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REGULATORY REQUIREMENTS FOR POST APPROVAL CHANGES, POST MARKET STUDIES OF BIOSIMILARS AND PHARMACEUTICAL PRICING OF DRUGS IN INDIA

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ABSTRACT

This paper aims to facilitate the regulatory requirements for the post approval changes, post market studies of Biosimilars. The approval process of biopharmaceutical drugs have become an essential part of modern pharmacotherapy. The expiry of patent protection of many biopharmaceuticals has initiated the development of a category of alternative versions of innovator biopharmaceuticals known as biosimilars. Biosimilars include monoclonal antibodies, soluble receptors, growth factors, and hormones. Biosimilars are biotherapeutic products with similar efficacy, safety, and quality to a licensed bio-originator. Biological products are now leading propeller for the global pharmaceutical business. Advantages such as cost efficiency, expanding figure of off-patented drugs.

INTRODUCTION

Biopharmaceutical drugs have become an essential part of modern pharmacotherapy. These comprise proteins derived from recombinant DNA technology and hybridoma technique. Examples include biological proteins (cytokines, hormones, and clotting factors), monoclonal antibodies, vaccines, cell and tissue based therapies. Living organisms such as plant and animal cells, bacteria, viruses and yeast are employed for the production of biopharmaceuticals. The expiry of patent protection of many biopharmaceuticals has initiated the development of a category of alternative versions of innovator biopharmaceuticals known as biosimilars. Because of the structural and manufacturing complexities, these biological products are considered as similar, but not generic equivalents of innovator biopharmaceuticals. Biosimilars are biotherapeutic products with similar efficacy, safety, and quality to a licensed bio -originator. Biosimilars include monoclonal antibodies, soluble receptors, growth factors, and hormones. The manufacture of biosimilars is a sophisticated multistep process; factors at each stage, such as production cell line, culture conditions, and formulation, may each alter the final product through post-translational modifications. [1] The Similar Biologics are regulated as per the Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (as amended from time to time) and Rules for the manufacture, use, import, export and storage of hazardous microorganisms/ genetically engineered organisms or cells, 1989 (Rules, 1989) notified under the Environment Protection) Act, 1986. Similar Biologic is developed through a 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 in accordance with international guidelines.(WH2013). Generally, a reduction in data requirements is possible for preclinical and /or clinical components of the development program by demonstration of comparability of product (Similarity to authorized Reference Biologic) and the consistency in production process, which may vary depending on the characteristics of the already authorized Reference Biologic. Identification of any significant differences in safety, efficacy and quality studies would mean the need for a more extensive preclinical and clinical evaluation and the product will not qualify as a Similar Biologic. [2] The biosimilar has to demonstrate comparable data of non- clinical studies viz., pharmacokinetics and toxicology (safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity) and clinical studies (efficacy and tolerability for each indication) before it gets approval for all indication of the reference medicine. Biosimilars in India consist primarily of vaccine, monoclonal antibodies, recombinant proteins and diagnostics, insulin (wosulin, insugen, recosulin), erythropoietin (hemax, epofer, wepox,ceriton, epofit), hepatitis B vaccine (Shanvac B, Revac B, Enivac B, Biovac B, Genevac B,Bevac), granulocyte colony stimulating factor (G-CSF– Grastim,Neukine),streptokinase(indikinase,shankinase,STPase),interferonalp-2B(shanferon), [3]

In Developed Markets (DM) there are well defined regulatory and established precedents which mandate comprehensive clinical programs. This in turn has necessitated very high upfront investments. Biosimilars are highly complex molecules manufactured by living cells. Their manufacturing needs to be managed through a highly controlled processes and manufacturing environments because of the risk of even minor variations introducing unacceptable changes to product quality. This entails a high focus on quality across the entire manufacturing process and raw materials, equipment used as well as the people who undertake the process. The process involved in Biosimilars is much advanced from what is typically expected for chemical processes and therefore it's a significant learning curve for companies that are new to the field. Also, significant investments are required in setting up these facilities as well as increasing capacities, so it is imperative to ensure facilities are fully utilized in order to keep costs under control. [4]

