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Review Article

SIMILAR BIOLOGICS: AN OVERVIEW

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A B S T R A C T

Biosimilars can be broadly defined as those medicines produced using a living system or genetically modified organism. They are different from conventional generics in many ways, in size, structure, stability, heterogeneity, and analytical characterization. Biosimilars are not true generics, but exhibit a high degree of similarity to the reference biologic. Biosimilars are biotechnological generated products and copy of original products in term of pharmacological effect with the difference in structure or process of manufacturing. Along with the difference, the biosimilar should be comparable to the innovator drug in safety, efficacy, and quality as demonstrated by analytical, preclinical, and clinical trials. Present review focused the biosimilar market of India in contrast with current challenges to face by Indian biosimilar manufacturer. This article will provide an overview of biosimilars discussing the differences between biosimilars and chemical generics, the scientific and regulatory challenges and concerns with the use of biosimilars.

INTRODUCTION

Biologics- Biologics represent one of the rapidly growing segments of the pharmaceutical industry. The term biologics have been originated from the word biology that means "the science of living organisms". They refer broadly to substances produced by living cells using biotechnology (i.e., recombinant DNA technology, controlled gene expression, or antibody technologies), that have established many new treatments of life – threatening and rare illness such as cancer, diabetes, anaemia, rheumatoid arthritis and multiple sclerosis etc. Biological products are a wide category of products and are generally large, complex molecules. These products are mostly produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more complicated to characterize than small molecule drugs. [1][2]

Types of Biologics

- Blood Derivatives
- Vaccines
- (Khomendra, 2016)Proteins
- Human Tissues
- Cellular and Gene therapies
- Allergic Extracts

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Reference Product - A reference product is the single biological product that has already been approved by FDA, against which a proposed biosimilar product is usually compared. A Reference Biologic is utilized as the comparator for comparability studies with the Similar Biologic in command to show Similarity in terms of safety, efficacy and quality. In India, a reference biologic is one which has been granted a marketing authorization in India by DCGI on the basis of a complete dossier and with a history of safe use in India. [3][4]

Biosimilars - A biosimilar or similar biologics can be defined as a biological product which is formed by genetic engineering techniques and is "similar" in terms of safety, efficacy and quality to a reference biologic. [5][6]

USFDA Definition A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.

Characteristics of Biosimilar

- High molecular complexity
- Quite delicate to changes in manufacturing processes
- Variances in impurities and/or breakdown products can have serious health implications
- Copies of biologics might achieve differently than the original exclusive version of the Products [7][8]

Difference between Biosimilars and Generics

Sno.	Key Attributes	Generics	Biosimilars
1.	Approval	No Clinical Trial Required	Clinical Trial is Required
2.	Indicators	Same as Originator	May not include all originator indications.
3.	Cost of Development	1-4 million$	100-250 million$
4.	Patent	Expired	Expired
5.	API	Identical	Highly Similar (never identical)
6.	Proof needed	BE (BioEquivalence)	Comparability
7.	Definition	A generic drug is a Pharmaceutical product i.e. equivalent to a brand name product in dosage, strength, route of administration, quality, performance and contains same API as original brand name formulations.	A Biosmilar is defined as one that is highly similar to reference product not withstanding minor differences in clinically active component and where there are no clinically meaningful differences in terms of safety, purity, and potency.
8.	Filing Application	Under Hatchwaxman, a generic drug manufacturer can file an application after 4 years of NME (5 years) exclusivity provided a patent challenge accompanies the filing.	Under PHSA act, an applicant can file after 4years of biologic structure (12 years) exclusivity.
9.	Exclusivity	6 months	1 year
10.	Manufacturing complexity	Relatively simple; uses organic medicinal chemistry reactions	Very complex; produced in living cells and involves several stages of purification, production, and validation of the final product

Regulatory Standards for Biosimilar Products

World Health Organization (WHO) Guidelines

The WHO issued guidelines on evaluation of similar biotherapeutic products (SBPs) in 2009. It provides globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier.

The key Principles of WHO guidelines are

On the basis of proven similarity, the licensing of a SBP will rely, in part, on non-clinical and clinical data generated with an already licensed reference biotherapeutic product (RBP).

The basis for licensing a product as a Biosimilar depends on its demonstrated similarity to a suitable reference product in quality, nonclinical and clinical parameters. If relevant differences are found in the quality, nonclinical or clinical studies, the product will not likely qualify as a Biosimilar

This guideline applies to well-established and well characterized biotherapeutic products such as recombinant DNA-derived the (Revers, 2010) (Paul, 2018)rapeutic proteins. Vaccines, plasma derived products, and their recombinant analogues are however, excluded from the scope of this document

WHO also states “although International Nonproprietary Names (INNs) served as a useful tool in worldwide pharmacovigilance, for biologicals they should not be relied upon as the only means of product identification or as an indicator of product interchangeability”.

It states that prescriptions of biologics should not be based on INN but on a unique name, for example the trade name. This guideline can be adopted as a whole, or partially, by National regulatory authorities (NRAs) worldwide or used as a basis for establishing national regulatory frameworks for licensure of these products. [9][10][11]

Regulatory Framework in Europe

The European Medicines Agency (EMA) was among the first guidelines issued for the approval of biosimilars. Biosimilar is defined by EMA as “A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use.

Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies”.

The approval pathway requires a Biosimilar manufacturer to demonstrate similarity for quality, safety and efficacy with a reference product already licensed Europe.

The Biosimilar must demonstrate in clinical studies, that it has no significant clinical differences with the reference product. EMA‟s clinical trial and pharmacovigilance data requirement makes the regulatory process rigorous. EMA revises the guidelines at regular intervals and the recent information can be found at EMA website.

