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Biosimilars: Current Regulatory Landscape in India

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ABSTRACT

Increasing need of Biologic medicine for chronic and life-threatening diseases in India opens the door for biotechnology derived Biologics. These biologics are different from traditionally produced generics in many ways including size, complexity of the active substance, indigenous variability of living cells, complexity of manufacturing process, post translational modifications. Development of Biologics requires huge capital, time and manpower investment which ultimately increases its cost to an unaffordable level. Need vs unaffordability, opens an opportunity for the low-cost product which is similar to Innovator Biologics in terms of quality, safety and efficacy termed as Biosimilars. European Union is the pioneer in establishing formal regulatory pathway for Biosimilar after which many countries had defined regulations for Biosimilar. In India, Biosimilars are termed as Similar Biologic, India released its first Biosimilar guideline in 2012. To align Indian guidelines with the global regulations and to overcome the lacunas of the previous guideline, India has released revised guideline on Biosimilar in 2016. This paper briefs about the Biosimilar regulations in India and the roles and responsibilities of various regulatory authorities involved in the approval of Biosimilars along with the regulatory principle for approval with special emphasis on manufacturing process, quality, preclinical and clinical study, post market regulations to ensure the product is similar to Innovator Biologic in terms of quality, safety and efficacy.

INTRODUCTION

India has created strong footprint in the global pharmaceutical markets specially in the generic medicines. India has huge market for Biotherapeutics as significant portion of 1.3 billion population is suffering from chronic diseases[1] and only small population of the country can afford them[2]. Biologic medicines have great potential in the treatment of numerous health conditions including life threatening and rare diseases, they are produced from living organism or contain living organism. Owing to its complexity, it is very difficult to characterize complex molecule with the currently available analytical tools and inherent variability of biological system produce a product with certain degree of dissimilarity[3]. For biologics, 'Process is the Product' i.e. consistency and robustness of manufacturing process is vital for product quality, purity, safety and efficacy. Small modifications in the manufacturing process may affect the final product significantly[4]. Despite the complexity, Biologics are very important in the treatment of life-threatening diseases. Indian regulators have realized the need of having more Biological medicines in the Indian market. Biological medicines are among the most expensive drugs as compared to generic medicines which puts a huge financial burden on health care system and affordability by a patient remains a big challenge. Once Inventor Company loses patent exclusivity or patent rights, it opens an opportunity for the companies interested in the manufacture of the product with similar safety and efficacy[5]. This paves the way for introduction of less expensive alternative. Significant cost reduction in Biosimilar development compared to innovator biologic is due to reduced clinical studies on the Biosimilars, provided that the Biosimilar shows analytical similarity with the innovator product. Biosimilar also have a shorter timeline for approval as compared to Reference Biologic[6]. Analytical characterization is the most important part in the Biosimilar development. Similarity in the physiochemical and functional characteristics of the proposed Biosimilar gives confidence to the manufacturer and the regulators regarding the similarity of the product to the Reference Biologic. Biosimilars are biopharmaceutical products which are similar to Innovator Biologic in terms of safety and efficacy, they are not generic medicines. Unlike small molecules with defined and entirely reproducible structure, Biosimilars are more complex and unlikely to be identical to reference product (table 1). Biosimilars can be approved only after patent expiry of innovator Biologic product.

Table No. 1: Generics Vs Biologics characteristics[7]

Generics	Biologics
Simple structure	Complex structure
Small size	Large size: up to 100–1000 times larger than traditional generics
Chemical manufacturing process	Genetically modified living cells
Minimal steps to synthesize product	Multifaceted manufacturing process
Simple, direct mechanism of action	Complex mechanisms of action
Simple, well characterized binding sites	Multiple targets, binding sites
Efficacy markers easily quantified	Efficacy markers not always clear
Product components limited, known	Hard to isolate, purify after production
Stable once produced	Generally unstable

Challenges in the development of Biosimilars

Development of Biosimilars is a big challenge for Indian Pharmaceutical industry due to complexity involved in the development of Biosimilar. Minor changes in the process may lead to significant deviations in the safety and efficacy of the product[8]. As biosimilars are developed in the living cell, inherent variability between the cells makes it very difficult to exactly replicate the original molecule and there could be lot to lot variations as well. Therefore, high end R & D and manufacturing set up along with highly qualified staff is very critical for the development of Biosimilars. Bringing Biosimilar molecule in the market requires approximately 150 million USD with major part of the investment spent on R & D, it's a long journey of 8-10 years for the molecule to enter the market. Investment and expertise are the challenges for new entrants to acquire this space.