1.1. REGULATORY IMPACT ON BIOSIMILAR REGULATION:

In 2005, the first biosimilar regulatory framework was launched by the EMA opening possibilities for biosimilars in the European Union. This paved path for launch of 21 biosimilar products in EU and many countries adopted the EU principles in their guidelines, making high quality biosimilars more accessible to people. Though in the US, a legal framework for biosimilars was established in 2009, Filgrastim was the first biosimilar approved in 2015. Till today, USFDA has approved only 4 biosimilars granulocyte colony-stimulating factor, a follow-on biological of insulin and two monoclonal antibodies. Biosimilar regulatory frameworks have been guided for most emerging markets with EMA being the leader, regulations still long way to go in China and Russia. Until recently, the USFDA has been strongly obstructing promotion of biosimilars approval, despite BPCIA's instructions to FDA for implementing a framework balancing biologics' and biosimilars' manufacturers and consumers interests. [6]

1.2. SIMILAR BIOLOGICS DEFINITION AND BASICS

Similar Biologics: A similar biologic can be defined as a drug product which is comparable to a reference product based on the quality, efficacy and safety of the same.

Biosimilar Product: A biological product which have been proved to be largely similar with a reference product already approved by US-FDA which shows very less clinical difference.

Biosimilar: According to WHO biosimilars can be defined as a biotherapeutic product that shows similarity to an already licensed reference product in terms of quality, efficacy and safety. Reference biotherapeutic product (RBP): It is defined as a product that can be employed for the comparability studies so as to prove their similarity of quality, efficacy and safety with

their biosimilars product. A RBP is valid only when the originator product is licensed on justification of a complete registration dossier. [9]

1.3.BIOSIMILAR MARKET TREND 2018

World is witnessing a rise in demand for Biosimilars as they offer an affordability factor equivalent to being ~30% cheaper than innovator drugs which have been driving healthcare costs to the ceiling. Lower prices increase market penetration and as the number of players increase greater price erosion is observed. These scenarios have triggered faster drug approvals, transformation of reimbursement policies and government support via initiatives to encourage biosimilar development worldwide to increase accessibility. Last year WHO launched a pilot program for prequalification of biosimilar drugs for various types of cancers to enhance accessibility of these drugs in the developed nations. Rituximab (targeting non-Hodgkin's lymphoma and chronic lymphocytic leukemia) and Trastuzumab (targeting breast cancer) were primarily covered under this program. Coupled with blockbuster drug expiries, high margins, increasing awareness among patients and doctors and rising interest from insurance companies biosimilars has become a lucrative market for various players. With worldwide biotechnology drug market projected to grow to $ 337 billion by 2022, the global biosimilar market which was pegged at USD 3.81 billion in 2016, with a conservative CAGR of ~26% is now expected to reach USD 15.43 (25-35) billion by 2022.

1.4. THE EVOLUTION OF REGULATORY PATHWAY FOR BIOSIMILARS

European Medicines Agency (EMA) has pioneered in biosimilars regulatory space by providing the first Biosimilar Regulatory framework in Oct, 2005 which paved way for the subsequent approvals of 41 biosimilars back in 2006.

USFDA: The U.S. biosimilar market is relatively new. The legislation to create a regulatory pathway for biosimilars was passed in 2010, with the Biologics Price Competition and Innovation Act (BPCIA), as part of the Affordable Care Act. In 2012 FDA issued the first draft guidelines for developing and registering a biosimilar in the United States, and it took further three years to approve Sandoz's Zarxio (filgrastim-sndz) as the first biosimilar. Since then FDA has gained momentum and has approved 7 products in 2017 alone. Close to 40 biosimilars are in clinical development, most of which are in late stages. In the last 5 years, there has been a rapid rise in the R&D projects in biosimilars. Over the next five years more players are expected to launch their biosimilar brands of blockbuster drugs in the U.S. biosimilar market.

