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REVIEW ARTICLE **OPEN ACCESS**

Biosimilars in India

J. Yuvaraj* and K. Kathiresan1
*PG student, Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India.
1Associate Professor, Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India.
Corresponding Author's : E-Mail: yuvajaga01@gmail.com

ABSRATCT
A biosimilar drug is a biopharmaceutical that is very similar to an already approved biologic product, but may have slight differences in inactive ingredients. It must be shown through various testing methods that there are no significant differences in purity, potency, or safety between the two products. The process of developing a biosimilar involves a series of steps, including comparisons to the reference product, and may also require nonclinical evaluations. The approval of biosimilars is strictly regulated, but the requirements may vary depending on the location. Regardless of these requirements, it must be demonstrated through scientific evidence that any differences between the biosimilar and the reference product do not have a clinical impact. Japan and the United States adopted the guidelines for biosimilars that Europe had established first. In June 2012, India also developed its own guidelines for biosimilars as part of its growing biopharma sector, which aims to provide affordable access to these drugs through technology innovation and economies of scale. India has become a major player in the biosimilars market, with the largest number of approved biosimilars over the past decade and a strong track record of growth in its biopharma sector. This review compares the regulatory structure for biosimilars in India to the guidelines established by the World Health Organization and discusses the challenges faced by pharmaceutical companies in developing these drugs.
Keywords: biosimilar, biological similar products, biologics, generic drugs and regulatory requirements

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INTRODUCTION

Since 2000, India has emerged as a biosimilar partner, approving and launching a biosimilar to treat hepatitis B before the United States and Europe. Reduced treatment costs increase patient access to many malignant and non-malignant diseases. India quickly adapted to global demand and demand for biosimilars by remaining true to its research and scalable manufacturing capabilities. Today, India leads the list of countries in the race to be a true healthcare partner in alleviating the hardships associated with diseases such as cancer, diabetes, and arthritis.

The Department of Biotechnology and the Central Drugs Standard Control Organization (CDSCO) published guidelines in 2012 titled "Guidelines on Similar Biologics," which created a regulatory process for biologics that claim to be comparable to a reference biologic that has already received approval.

These guidelines are intended to provide direction to all stakeholders, and they do not supersede or replace the" Drugs and Cosmetics Act, 1940" or any other legislation as amended from time to time.

SPECIFIC FEATURES OF BIOSIMILAR [1]

Specific features of biosimilar medicine are listed in **Table 1**

Table 1 Specific features of biosimilar medicine

Very similar to reference medicine	In terms of their biological, chemical, and physical properties, biosimilars and reference drugs are very similar. There may be insignificant differences from reference drugs in terms of safety or efficacy that are not clinically significant.
There were no clinically significant differences when compared to the reference medicine.	Clinical efficacy differences were unanticipated. Clinical studies in support of a biosimilars approval show that there are no differences in safety or effectiveness.
The variability of biosimilars is strictly controlled.	Minor variations are permitted only if scientific evidence shows that they have no effect on the efficacy and safety of biosimilars. A biosimilar can have the same amount of variation as the reference drug. This is accomplished through a dependable manufacturing process.
The same high quality, safety, and performance standards	Biosimilars are subjected to the same stringent quality, safety, and efficacy standards as other medicines.

METHODOLOGY [2]

Following four parameters are selected for the understanding the regulatory requirements:

i Research Stage
ii Development Stage
iii Regulatory Stage
iv Post approval requirements

The steps below shows the general progression and gate points of product development **Fig. 1**

A. Research Stage

i. Target Validation

Validation methods include in vitro methods, whole animal models, and target manipulation verification in sick humans. A protein target's validity cannot be determined with a single validation tool. Basic research in medicine and biology confirmed the targets of the marketed drugs **[3]**.

ii. Hit to lead selection

Clusters of several compounds will be chosen according to their characteristics by carrying assay development, and high throughput screening.

iii. Lead discovery & Optimization

Several parameters primary and secondary screening have compound members that exhibit a high affinity towards the target, show chemical tractability, and be free of intellectual property.

B. Development Stage

I. Required Data for Applications to Clinical Trials

i. Pharmacokinetic (PK) Studies

Pharmacokinetics data should support subsequent "Phase III" clinical development because similar biologics will be established as the reference biologic product. An appropriate number of patients and/or healthy volunteers can be used in a pharmacokinetics study of a similar biologic in comparison to a reference biologic product **[4].**

ii. Comparative studies of pharmacokinetics for a single dose

The pharmacokinetics study should use a dose that falls within the therapeutic range of the biological indication. The rationale for choosing the dose should be adequate. The greatest sensitivity ought to be for distinguishing between administration route variations. The sample size must be statistically justifiable before the study can begin, and the limits of comparison must be defined and justified **[4].**