In depth knowledge of manufacturing process of Reference Biologic is required for the development of Biosimilar to evaluate any analytical differences and their impact on the function of Biosimilar. The main challenge for Biosimilar manufacturer is to produce highly similar product without knowing the manufacturing process of the Reference Biologic as the information is proprietary and not publicly available[9, 10].

Protein undergoes chemical changes after translation, these changes are called Post Translational Modifications (PTMs). Some of the PTMs are methylation, acetylation, deamidation, glycosylation etc. PTMs play an important role in cellular function by

regulating protein folding, interacting with ligands and other proteins. Thus, selection of appropriate expression system which gives desired PTMs profile is very crucial[9, 11].

Apart from these technical aspects, high end state of art technologies needs to be used at various stages in the Biosimilar development. All these factors increase cost, time and risk in the development of Biosimilar which is a big barrier for Indian pharmaceutical companies to develop Biosimilars.

Government initiative for promoting Biotechnology products

Department of Biotechnology (DBT) and its public sector enterprise Biotechnology Industry Research Assistance Council (BIRAC) have made efforts for promoting innovation and infrastructure creation of Indian Biopharma. National Biopharma Mission is supporting Indian Biopharmaceutical industry by providing trainings and education to young researchers, entrepreneurs and by promotion of entrepreneurship and start-ups. There is a great potential for Indian Biotech Sector to become a global hub for manufacturing of biologics. In the recent past Indian Biopharma has emerged as one of the important global players[12].

Government Regulations and Guidelines for Biosimilars

Biosimilars falls under the category of Drugs as per Drugs and Cosmetic Act 1940 and Drugs & Cosmetics Rules 1945 (D&C), hence regulated under this act and rules. In India, Biosimilars are termed as Similar Biologics. Similar Biologics means the product which is similar in terms of quality, safety and efficacy to an approved Reference Biological product based on comparability [13]. First guideline for Similar Biologics was released in 2012 which is then further revised in 2016. In the revised guidelines many terminologies are redefined to meet global standard and Post Marketing Surveillance is included in a detail.

Similar Biologic approval process in India is multi institutional. The Central Drugs Control Standards Organization (CDSCO), Genetic Engineering Appraisal Committee (GEAC), Review Committee on Genetic Manipulation (RCGM), Institutional Biosafety Committee (IBSC) are involved at various stages of approval of Similar Biologic. Various rules and guidelines need to be referred for approval. These include:

- Guideline on Similar Biologics: Regulatory Requirements for Marketing Authorization in India, 2016

- CDSCO guidance for Industry, 2008

- Recombinant DNA Safety Guidelines, 1990

- Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other Biologicals, 1999

- Guidelines and Handbook for Institutional Biosafety Committee, 2011

- New Drugs & Clinical Trial Rules, 2019

- Rules for Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/Genetically Engineered Organisms or Cells, 1989

- Regulations and Guidelines on Biosafety of Recombinant DNA Research and Biocontainment, 2017

Development of Similar Biologic

Guideline on Similar Biologics-Regulatory Requirements for Marketing Authorization in India, 2016' has given extensive guidance on the regulatory requirements to demonstrate similarity of Similar Biologic in terms of quality, safety and efficacy to an approved Reference Biologic. Reference Biologic is an innovator product which is used as comparator with Similar Biologic for comparing safety, efficacy and quality, Reference Biologic is alternatively termed as Innovator Biologic. The Reference Biologic to be used in the development of Similar Biologic must be approved in India or ICH countries as an Innovator's product. Another Similar Biologic cannot be considered as a choice of Reference Biologic[13].

Robust manufacturing process shall be established for Similar Biologic. Identification of host cell line is one of the most critical components as this may affect Critical Quality Attributes and can impact clinical outcome. A well-defined manufacturing process as per GMP with proper in process controls gives confidence on consistency of the product yield.

Following are the key steps in the development of Similar Biologic:

a. Quality Based Considerations

Analytical characterization is the key for establishing similarity. Unlike Innovator Biologic wherein most of the resources are utilized for the clinical phase, Similar Biologics are rigorously tested for its physicochemical and biological characterization. Determination of protein structure, biological activity, immunological properties, impurity profile in comparison with Reference Biologic should be done to give a first level of confidence to the manufacturer and the regulators regarding similarity.