Rest of the World (ROW market):

Emerging markets including the Asia Pacific region will continue to be of key focus in any company's business strategy owing to lower regulatory barriers resulting is early revenue streams. These countries have mix out of pocket, payer and government payment models, flourishing medical tourism and developing health infrastructure which will contribute greatly towards the growth of the market in next 5 years. Countries like Japan, Singapore, South Korea, ANZ, Taiwan and Brazil already have biosimilar pathways in place while other countries like Columbia, Jordan and Venezuela are playing catch up and are in the process of developing and establishing the same. Some countries like Vietnam and Philippines have also been seen to adopt approval pathway similar to generic products. [7]

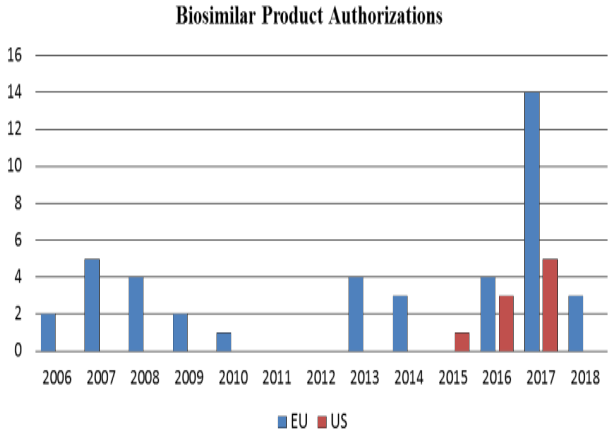

Fig:1 Comparison of biosimilar market of Europe and US

1.5. MARKET ANALYSIS:

India has firmly established itself in the global pharmaceutical market; it has been predicted that India will be the sixth largest market for pharmaceuticals by 2020, and the country exported pharmaceutical products worth more than $17bn in 2017-8. Indian pharmaceutical

companies are especially known for producing generics, identical copies of branded drugs marketed under different names once the patent for the original drug has run out. Many of these companies are starting to move into the global biosimilars market. According to Associated Chambers of Commerce of India's 2017 report, biosimilars are worth $2.2bn out of the $32bn total Indian pharmaceutical market and are expected to reach $40bn by 2030, which represents a 30% compound annual growth rate. This growth will be aided by a range of biologic patents expiring in the next few years. India's first biosimilar, a vaccine for hepatitis B, was marketed and approved in 2000, according to the global Generics and Biosimilar Initiative (GaBI); more than a decade before the US Food and Drugs Administration (FDA) approved its first biosimilar. Approximately 70 biosimilar products have been approved in India and, according to GaBI's list, more than 25 have been developed in India since 2000.

Biocon and Mylan's fulphila (trastuzumab), a biosimilar of Neulasta indicated to minimize febrile neutropenia while cancer patients undergo chemotherapy, was approved by the US FDA in June Fulphila is currently under review in Australia and the European Union. This is the first biosimilar produced by an Indian company to be approved in the US. [8]

Patents on many major biologics has expired in 2016, it's estimated that $240 billion biosimilar market opportunity is now open for Indian pharmaceuticals industry.This provided an opportunity to Indian pharma companies, active in biotechnology arena, to exploit the world's largest biologics market. Dr Reddy's Laboratories Ltd, is the first Indian firm to rollout with world's first biosimilar antibody with the launch of Reditux (rituximab) in 2007 and now products are currently being sold in over 10 emerging markets. [9]

2. METHODOLOGY:

The research was carried out to describe in detail about the post approval changes, post marketing studies of similar biologics along with understanding the drug pricing policies in Indian market. An orderly method was utilized to attain the goal of the study.