iii. Comparative studies of pharmacokinetics for a Multiple-Dose

Multiple-dose regimens using similar biologics should be studied using comparative steady-state pharmacokinetics methods with parallel arms where the concentration may be different from single-dose data and there may be time and dose-dependent pharmacokinetics parameters. If multiple-dose pharmacokinetics studies are not conducted, there should be sufficient justification provided **[4].**

iv. Studies of Pharmacodynamics

Pharmacodynamic (PD) research should be designed to compare the effects of different drugs or biologics. Similar to pharmacokinetics studies, which are also often, conducted during drug development, comparative PD studies using parallel-arm or cross-over designs can be conducted in patient or healthy volunteer populations to determine any differences between similar biologics and reference biologics. However, in cases where the drug being studied may cause adverse events or toxicity, such as in the case of oncology drugs, PD studies may only be conducted in patients if a PD marker is present and it is deemed ethical to do so **[5].**

v. Safety and Effectiveness Study

Establishing in-vitro, pre-clinical, and pharmacokinetics/pharmacodynamics concordance enables the creation of robust, high-quality processes, a comprehensive quality comparison, and comparative preclinical and PK/PD studies in these contexts **[5].**

vi. Waiver of the safety and effectiveness research

If the following conditions are met, a confirmatory clinical safety and efficacy study may be required:

a. Utilizing physicochemical and experimental methods, high-confidence structural and functional comparison of comparable and reference biologics.
b. In every preclinical assay, a comparable biologic performed similarly to the reference biologic.
c. Comparability of validated pharmacodynamics markers for clinical effect, safety measurements (including meaningful immunoassay), and efficacy/pharmacodynamics

measurements for an extended period of time that is justified by the applicant are preferred in the inpatient setting.

d. An extensive post-marketing risk control plan is provided to collect extra safety data, with a focus on immunological data collection **[6].**

vii. Data on Immunogenicity and Safety

The number of patients in the Phase IV study can be adjusted if the company conducts pre-approval studies on the proposed similar biologic drug that involve more than 100 patients. Derived from at least 300 patients who received similar biologics.

viii. Data on Safety and Efficacy Extrapolation to Other Indications

II. Application for Market Authorization

III. Data of Post-Market for Similar

i. Plan for Pharmacovigilance
ii. Reporting of Adverse Drug Reactions (ADRs)
iii. Phase IV Study

C. Regulatory Stages [7]

i. Applicable Regulations and Guidelines:

a. DCA 1940, Drugs Rules, 1945
b. rDNA Safety Guidelines, 1990.
c. Guidelines for generating pre-clinical and clinical data for rDNA vaccines, diagnostics and other Biologicals, 1999.
d. CDSCO guidelines for industry, 2008:
e. Guidelines and Handbook for IBSCs, 2011.
f. "Guidelines on Similar Biologics" - India 2012

ii. Indian authorities in charge

The authorities involved in the approval process are as follows:

a. IBSC
b. RCGM
c. GEAC
d. CDSCO

iv. The approval procedure in India [8]

The approval procedure in India is listed in **Fig. 2**

iv. Application Forms for Biosimilars in India [9]

a. Form 30 is submitted to State FDA for Manufacturing License for test, analysis and examination
b. Form 12 is submitted to Zonal CDSCO for Import license for test, analysis and examination
c. Form B1/B3/ B5/B7 is submitted to RCGM for Cell bank import / export / transfer / received
d. Form C1 is submitted to RCGM for Carrying out Research and Development
e. Form C3a is submitted to RCGM for Preclinical studies permission
f. Form C5a is submitted to RCGM for Submission of Preclinical study report
g. Form 44 is submitted to CDSCO for Clinical Trial
h. Form 44 (separate for DS and DP) is submitted to CDSCO for Import /Manufacturing and marketing permission
i. Form 27 D is submitted to State FDA for Manufacturing License
j. Form 40 is submitted to CDSCO for Registration certificate for import
k. Form 8 & 9 is submitted to CDSCO for Marketing permission / License for imported product

CURRENT ENVIRONMENT FOR BIOSIMILARS DEVELOPMENT [10]

The list of 201 active biosimilars being developed by 52 Indian pharmaceutical companies and the current & future market value of biosimilars in India are showed in **Fig. 3** and **Fig. 4** respectively.

Between February 2015 and August 2019, sixteen additional biosimilars were launched in India across multiple indications shown in **Table 2.**

The details the biosimilars approved in India between 2014 and 2019 are listed in **Table 3.**

CONCLUSION

Biosimilars are now used to manage treatments for diseases such as cancer, dermatology, and other connective tissue disorders. Biosimilars have successfully demonstrated benefits in preventing disease progression, alleviating symptoms, and improving patients' overall quality of life. Vaccines, monoclonal antibodies, insulin, and recombinant proteins are among the biosimilars approved and used in India, and they are available to consumers at significantly lower prices. Overall, biosimilars have given healthcare

professionals a more cost-effective option for treating serious health conditions that were previously treated with expensive biologics.