Quality comparison between Similar Biologic and Reference Biologic is essential. Applicant shall submit full quality dossier as per CDSCO Guidance for Industry, 2008. The quality comparison between two should be governed by Quality Attributes which include high resolution analytical techniques and methods that are sensitive enough to detect possible changes. Critical Quality Attributes (CQAs) are those which have direct impact on clinical safety and efficacy. Some of the examples of CQAs are structure of the molecules, expression pattern, efficacy etc. Key Quality Attributes (KQA) are those which are not known to impact clinical safety and efficacy but are considered relevant from product and process consistency prospective. Product related variants and impurities, process related impurities, protein content, pyrogen content are some of the examples of KQAs.

b. Preclinical study

The applicant shall be complied with RCGM requirement like demonstration of consistency of the process and product, product characterization and product specifications before conducting preclinical studies. Basic clinical information about Reference Biologic and Similar Biologic along with preclinical study protocol shall be submitted to RCGM for obtaining permission along with IBSC and Institutional Animal Ethics Committee (IAEC) if available.

Comparative preclinical studies with same dosage form, dose, strength and route of administration as that of Reference Biologic needs to be conducted with final formulation to detect differences if any.

In vivo/ in vitro Pharmacodynamics (PD) study, toxicological study in pharmacologically relevant species, immune toxicity studies shall be a part of preclinical evaluation.

When the study is completed, final report shall be submitted to RCGM. After successful evaluation of preclinical study reports, RCGM will recommend DCGI to allow for appropriate clinical trials as per CDSCO requirement. Applicant can submit parallel application to RCGM and DCGI. However, permission of conducting clinical trials shall be issued only after receiving recommendation from RCGM.

c. Clinical Study

Application shall be submitted to CDSCO for conducting clinical trials along with quality data which should demonstrate no difference between Critical Quality Attributes and Key Quality Attributes are under control.

Comparative Pharmacokinetic (PK) studies shall be performed in suitable population between Similar Biologic and Reference Biologic with Parallel arm or cross over depending on the shelf life of the product. Normal Healthy Population or patients can be used in the study. Various parameters like half-life, disease to be treated, route of administration, indications shall be taken into consideration while designing PK study. Dose used in the PK study shall be within therapeutic dose of Reference Biologic. Study population size should have statistical significance. Multidose comparative PK study is done if the product is used in a multidose regime.

To identify the differences between Reference and Similar Biologic; comparative parallel arm, cross over PD study in relevant population shall be performed. Acceptance criteria for defining similarity for PD parameters shall be predefined.

These comparative preclinical studies and PK/PD studies help determine similarity of Similar Biologic with Reference Biologic.

Although similarity in the analytical and preclinical studies are important in the Biosimilar approval, to eliminate any residual risk, additional safety and efficacy trials may be required. In such cases where no uncertainty left in the earlier studies regarding similarity of the product to Reference Biologic, additional safety and efficacy trials may not be required.

Good Clinical Practice (GCP) guidelines shall be followed for conducting Phase III clinical studies for Similar Biologic. Marketing approval may be granted if the product demonstrated similarity with Reference Biologic. After the marketing approval, Phase IV clinical trials may be required to be conducted in 200 patients. Confirmatory clinical trials can be waived off if Similar Biologic shows high degree of similarity in physiochemical, preclinical studies and PK/PD study and has demonstrated comparability of PD markers validated for clinical outcomes in patients along with Post marketing risk management plan which can generate additional safety data with emphasis on immunogenicity. In the absence of validated PD markers, clinical studies cannot be waived off. If waiver is granted for phase III study, then immunogenicity data shall be generated in PK/PD study and phase IV study. However, for large molecules like monoclonal antibodies, confirmatory clinical trials cannot be waived off.

If the Similar Biologic demonstrates high degree of similarity with Reference Biologic, then extrapolation of safety and efficacy data to other indication can be done if mechanism of action and receptors are same for other indications.

d. Marketing authorization

Once quality, preclinical, clinical data is generated, application shall be submitted to CDSCO as per guidance document for Industry, 2008 for getting marketing approval. Phase IV protocol needs to be submitted along with the application. CDSCO office shall grant the marketing authorization after reviewing all the documents and recommendations.

e. Postmarketing data

Postmarketing surveillance is very important to ensure safety of the product for its entire life cycle. It will help overcome some of the lacunas of clinical trials as clinical trials are conducted in a controlled environment with limited number of patients or healthy volunteer. Pharmacovigilance system must be followed to monitor safety and efficacy of the product while patients are using the medicine to get relief for disease or disorder.

