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Short Communication

Biosimilar approval and checkpoints

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ABSTRACT

Biologic drugs and subsequently developed biosimilars treat chronic inflammatory autoimmune conditions such as rheumatoid or psoriatic arthritis, ankylosingspondylitis, crohn's disease, ulcerative colitis, and psoriasis. Biologics can target the cancer in a specific way and may work synergistically with chemotherapy to improve outcome. It is expected that in the next five years, 50% of biological products will originate from biotechnology. Biological products, including those manufactured by biotechnology, tend to be heat sensitive and susceptible to microbial contamination. There are no expected clinically meaningful differences in efficacy and safety between a biosimilar and the biologic drugs which are authorized for sale. The global market for Biosimilars is dominated by oncology (nearly 39% share) whereas the total biosimilar market size is expected to reach nearly 70 billion by 2025.
Biosimilars are generally marketed at prices 25 to 40 percent below original branded productsie Biologics. The number of biosimilars approved by US FDA are nearly 30. There are about 25 top global manufacturers of biosimilars. Many Domestic companies in India are making strong presence even in regulated markets. *Biologics Price Competition and Innovation Act* (BPCIA) guidelines in the United States (US), mention that a biosimilar can be designated as "interchangeable", whereby it may be substituted for the reference product (original biological drug).

1. Introduction

Biosimilar is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. EMA (EMEA - Europa) defines Biosimilar medicine is similar to the one of biological reference medicine.

Biological therapeutics, also referred to as Biologicals, are those class of medicines which are grown and then purified from large-scale cell cultures of bacteria or yeast, or plant or animal cells. Biologicals are a diverse group of medicines which includes vaccines, growth factors, immune modulators, monoclonal antibodies, as well as products derived from human blood and plasma.

Biologics are used to prevent, treat or cure a variety of diseases including cancer, chronic kidney disease, diabetes, cysticfibrosis, and autoimmune disorders. A biosimilar is exactly what its name implies — it is a biologic that is "similar" to another biologic medicine (known as a reference product) which is already licensed by the U.S. Food and Drug Administration (FDA). Biosimilar applications are not permitted within 4 years of licensure of the reference product or Reference biologicals. [1,2]

Studies conducted for approval of Biosimilar: Reference Biologic for study for purpose of approval in India for Similar Biologic

The confirmatory clinical safety and efficacy study cannot be waived especially for large molecular weight

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Table 1: Clinical study for the biosimilars

1.	Reference Biologic is an innovator's product approved after evaluation of complete dossier is critical for the development of Similar Biologic
2.	The dosage form, strength and route of administration of the Similar Biologic should be the same as that of the Reference Biologic
3.	The active drug substance (active ingredient) of the Reference biologic and that of Similar Biologic mustshown to be similar.
4.	The manufacturing process and analytical methods for Similar Biologics should be validated and demonstrated
5.	The Similar Biologics manufacturer should develop the manufacturing process to yield a comparable quality product in terms of identity, purity and potency to the Reference Biologic.
6.	Similar Biologics include physicochemical properties, Biological activity, immunological properties, functional assays, purity (process and product-related impurities etc.), contamination, strength and content. Principles outlined in the ICH Q6B guideline should be followed.
7.	Immunogenicity of the product of Similar Biologic should not be much different than Reference Biologic
8.	Final PK results for both the Biosimilar samples and samples containing the reference compound(s) must be supported by relevant stability data.
9.	The shelf-life and storage condition of drug substance and drug product should be assigned based on real-time stability studies
10.	Head-to-head characterization studies are required to compare the Similar Biologic and the Reference Biologic at active drug product level.
11.	The preclinical studies should be conducted prior to the initiation of any clinical studies.
12.	In case of in vivo toxicity studies, at least one repeat dose toxicity study in a pharmacologically relevant species is required to be conducted with an intended route of administration
13.	The PK data should support the subsequent Phase III clinical development given that the Similar Biologic would be established to be similar as the Reference Biologic product.
14.	Single Dose Comparative PK Study, Multiple Dose Comparative PK Studies, Pharmacodynamic Studies, Confirmatory Safety and Efficacy Study should be conducted