Biosimilars offer a significant opportunity for the Indian pharmaceutical and biotechnology industry. The government's support, including investment in infrastructure and global partnerships, will enable the industry to take advantage of this opportunity and close any technological gaps. Regulatory guidelines will aid in the growth of the biosimilars market in India, which is expected to reach a value of $12 billion by 2025.

Table 2 Biosimilars introduced in India by Indian pharmaceutical companies between 2015 and 2019

Name of the Drug	Therapeutic area	Launched date
Teriparatide	Osteoporosis	February 28, 2015
Ranibizumab, Viropro	Age related macular degeneration	June 19, 2015
Rituximab	Chronic lymphocytic leukemia; non-hodgkin lymphoma; rheumatoid arthritis	August 5, 2015
Erythropoietin	Anemia	Dec. 17, 2015
Trastuzumab	Breast tumor	Jan 9, 2016
Adalimumab	Psoriasis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis are all examples of inflammatory bowel disease.	January 12, 2016
Rituximab	Non-hodgkin lymphoma; rheumatoid arthritis	January 12, 2016
Bevacizumab	Metastatic colorectal cancer	June 27, 2016
Bevacizumab	Cancer	Sept. 6, 2016
Bevacizumab	Cancer; non-small-cell lung cancer	Sept. 30, 2017
Bevacizumab	Metastatic colorectal cancer; non-small-cell lung cancer; ovary tumour; renal tumour; uterine cervix tumour	Nov. 23, 2017
Adalimumab	Rheumatoid arthritis	January 3, 2018
Pegfilgrastim	Neutropenia	June 30, 2018
Pegfilgrastim	Neutropenia	July 25, 2018
Trastuzumab	Breast tumour; metastatic breast cancer; metastatic stomach cancer	July 26, 2018
Bevacizumab	Metastatic breast cancer, metastatic colorectal cancer, metastatic non-small cell lung cancer, metastatic renal cell carcinoma, ovary tumour, peritoneal tumour, uterine cervix tumour	Aug. 19, 2019

Table 3 Biosimilars approved in India (2014 – 2019)

Year	Biosimilars
2019	03
2018	18
2017	05
2016	08
2015	15
2014	12
127 biosimilars have been approved in India till January 2022	

