C. The recombinant DNA pharmaceuticals approved for manufacturing in India are HepatitisB surface antigen (HBsAg) vaccine, erythropoietin, G-CSF, interferon alpha, and insulin. In addition to vaccines, India's capabilities to manufacture recombinant protein products have also grown.
- Companies like Bharat Biotech, Wockhardt, and Biocon manufacture recombinant products such as vaccines, human insulin, and erythropoietin as generic products for the domestic and export market[4]

***Table 1*: *Indian biopharmaceutical companies and their performance* [4]:**

Name of company	What is into?	Net sales (in Rs. Cr.)			Net profit (in.Rs. cr.)			Six yrs avg NPM
		2005	2011	5 years CAGR	2005	2011	5 years CAGR	
Ranbaxy laboratories Ltd	Formulations & API	5,247.9	8,882.1	11.1%	235.8	1,357.3	41.9%	4.8%
Dr. Reddy's laboratories Ltd.	Formulations and API	1,832.7	6,988.6	30.7%	27.1	569.9	83.9%	7.1%
Cipla Ltd.	Formulations and API	2,181.3	5,359.5	19.7%	409.6	1081.5	21.4%	18.8%
Sun pharmaceuticals	Formulations and API	1,191.1	3,904.0	26.8%	390.3	1,349.9	28.2%	36.5%
GlaxoSmithKline	Formulations	1,485.3	2,111.6	7.3%	306.3	581.4	13.75%	25.1%
Aventis pharma Ltd.	Formulations	807.8	1,085.0	6.1%	145.1	155.0	1.3%	16.8%
Jubilant life sciences Ltd.	CRAMS	1,167.8	3,781.3	26.5%	113.2	424.4	30.2%	11.2%
Divis Laboratories Ltd.	CRAMS	347.4	929.3	21.8%	66.0	344.2	39.1%	28.5%

Table 2: Similar Biologics' approved and marketed in India **[5]**

Product name	Active substance	Therapeutic area*	Company
Basalog	insulin glargine	Diabetes	Biocon
Biovac-B	hepatitis B vaccine	Hepatitis B	Wockhardt
Ceriton	epoetin alfa	Anaemia Cancer Chronic kidney failure	Ranbaxy
Choriorel	chorionic gonadotrophin hormone r-hCG	Female infertility	Reliance Life Sciences
Cresp	darbopoetin alfa	Anaemia Cancer Chronic kidney failure	Dr Reddy's Laboratories
Epofer	epoetin alfa	Anaemia Cancer Chronic kidney failure	Emcure
Epofit/Erykine	epoetin alfa	Anaemia Cancer Chronic kidney failure	Intas Biopharmaceuticals
Epotin	epoetin alfa	Anaemia Cancer Chronic kidney failure	Claris Lifesciences
Erypro	epoetin alfa	Anaemia Cancer Chronic kidney failure	Biocon
Fegrast	filgrastim	Cancer Hematopoietic stem cell transplantation Neutropenia	Claris Lifesciences
FostiRel	follitropin beta	Female infertility	Reliance Life Sciences
Glaritus	insulin glargine	Diabetes mellitus	Wockhardt
Grafeel	filgrastim	Neutropenia Hematopoietic stem cell transplantation Cancer	Dr Reddy's Laboratories
Insugen	human insulin	Diabetes mellitus	Biocon
Intalfa	interferon alpha-2b	Characinoid tumour Chronic hepatitis B Chronic hepatitis C Hairy cell leukaemia Chronic myelogenous leukaemia BCR-ABL positive Follicular lymphoma Malignant melanoma Multiple myeloma	Intas Biopharmaceuticals
Mirel	reteplase (tissue plasminogen activator)	Myocardial infarction	Reliance Life Sciences
Myokinase	streptokinase	Acute myocardial infarction Deep venous thrombosis Acute pulmonary embolism	Biocon
Neukine	filgrastim	Neutropenia Hematopoietic stem cell transplantation Cancer	Intas Biopharmaceuticals
Neupeg	peg-filgrastim	Cancer Neutropenia	Intas Biopharmaceuticals