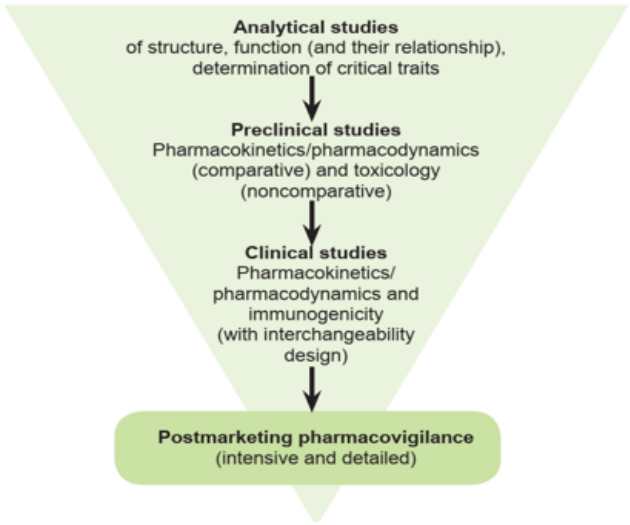

Fig. 1: Proposed approval of biosimilars

biologics like Monoclonal antibodies. Wherever the phase III trial is waived, the immunogenicity should have been gathered in the PK/PD study and will also need to be generated during post- approval Phase IV study.[3]

The European guidelines were adopted in 2006 and then updated in 2015. Austria was the first country to develop biosimilar guidelines in response to emerging patient deadlines for the number of biological medicines.

US FDA has regulatory pathway for biosimilar development under (351[k]) which mandates a sequential series of rigorous comparative studies to demonstrate bio similarity of the biosimilar candidate to its reference product. CDER (Centre for Drug Evaluation and Research) & CBER (Centre for Biologics Evaluation and Research). 21 CFR 314.50(d) (1) Wherein the application is required to contain a full description of the chemistry, manufacturing, and controls (CMC) information. The list of biosimilarshas givenin the "Purple Book" that explains the date on which product is being licensed. The 505(b) (2) pathway or Abbreviated Approval Pathways are also available for a category of biologics. Itsa new drug application which contains full safety and effectiveness reports, but allows at least some of the information required for approval to come from studies not conducted by or for the applicant.

Biosimilars are manufactured by means of a complex process which can be divided into multiple phases: 1. Preparation of the material.2. Preparation of fluids.3. Cellular expansion, which is essentially the cultivation of cells for producing the biosimilar. 4. Harvesting. 5. Purification process.6. Packaging. 7. Quality control procedure.

1.1. Control strategy

The term "control strategy" refers to a combination of input, procedural, and testing controls that ensure that

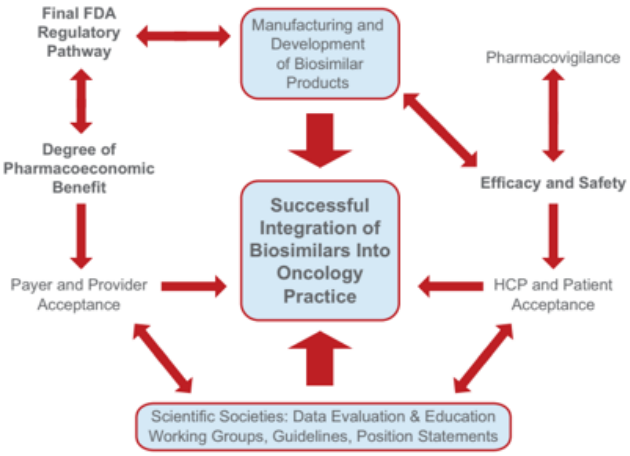

Fig. 2: Biosimilars development process

Table 2: Comparison between generics and biosimilars[7]

Generics	Biosimilars
Small molecules	Heavy molecules
(Bioequivalence studies)	Highly similar and not identical to theoriginator (comparative studies)
Immunogenicity – Nil	Immunogenicity- seen
Interchangeability can be done	Interchangeability Not yet assessed, established orapproved
ADR- Report the International non proprietary name	ADR-Report the INN manufacturer andbatch number
Risk management plan – No	Risk Management plan – Yes
Timeline Development 3-5 years	Timeline Development 8-10 years

a bioprocess consistently delivers products that meet qualityrequirements.[4,5]

For the Pharmacovigilance of Biologics and Biosimilars both the company and the authorities have the responsibility to raise alarms.