Marketing authorization holder (MAH) shall have Risk Management Plan (RMP). MAH shall submit Periodic Update Safety Reports (PSURs) to DCGI six monthly for first two years after approval of Similar Biologic and annually for subsequent two years. All cases of serious unexpected adverse reaction shall be reported to DCGI within 15 days after becoming aware.

Further to reduce any residual risk, Post Marketing Studies shall be done in more than 200 patients within 2 years of marketing approval where Safety is the most important aspect monitored during phase IV study. However, in rare diseases where enrolment of volunteer is a bigger challenge, population size can be reduced.

Mashelkar Committee Task Force Recommendations: Protocols for Living Modified Organisms (LMOs)

In 2004 under the chairmanship of Dr. Mashelkar, Task Force Committee was constituted to define the protocol for recombinant pharma sector. Taskforce had defined regulatory procedure for use of LMOs in the manufacture and import of pharma products. LMOs are those organisms modified by r-DNA techniques through human intervention where the product is Living Modified Organism[14].

There were various challenges in the approval process of genetically modified/hazardous microorganisms, therefore Taskforce has given several recommendations to streamline the process of approval and the recommendations given by Taskforce were implemented in 2006. In the recommendations, committee has defined 5 scenarios for recombinant pharma sector and their process of approval[15, 16].

The product in which final product is LMO has the potential of propagating in the environment thus higher level of regulations are required than the product where product is not LMO.

GEAC approval is required depending on the below two factors:

1. If the final product is LMO or not.

2. Risk Category I, II, III, IV

Five scenarios defined by Taskforce

i. Indigenous product development, manufacture and marketing of pharmaceutical products derived from LMOs but the end product is not a LMO.

IBSC will review biosafety aspect of the product. RCGM will examining preclinical study protocol and final report. After reviewing preclinical data, RCGM will give recommendations to DCGI for deciding on human clinical trial. In this scenario, end product

is not LMO therefore GEAC approval is not required for conducting human clinical trial. But if risk category of product is III and above, GEAC approval is required prior to manufacture and marketing of the product. Based on the recommendation from all stakeholders, DCGI will give approval for manufacture and market authorization under Drugs and Cosmetic Act of India, 1940 and rules thereunder.

ii. Indigenous Product Development, Manufacture and Marketing of Pharmaceutical Products where the End Product is a LMO.

IBSC and RCGM continue to perform their assigned task of biosafety and preclinical studies respectively. In addition to this RCGM also share its views on containment facility to GEAC. GEAC will ensure infrastructure available with applicant is adequate for safe handling of LMO at all the stages of product lifecycle. Since product is LMO, risk due to accidental release is higher. Therefore, GEAC will evaluate environmental impact caused by release of LMO and based on their findings, GEAC will recommend human clinical trial. GEAC will also forward their views on safety from environmental perspective to DCGI.

DCGI after reviewing allergenicity, toxicity data, QC tests and recommendations from RCGM, GEAC gives approval for conducting human clinical trial. DCGI is ultimately responsible for evaluation of safety and efficacy of product, market authorization and post marketing surveillance. DCGI shall take GEAC clearance under Rule 1989 of Environmental Protection Act prior to granting of approval for commercial release of LMOs as a drug,

iii. Import and marketing of recombinant pharma products in finished formulation where the end product is a LMO.

In this scenario, risk of environmental damage reduces significantly as compared to indigenously manufactured product. For the import of such product human clinical trials needs to be conducted based on the data available in the country of origin. GEAC evaluates environmental impact and give recommendation to DCGI regarding safety of the product from environmental perspective. DCGI is responsible for safety, efficacy of the product prior to market authorization and post market surveillance.

iv. Import and marketing of recombinant pharma products in bulk for making finished formulation where the end product is a LMO.

In case of import of LMOs as bulk, environmental risk is higher as compared to import of LMOs as finished product as processing step would involve partial manufacturing and storage of LMOs. GEAC will evaluate impact on environmental safety based on the data provided by country of origin. GEAC will instruct applicant to set up IBSC and will also provide recommendation to DCGI. As per the procedure outlined in Protocol II approval of RCGM, GEAC and DCGI is accorded.

v. Import and marketing of recombinant pharma products in bulk/finished form where the end product is not a LMO.