Fig. 1 General progression and gate points of a product development

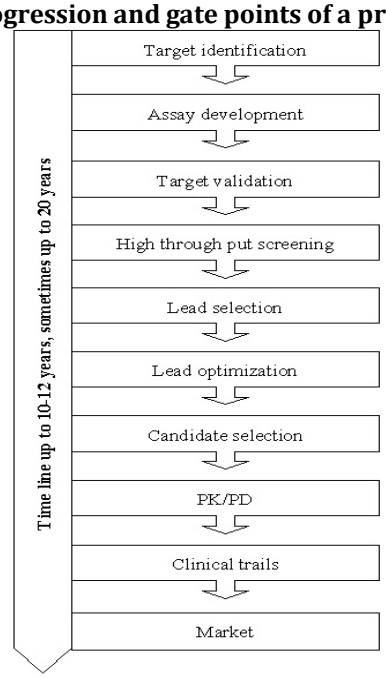


Fig. 2 Approval procedure in India

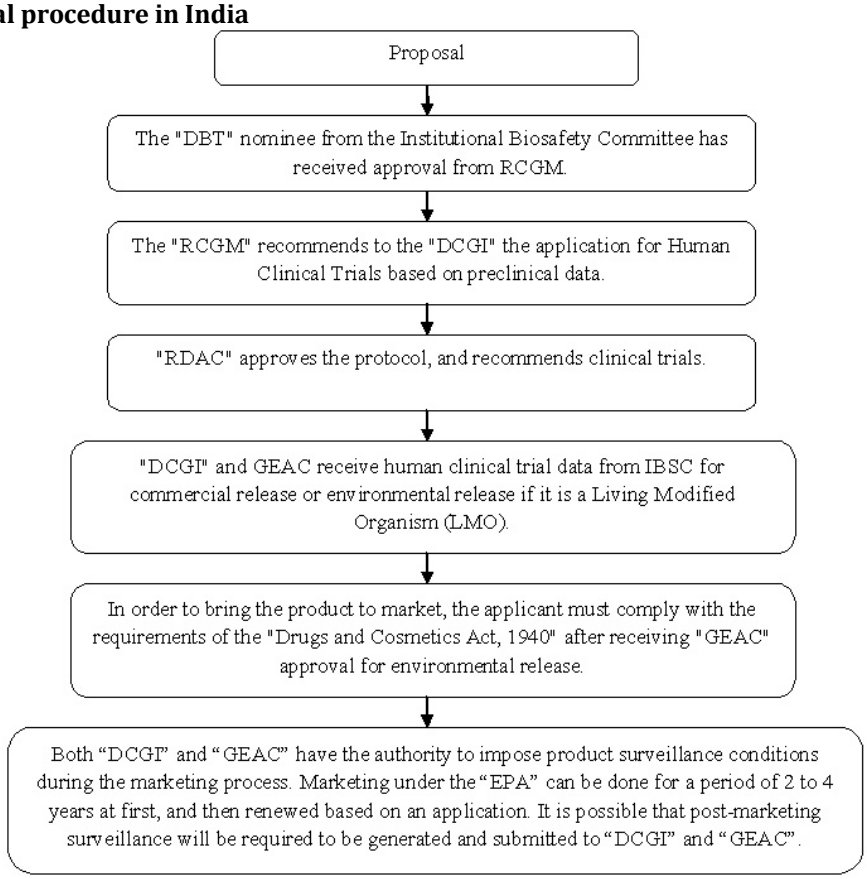


Fig. 3 Biosimilars pipeline for Indian Pharmaceutical Companies

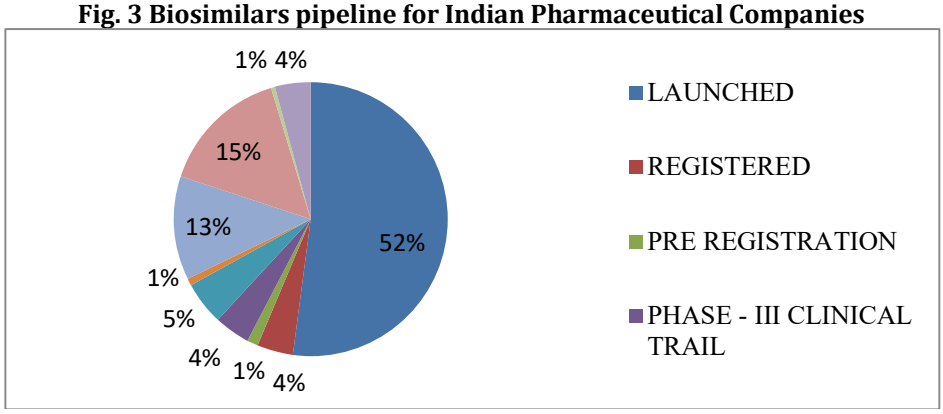
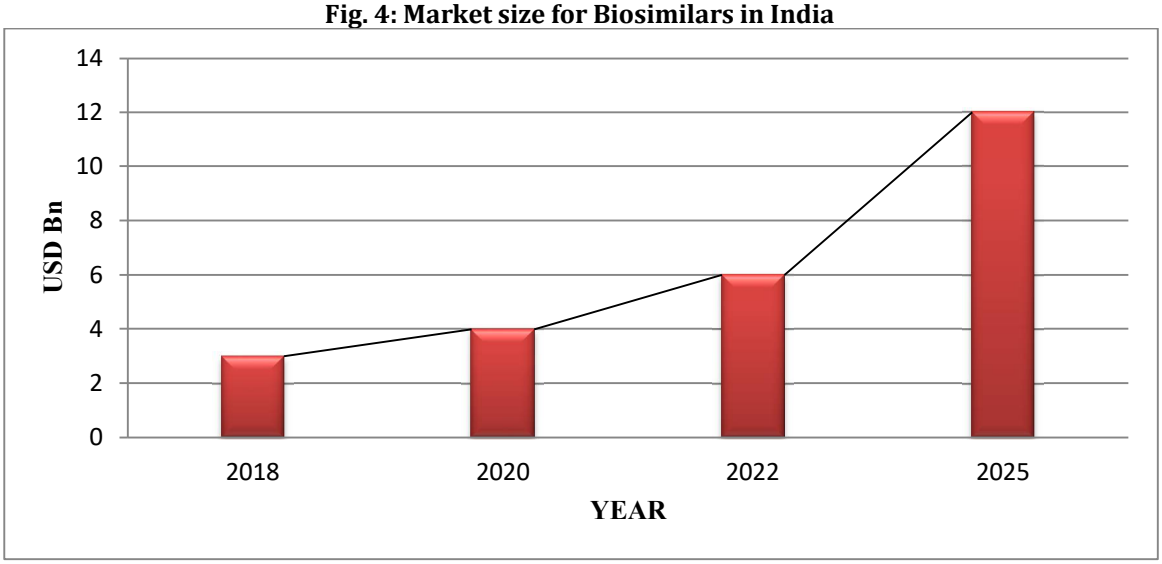


Fig. 4: Market size for Biosimilars in India



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