Pharmaceutical companies produce biosimilars by using different cell lines as well as different manufacturing processes resulting in differences of tertiary and quaternary structure, with a putative effect on immunogenicity.[6]

Biosimilars are highly complex molecules produced by living and recombinant cells through a multistep manufacturing process.

The first biosimilar was approved and marketed in India in 2000 was for hepatitis B, although no specific guideline was available at that time for the development and marketing of biosimilar in India. The strong pipeline of biosimilars is developed by Reliance Life Sciences which have acquired the global rights for Infliximab from Boston based Epirus Biopharmaceuticals. The company also manufactures Abciximab for Abbott India. Presently, there are more than 100 Indian biopharmaceutical companies, which are engaged in manufacturing and marketing of biosimilars.[2]

A biosimilar can be used for all indications approved for the innovator drug and there is no need for independent clinical studies. However, the final decision rests with the regulators. The manufacturer of the proposed biosimilar is not as familiar with the manufacturing process of the originator biologic.

1.2. Biologics used in cancer treatment: monoclonal antibodies (MAB)

The use of monoclonal antibodies for the therapy of cancer is one of the major contributions of tumour immunology to cancer patients. Monoclonal antibodies elicit anti-tumor effects by complement-mediated cytolysis and antibody-

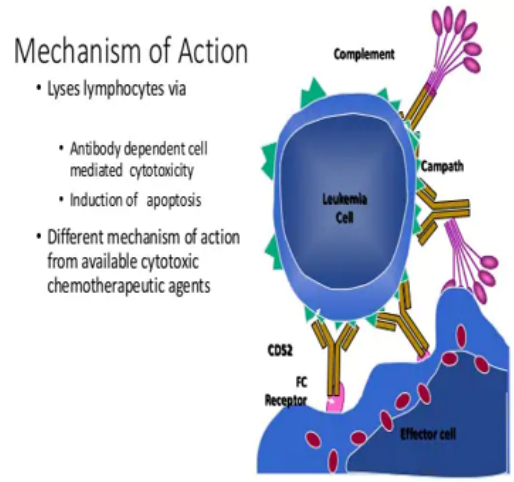

Fig. 3: Mode of action of MABs (Monoclonal antibodies)

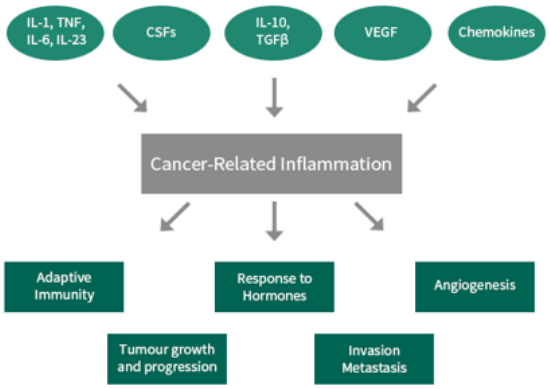

Fig. 4: Cytokines related cancer inflammation

Table 3: Examples of few biosimilars in market

Biologic	Utility	Market Introduction
Adalimumab	Reduces signs and symptoms, in adult patients with moderately to severely active RA.	Abbvie in the US and approved in 2002 by the FDA.
Bevacizumab	Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer	Bevacizumab was approved in the United States in February 2004,
Once-Monthly Continuous Erythropoietin Receptor Activator (CERA)	indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis	EMEA authorized its earlier drug EPO in market for Renal Patients in 2007.
Insulin Lispro	Insulin lispro is available only by prescription and is indicated for the management of hyperglycemia in patients with diabetes mellitus.	Sanofi started development of biosimilar in 2014
Rituximab – Evaluated by Ronald Levy for targeting malignant B cells. In 1982,	Rituximab is used to treat certain types of cancer (such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia).	Many biosimilars are available in market with cost in US 25 % lower and in India nearly 50% lower
Teriparatide	Recombinant parathyroid hormone used for the treatment of osteoporosis	Two teriparatide biosimilars approved for use in the European Union and Few in Indian market
Trastuzumab	HER2-positive breast cancer that is either early-stage or advanced-stage/metastatic.	4 major brands available in global market and many in India