In this scenario, end product is not LMO. Therefore, environmental risk reduces as no manufacturing facility is required for finished product and for bulk only partial processing facility is required. Such a product will not fall under Rule 1989 of EPA Act as there will not be use of LMO within country and product falls under least risk group. As per the recommendation from Taskforce, DCGI may obtain views of RCGM on the process, purity, pre-clinical and clinical data prior to approval of human clinical trial or market authorization.

Summary of five protocols

Approval for import of recombinant organisms for the purpose of research and development is within the purview of RCGM. The regulatory agency to authorize human clinical trials is DCGI in all cases. GEAC approval is necessary prior to conduct of Phase-III clinical trials for protocol II, III, IV. In situations where approval of both DCGI & GEAC is mandatory, both agencies can process their case concurrently.

The timeline required by the regulatory authority for the approval of biosimilar[17]:

Description	Timeline
Approval for pre-clinical studies by RCGM	45 days
Approval for Human Clinical Trials protocol by DCGI	45 days
Clinical trial data examination by DCGI	90 days
GEAC and DCGI decisions	45 days

Future Prospects

India approved its first Biosimilar vaccine for Hepatitis B in year 2000[18], since then Indian Biosimilar market and Indian regulations are evolving rapidly. Indian Biosimilar companies

have realized the need of global partnership to speed up the launch of Biosimilars in the global market. Biocon-Mylan is the best example of how partnership with global players helps faster entry of Biosimilars in the regulated market. Recently on 28 April 2020, Biocon-Mylan have announced launch of Pegfilgrastim biosimilar, Fulphila in Canada[19]. In the subsequent years, many Indian companies with global partnerships will enter this space and bring new Biosimilars to the regulated market (Surge of Indian biosimilars market forecast in 2019[20]. According to Associated Chambers of Commerce of India's 2016 report, Indian Biosimilars market expected to reach $35bn by 2030 and that global biosimilar market will be worth of $ 240 bn[21].

Indian regulations are evolving at a faster pace but considering factors like affordability by the patient and investment potential of the pharma industry, there must be a step wise process of continuous evolution in Indian Biosimilar regulations. Alignment of Indian regulations with global standards will ease the entry of Indian manufactured Biosimilars in the global markets.

To encourage Indian Industry to enter Biosimilar domain, Government shall refine policies and regulators shall engage with industry people from the conceptualization of the product to avoid financial loss and delays in the approval. The government shall also provide funding to entrepreneurs and training to young researchers and scientists from biopharmaceuticals. For better penetration of Biosimilars in India and the mindset shift of physicians and patients, education and awareness need to be created. The government shall implement schemes which make Biosimilars accessible to economically weak population suffering with cancer, diabetes and other immune modulated diseases.

CONCLUSION

Developing Biosimilar is a complex process which requires skilled manpower, use of high-end equipment and technology and more stringent and robust manufacturing process requiring significant amount of investment. Low penetration, lack of awareness and brand consciousness amongst patients and physicians, pricing pressure, patent litigation, regulatory compliance makes it difficult for Indian pharmaceutical industry to enter Biosimilar domain. Biosimilar also face strong competition for the innovator company as they might reduce the cost of the product drastically. Funding from government and different organizations across India for promotion of entrepreneurship, new policies to ease business development,

evolving regulations, awareness amongst physicians and patients will encourage Indian pharmaceutical industry for Biosimilar development.

Timing the market is very critical for launching biosimilar. Collaboration with local players and sharing an asset will accelerate the process and global competitiveness. Sharing the risk reduces financial burden for each of the players and confidence level will increase amongst them. Biosimilar growth will be driven by entering more and more industries in this segment. International collaboration with global partners will help India to make faster entry into global markets by elevating quality, confidence and reputation.

Globally, in last three decades, hundreds of recombinant biopharmaceuticals are patented or approved[6]. As older biopharmaceuticals expire the patent rights, this gives huge opportunity for growth of Biosimilar sector worldwide. In response to the high commercial potential and the need for development of indigenous drugs to cater to the large Indian population pool, the Government of India has taken steps to encourage India's development as a hub for biotechnology-based drugs.

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