SOURCES OF DATA:

The majority of the data collection was done from the Guidance documents released by the Government of India. Search engines such as Google, Google Scholar were exploited to obtain the data for the study. Official guidelines and recommendation provided by the CDSCO were obtained from the Official website of CDSCO. Several literatures were reviewed as the secondary source.

Work plan of the research were as follows:

- Understood the biologicals and similar biologics guidelines followed in India
- Reviewed the articles and Guidelines obtained from various domains and official websites.
- Studied various post approval changes and marketing studies of similar biologics.

3 .STUDY AND DISCUSSION:

The following were the titles included in the research

- Basic definition: Definition of biologics and similar biologics.
- Basics of Similar Biologics regulations in India
- Difference between biological and similar biologics.
- Similar Biologics history in India.
- Detailing regarding the post market studies regulatory requirements of similar biologics in Indian market.
- Post approval changes.
- National Pricing policies of India.
- Pricing of similar biologics in India. Challenges faced by Indian Pharmaceutical companies in the drug pricing of similar biologics

3.1. SIMILAR BIOLOGICS REGULATION IN INDIA

While considering the global bio generic market, India was considered a major backer close to China market. CDSCO along with DBT had issued the Guidelines for Similar Biologics in the year 2012. Regulation of Similar Biologics for the production, import, export, usage and storage were under the Drugs and cosmetics Act and Rules for hazardous microorganisms or GMO's. Various guidelines which regulate the regulations of similar biologics were listed below:

- Guideline on similar biologics: Regulatory requirement for marketing authorisation inIndia

- Recombinant DNA Safety Guidelines
- CDSCO Guidelines for Industry
- Safety and efficacy evaluation by submission to CTA.New drug approval permission requirements.Quality, safety and efficacy documents: Post approval changes in Biological products
- New drug approval: Quality information preparation of Biotechnological/biological products
- **Guidelines and handbook for IBSC**
- Guidelines for preparing preclinical and clinical information for r-DNA vaccines, diagnostics and other biological
- Guidance documents for regulatory approval of Stem cell and cell based products
- Guidelines on Good distribution practice for biological products
- Pharmacovigilance requirements for biological products.

The below produced pathway provide a basic knowledge on the regulatory

1.Product development

- ✓ Approval required from IBSC.
- ✓ Approval required from DBT.

2.Animal toxicity studies:

- ✓ Protocol to be designed as per Schedule Y, approved by RCGM and DBT.
- ✓ GLP accredited laboratories were utilised for conducting studies.

3.Clinical Trial

- ✓ Manufacturing licence required for CT batch.
- ✓ Ethics committee approval required for protocol.
- ✓ Any deviations needed to be approved by DCGI and DSMB.

4.Marketing and manufacturing licence

- ✓ CT report should be submitted and the dossier should be approved by DCGI.
- ✓ Manufacturing licence was issued after the facility inspection.

5.First three Commercial batches needed to be tested at NIB

6.Post approval committee

- ✓ PMS study was considered mandatory for four years and all along the PV study.
- ✓ Six months report should be submitted to DCGI for two years and annually for remaining years.
- ✓ DCGI approval mandatory for process changes.
- ✓ Application for animal toxicity studies along with the clinical trials can be filed to RCGM and DCGI concurrently in order to decrease the time period of approval.[10]

- Specifications
- Multiple related changes

3.2.1. COMPETENT AUTHORITIES:

Below are the lists of the competent authorities involved in the procedure of approval along with their functions

POSTAPPROVAL CHANGES FOR SIMILAR BIOLOGICS:

A change to pharmaceutical product can be defined as any change which is not restricted to change in the formulation, finished products and raw materials specifications, procedures and manufacturing sites, finished final product and ingredients specifications, container details and container labelling information. Impact on the product safety, efficacy and quality should be assessed to evaluate the changes to an already approved product. Proper documentation should be done for the same. Different mechanisms and procedures were followed by different regulatory authorities to report the above mentioned post approval changes of drug products. The previously mentioned methodology might fluctuate from a annual report to a revision or variety application to another permit application. [13]