On average originator biologic was competing with neatly 4 biosimilar entrant in 2019. [8]

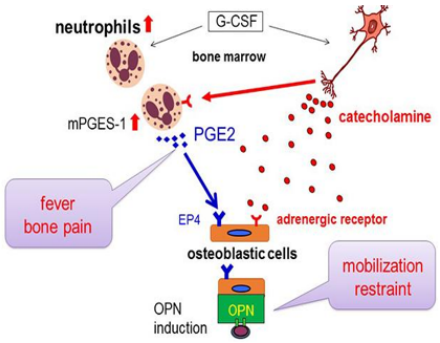

Fig. 5: Action of G-CSF (Granulocyte colony stimulating factor)

dependent cell-mediated cytotoxicity. Over two-thirds of MAB are for transplant rejection, cancer, autoimmune diseases, infectious diseases, antiviral prophylaxis, and anti-thrombotic treatment.

1.3. Checklist before using a biologic

IL-2 plays a pivotal role in the treatment of patients with metastatic melanoma and renal cell carcinoma. TNF-α can enhance the cancer proliferation in oral squamous cell carcinoma. Elevated serum IL-6 levels have been detected in patients with systemic cancers VEGF plays an essential role angiogenesis. VEGF is also implicated in intraocular neovascularization associated with diabetic retinopathy and age-related macular degeneration. Bevacizumab targets a cancer cell protein called vascular endothelial growth factor (VEGF). Biosimilars of the same are now available for therapeutic intervention.

Table 4: Clinical checklist before using biosimilars [9]

1. A history suggesting current or recent infections
2. Routine laboratory investigations including hemogram and renal and liver function tests should be done as screening before biologic therapy.
3. There is a significant risk of tuberculosis (TB) reactivation or new onset TB can occur with some biologics, especially anti-TNF agents.
   Monteux test: It should be done in patients receiving biologic response modifiers with increased risk of TB
4. Chest X-ray needs to be done within the past 6 months and should be reviewed by the treating rheumatologist
5. Live vaccines should not be given during biologic therapy. Proper history of vaccination is to be recorded
6. Class III or IV cardiac dysfunction (Risk of worsening heart status)
7. Prescence of demyelinating diseases

Table 5: The following are major advantages of biosimilars as depicted in

1. Shorter time to market than the originator product.
2. Lower price point and similar efficacy as originator product.
3. Higher return of investment, than with new product for research and development
4. Due to rapidly increasing healthcare costs, there is high consumer demand for biosimilars

Colony stimulating factors (CSF) Granulocyte colony-stimulating factor (G-CSF or GCSF) are glycoproteinswhich stimulate the bone marrow to produce granulocytes and stem cells and release them into the bloodstream

There are many biosimilars available for various therapeutic disorders. The EMA and the FDA have been clear in their communication that Physicians and patients can be reassured that biosimilars approved in the EU and the USA are as safe and effective for their intended use as their respective reference biologicals.

CDSCO recommends a confirmatory Phase III Clinical Trial to evaluate safety and efficacy is mandatory before approval. The trial should be multicentre but can be single-arm, open label and non-comparative with the originator molecule.

2. Conclusion

There is market shift towards chronic diseases such as cardiac, diabetes and cancer which have treatment options with better drugs acting on specific sites. Biosimilars cannot be protected by patents, because they have expired, there are regulations to ensure a period of in marketing, so that their return is guaranteed. To substantiate the claim of similarity between a biosimilar and the reference biopharmaceutical, there is a need for adequately powered non-inferiority studies. Such studies are generally available for biosimilars.

3. Source of Funding

None.

4. Conflict of Interest

None.

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