Nufil	filgrastim	Cancer Neutropenia	Biocon
Peg-grafeel	peg-filgrastim	Cancer Neutropenia	Dr Reddy's Laboratories
Reditux	rituximab	Leukaemias Lymphomas Rheumatoid arthritis	Dr Reddy's Laboratories
Relibeta	interferon beta-1a	Multiple sclerosis	Reliance Life Sciences
Reliferon	interferon α2b	BCR-ABL positive Characinoid tumour Chronic hepatitis B Chronic hepatitis C Chronic myelogenous leukaemia Follicular lymphoma Hairy cell leukaemia Melanoma Multiple myeloma	Reliance Life Sciences
Religrast	filgrastim	Neutropenia	Reliance Life Sciences
Relipoietin	epoetin alpha	Anaemia Autologous blood transfusion Chronic kidney failure HIV	Reliance Life Sciences
Shankinase	streptokinase	Arterial occlusions Deep vein thrombosis Pulmonary embolism	Shantha Biotechnics/ Merieux Alliance
Shanferon	interferon α2b	BCR-ABL positive Characinoid Tumour Chronic hepatitis B Chronic hepatitis C Chronic myelogenous leukaemia Follicular lymphoma Hairy cell leukaemia Melanoma Multiple myeloma	Shantha Biotechnics/ Merieux Alliance

APPROVAL PROCESS FOR SIMILAR BIOLOGICS IN INDIA:

Before to 2012 approval process lay down for similar biologics in India, It has different guidelines according to department of biotechnology and central drug standard control organisation. But in 2012 September Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) lay down the regulatory pathway for a similar biologic claiming to be similar to an already authorized reference biologic.

DEVELOPMENT OF SIMILAR BIOLOGIC [1, 6, 7]:

Similar biologics are developed through sequential process to demonstrate the similarity by extensive characterization studies revealing the molecular and quality attributes with regard to the reference biologic. Although the extent of testing of the similar biologic is likely to be less than that required for the reference biologic, it is essential that the testing of the similar biologic be sufficient to ensure that the product meets acceptable levels of safety, efficacy and quality to ensure public health.

Step-1 Selection of Reference Biologic:

The following factors should be considered for selection of the reference biologic:

- The reference biologic should be licensed in India and should be innovator product. It should be licensed based on a full safety, efficacy and quality data. Therefore another

similar biologic cannot be considered as a choice for reference biologic.

- In case the reference biologic is not marketed in India, the reference biologic should have been licensed and widely marketed for 4 years post approval in innovator jurisdiction in a country with well established regulatory framework.
- In case no medicine or palliative therapy is available or in national healthcare emergency, this period of 4 years may be reduced or waived off.
- The same reference biologic should be used throughout the studies supporting the safety, quality, and efficacy of the product (i.e. in the developmental programme for the similar biologic)
- The dosage form, strength, and route of administration of the similar biologic should be the same as that of the reference biologic.
- The active substance (active ingredient) of the reference biologic and that of the similar biologic must be shown to be similar.

Step-2 Manufacturing Process:

The manufacturing process for similar biologic should be highly consistent and robust. If the host cell line used for the production of reference biologic is disclosed, it is desired to use the same cell line as the reference biologic.

Alternatively any cell line that is adequately characterized and appropriate for intended use can be used to develop a similar biologic, with appropriate justification in order to minimize the potential for significant changes in critical quality attributes of the product and to avoid introduction of certain types of process related impurities that could impact clinical outcomes and immunogenicity.

In manufacturing process molecular biology considerations, fermentation and downstream process is checked.

Step-3 Quality Based Considerations:

***Analytical method*:**

- The analytical methods should be chosen for establishing product comparability as per the critical quality attributes of the product. For certain attributes (e.g. product aggregation) it is customary to use multiple, orthogonal methods for characterization.
- Extensive state of the art analytical methods should be applied to detect even "slight differences" in all relevant quality attributes. Pharmacopoeia monograph should be followed, if available. The measurement of quality attributes in characterization should entail the use of appropriately qualified assays, which are reproducible and reliable. The methods used to measure quality attributes for batch release, stability studies and in process controls should be validated in accordance with ICH guidelines.