The various sorts of post approval changes were observed in the following

- Container closure system
- Components and composition
- Manufacturing process
- Labelling
- Manufacturing sites

Miscellaneous changes and

POST APPROVAL CHANGES EXECUTION: The post approval change can be described as the management of changes

which were implemented during the life cycle of the drug product along with the verification and preparation of the same. Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the marketing Authorization Holder will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality. In US, EU , Saudi Arabia , Singapore and India Post approval changes are designated as:

- US: Scale Up and Post Approval Changes
- EU: Variations
- Saudi Arabia: Variations
- Singapore: Variations
- India: Post approval changes

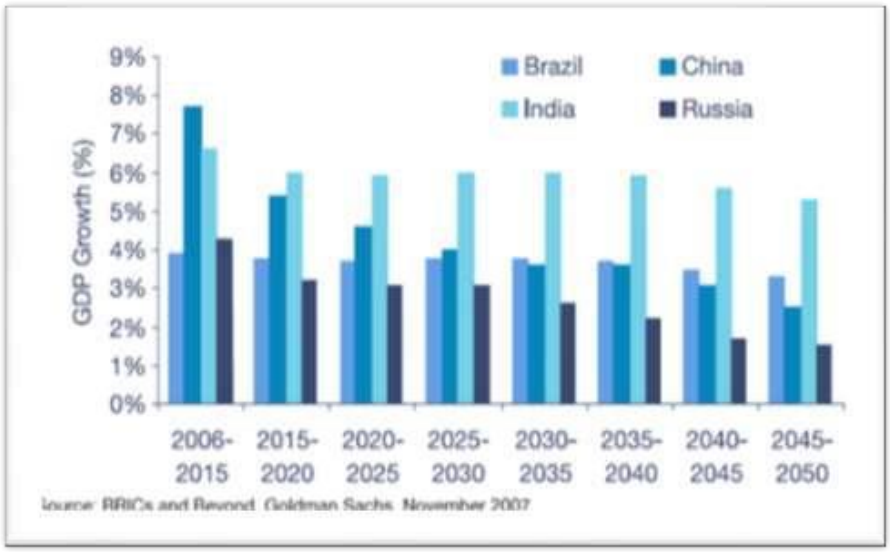

Fig. 2: GDP growth percentage of biosimilar market

Table 1: Time period for approval process of similar biologics

PROCEDURE	TIME PERIOD
Approval for preclinical animal studies:RCGM	Forty five days
Approval for human clinical trialsprotocol: DCGI	Forty five days
Observation of clinical trial data andResponse	Ninety days
GEAC and DCGI decision(simultaneous)	Forty five days

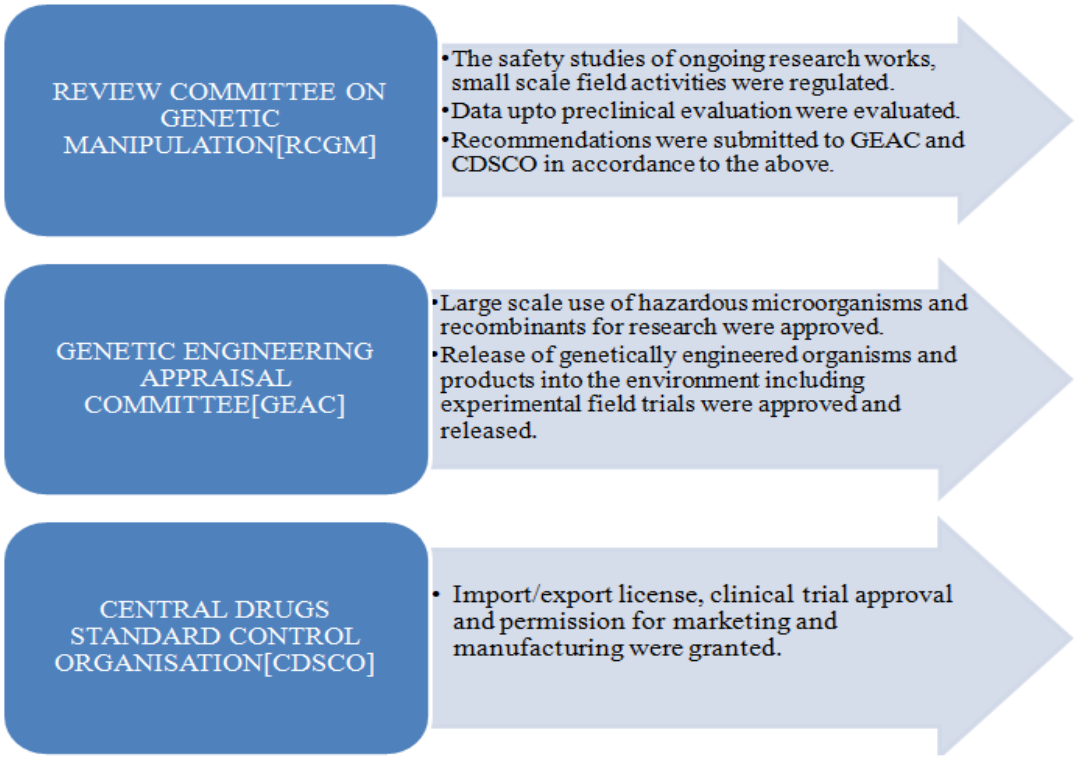

Figure 3:Competetnt authorities involved in the approval procedure

Table.2: Indian regulatory guidelines for the procedures followed during approval

AREA	**CDSCO: Indian Regulatory Guidelines**
PROCESS	GMP Certified Facility Full cell Bank Characterization as per ICH Guidelines. Post Approval changes warrant comparability study. Extractable studies are needed. Viral validation studies are not needed
ANALYTICAL	Detailed characterization is expected. Specification needed to be justified. CMC requirement as per DCGI guidelines
NON-CLINICAL	In vitro cell based assay is needed In vivo evaluation may be dispensable if in vitro assay are available
CLINICAL	Comparative PK/PD is required. Phase III Comparative CT is not mandatory. Scientific advice process is done by SEC, Apex committee, Technical Committee Exploration to other indication can be obtained PMS is mandatory for 4 years with 6 months PSURs for first 2 yrs. Immunogenicity is not mandatory but expected

4. SUMMARY AND CONCLUSION:

Biosimilar are not conventional; biologics are bigger and more convoluted than synthetic medications, because of the intricacy of biological/biotechnology inferred products. The generic methodology is experimentally not suitable for biosimilar products. There is have to utilize well designed clinical preliminaries to set up biosimilarity. The test with biosimilars is to know the distinctions which matter clinically. The particular item given to the patient ought to be plainly distinguished. India has a flourishing

biosimilars advertise for the sheer number of biosimilars accessible, while Europe has 31 biosimilars available and the US has 5, in India there are 66 approved biosimilar products. Biosimilar therapeutic products in India comprise fundamentally of immunization(Hepatitis B antibody), monoclonal antibodies, recombinant proteins and diagnostics, insulin, erythropoietin, granulocyte colony stimulating factor, streptokinase, interferon alpha-2B, Rituxinab, epidermal growth factor receptor, chorionic gonadotropin and heparin. Indian pharma organizations are presently making critical speculations into biosimilar improvement and generation trying to verify the early mover advantage and progressively banding together with western partners to dispatch a more prominent number of bio therapeutics in both neighbourhood and worldwide markets. In the meantime, trend- setter organizations are equipping to guard their patents.

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