Stability

- To set a shelf-life and storage condition of drug product and drug substance, its real time stability test should be conducted. Stability studies on drug substance and drug product should be carried out using containers and conditions that are representative of the actual storage containers and conditions, according to relevant guidelines (e.g. ICH Q5C10, WHO TRS11).
- Side-by-side accelerated and stressed studies comparing the similar biologic to the reference biologic will be of value in determining the similarity of the products by showing comparable degradation profiles.

DATA REQUIREMENTS FOR APPROVAL PROCESS [2,8]

Pre clinical data:

- ***Prerequisite before Conducting Preclinical Studies:***

The basic information about the reference biologic and similar biologic may include the following:

Basic information about the reference biologic

- Information about the drug, route of administration, absorption and elimination rate, therapeutic index, dose, vehicle, mode of administration, dose response etc.
- Bioequivalence range, if available.

- Tissue-specific localization, if available.
- Available toxicity data on reference biologic.
- Mode of action.

Basic information about the similar biologic

- Known / proposed clinical use
- Target population (Age, sex, pregnancy, lactating, children etc.)
- Dosage (frequency and intervals) – units/mg/mcg
- Route / alternate routes of administration
- Final formulation + adjuvants, additives etc. - Toxicology data of adjuvants
- Diluents

Preclinical *Studies (Pharmacodynamic and Toxicology Studies)*

Pharmacodynamic Studies:

- ***In vitro* studies:** Comparability of test and reference biologic should be established by *in vitro* cell based bioassay (e.g. cell proliferation assays or receptor binding assays).
- ***In vivo* studies:** *In vivo* evaluation of biological/ pharmacodynamic activity may be dispensable if *in vitro* assays are available, which are known to reliably reflect the clinically relevant pharmacodynamic activity of the reference biologic. In cases where the *in-vitro* assays do not reflect the pharmacodynamics, *In vivo* studies should be performed.

Toxicological Studies:

- The protocols and the study reports should provide complete details of various steps in the toxicity testing as indicated below:
  - Procedures prior to euthanasia e.g. blood drawing, body weight, etc.
  - Events immediately after euthanasia, necropsy, gross – description, organ weights and organs sampled for histopathology.
  - Biochemical parameters – Equipment and methods used - units of measurement and expression.
  - Haematology procedures and parameters – method to be used (automated or manual).
  - Statistical methods used.
  - Bone marrow either examined as an aspirate /smear or on histopathology section.

Immune Responses in Animals

- Antibody response to the similar biologic should be compared to that generated by the reference biologic in suitable animal model. The test serum samples should be tested for reaction to host cell proteins.
- For evaluating immune toxicity of the similar biologic under study, the results of local tolerance (part of repeat dose or stand alone test) should be analyzed with the observations regarding immunogenicity in sub-chronic study. Therefore, the immunogenicity testing should be included as part of the sub-chronic repeat dose study while developing the protocols.

DATA REQUIREMENTS FOR CLINICAL TRIAL APPLICATION:

Pharmacokinetic studies:

- Comparative single dose and multiple dose pharmacokinetic (PK) studies should be performed in healthy volunteers or patients to demonstrate the similarities in pharmacokinetic characteristics between similar biologic and reference biologic on case to case basis.
- The design of comparative pharmacokinetic studies should take the following factors into consideration.
  - Half life
  - Linearity of PK parameters
  - Endogenous levels and diurnal variations of similar biologic under study (where applicable)
  - Conditions and diseases to be treated
  - Route(s) of administration, and
  - Indications.

Pharmacodynamic studies:

- As for the PK studies in the similar biologic clinical development program, the Pharmacodynamic (PD) studies should also be comparative in nature.

- Comparative, parallel arm or cross-over, Pharmacodynamic study in most relevant Population (patients or healthy volunteers) is required for detecting differences between reference biologic and similar biologic. If PD marker is available in healthy Volunteers, PD in healthy volunteers can be done.
- Comparative PD studies are recommended when the PD properties of the reference biologic are well characterized with at least one PD marker being linked to the efficacy of the molecule.

Safety and Immunogenicity Data

- Both pre-approval and post-approval assessment of safety is desired to be conducted for similar biologic.
- Regarding pre-approval safety assessment, comparative pre-approval safety data including the immunogenicity data is required for all similar biologics including those for which confirmatory clinical trials have been waived. This pre-approval safety data is primarily intended to provide assurance of the absence of any unexpected safety concerns.

Extrapolation of Efficacy and Safety Data to Other Indications

- Extrapolation of the safety and efficacy data of a particular clinical indication (for which clinical studies has been done) of a similar biologic to other clinical indications may be possible if following conditions are met:
  - Similarity with respect to quality has been proven to reference biologic
  - Similarity with respect to preclinical assessment has been proven to reference biologic
  - Clinical safety and efficacy is proven in one indication
  - Mechanism of action is same for other clinical indications
  - Involved receptor(s) are same for other clinical indications.

DATA REQUIREMENTS FOR MARKET AUTHORIZATION APPLICATION [9]

The applicant should submit application for market authorization as per CDSCO Guidance document for industry. For cases where commercial manufacturing is performed either at a different scale and/or with a different process as compared to that used for manufacturing phase III clinical trial batches, then information on comparability of quality needs to be additionally submitted with appropriate justification and will be dealt with on a case to case basis.

POST-MARKET DATA FOR SIMILAR BIOLOGIC

Though similar biologics are not new drug products and their risk will be similar to reference biologic; however as similar biologics are authorized based on a reduced preclinical and clinical data package, it is important to submit the Risk Management Plan to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the similar biologics. The reference biologic shall be maintained throughout the life cycle of the product.

The risk management plan should consist of pharmacovigilance plan, adverse drug reaction monitoring (ADR), and post marketing studies (PMS).

APPLICATION FORMS:

Various application forms required for submitting request to regulatory agencies are under

Table 3: *Application forms*

Stage	Agency involved	Application	Approval
Manufacturing License for test, analysis and examination	State FDA / CDSCO	Form 30	Form 29
Preclinical studies permission	RCGM	Form C3	Form C4
Submission of Preclinical study report	RCGM	Form C5	Form C6
Clinical Trial	CDSCO	Form 44	Permission letter
Manufacturing and Marketing permission	CDSCO	Form 44	Form 45/46 (Finished product) Form 46A (Bulk product)
Manufacturing License	State FDA/ CDSCO	Form 27 D	Form 28 D
Registration and Import License	CDSCO	Form 40/Form 8	Form 41/Form10

CONCLUSION:

Biotechnological medicines shall become an important part of future healthcare landscape. With patent expiration of innovator products, the biosimilars will increasingly become available. Awareness of the deviations between biosimilars and innovator products in terms of efficacy, safety and immunogenicity is essential for proper prescription and safety of the patients.The Indian government has taken several initiatives towards streamlining the way biosimilars/SBP will be regulated in our country thereby showcasing India as a key player in the biosimilar segment.

REFERENCES:

1. *http://www.gphaonline.org/gpha-media/gpha-resources/manufacture-and characterization -of-biologics and -biosimilars*
2. *Guidelines on similar biologics: regulatory requirements for marketing authorisation in India. Available from www.cdsco.nic.in/Bio Similar Guideline.pdf 2012Sep.*
3. *. Draft guideline for preclinical evaluation of similar biologics in India by DBT, Ministry of Science and Technology, GoI, 2011*
4. *.Indian bio generic companies on the threshold of globalization june2010. Available from www.biospectrumasia.com*
5. *India defines pathway for Biosimilars development. Available from http://www.biospectrumasia.com/regulatory/2207.*
6. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/49348/05), Effective from Jun 2006*
7. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non clinical and clinical issues (EMEA/CHMP/42832/05), Effective from Jun 2006.*
8. *.Draft guidance for preclinical evaluation of similar biologic in India by DBT, ministry of science and technology, Goi,2011.*
9. *Post approval changes in biological products: quality, safety, and efficacy documents.CDSCO guidance, PAC/1108, Ver01,Dec2010.*