In addition to general guidelines for Biosimilar medicines, EMA has also issued product specific Biosimilar guidelines for individual drugs, for e.g., recombinant human insulin, follicle-stimulating hormone, low molecular weight heparins and somatropin. There are some cases where the application was rejected by EMEA, for e.g. aplheon, the biogeneric of interferon, due to the concerns over manufacturing technique and quality control.

The application of Biosimilar Marvel Insulin was also disapproved because of inadequate data to prove similarity with innovator product. [12][13][14]

Regulatory framework in United States

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of The Patient Protection and Affordable Care Act, and has laid down regulations for approval of Biosimilar products. U.S. Food and Drug Administration (U.S.FDA) define biosimilarity and interchangeability follows.

Biosimilarity means “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there

are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product".

"Interchangeability means that the biologic product is Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient. For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product will not be greater than the risk of using the reference product without such alternation or switch. Interchangeable biological products may be substituted at the pharmacy level without the intervention of a healthcare provider".

The US FDA issued draft guidance documents recently in 2012 on Biosimilar product development to assist industry in developing such products. The guidelines mention structural analysis of the Biosimilar followed by its functional analysis to justify animal testing, followed by animal toxicity and immunogenicity studies. Lastly human clinical data, immunogenicity studies and post marketing safety considerations.

According to this new guidelines, biological products will be approved on demonstrating that they are Biosimilar to, or interchangeable with, a biological product that is already approved by the US FDA. These regulatory guidelines will help biosimilars manufacturers to enter the US market. So far, the biggest challenge for manufacturers was the absence of clearly defined regulations in different countries to develop biosimilars. [15][16][17]

Regulatory framework in India

In India, Central Drugs Standard Control Organization (CDSCO) and the Department of biotechnology have issued guidelines on similar biologics in 2012. The important features of the guidelines are summarized below:

Applicable Regulations and Guidelines 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.

Various applicable guidelines are as follows

- Recombinant DNA Safety Guidelines, 1990
- Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other biologicals, 1999
- CDSCO guidance for industry, 2008: Submission of Clinical Trial Application for Evaluating Safety and Efficacy Requirements for permission of New Drugs Approval
- Post approval changes in biological products: Quality, Safety and Efficacy Documents Preparation of the Quality Information for Drug
- Submission for New Drug Approval: Biotechnological/Biological Products
- Guidelines and Handbook for Institutional¬ Biosafety Committees (IBSCs), 2011

Competent Authorities Three competent authorities are involved in the approval process:

Review Committee on Genetic Manipulation (RCGM) - RCGM functions in the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India. RCGM is responsible for authorizing import/export for research and development and review of data up to preclinical evaluation.

Genetic Engineering Appraisal Committee (GEAC) - GEAC functions under the Ministry of Environment and Forests as statutory body for review and approval of activities involving large scale use of genetically engineered organisms (also referred as living modified organisms) and products thereof in research and development, industrial production, environmental release and field applications.

Central Drugs Standard Control Organization (CDSCO) - CDSCO is responsible for grant of import/ export license, clinical trial approval and permission for marketing and manufacturing. State Food and Drug Administration works with CDSCO in each state and is responsible for issuance of license to manufacture similar biologics in India.

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. The reference biologic 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 only 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, efficacy and quality of the product (i.e. in the development programmed 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 Pharmacodynamics 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- "In case of in vivo toxicity studies, at least one repeat dose toxicity study in a relevant species is required to be conducted. The duration of the study would be generally not less than 28 days with 14 days recovery period. However the duration may vary depending on the dosage and other parameters on case by case basis. Regarding the animal models to be used, the applicant should provide the scientific justification for the choice of animal model(s) based on the data available in scientific literature.

However if the relevant animal species is not available and has been appropriately justified, the toxicity studies need to be undertaken in two species i.e. one rodent and other non rodent species, as per the requirements of Schedule Y". Study groups of animals in repeat dose toxicity testing will consist of:

i. Historical Control (Optional)
ii. Vehicle Control
iii. Vehicle Control for recovery group
iv. Formulation without protein (for vaccines) if multiple adjuvants-each to be checked independently
v. 1X similar biologic for study duration (lowest dose)
vi. 1X Reference biologic for study duration
vii. 2X Medium dose similar biologic
viii. 5X High dose similar biologic
ix. Similar biologic with a recovery group going beyond the end of study period for 7 to 14 days. Other toxicity studies, including safety pharmacology, reproductive toxicity, mutagenicity and carcinogenicity studies are not generally required for evaluation of a similar biologic unless warranted by the results from the repeat dose toxicological studies 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. The other parameters for evaluating immune toxicity include immune complexes in targeted tissues may be considered while evaluating histopathology observations, etc". Pharmacokinetic Studies Comparative 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 Appropriate design considerations can be combined into single dose or multiple dose studies with adequate justification.

These Design Considerations include

- Single dose, comparative, PK studies
- Parallel arm or
- Cross over
- Multiple doses, comparative parallel arm steady state PK studies 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, PD 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.

PD study can also be a part of Phase III clinical trials wherever applicable". The detailed guidelines on other issues such as safety and immunogenicity data, extrapolation of efficacy data, pharmacovigilance, archiving of data, etc are described in the relevant sections in the article. Additional detailed information can be obtained from the CDSCO website. [18][19][20]

CONCLUSION

Biosimilars are a growing drug class designed to be used interchangeably with biologics. Biologics are created in living cells and are typically large, complex proteins that may have a variety of uses.

Within the field of gastroenterology alone, biologics are used to treat inflammatory bowel diseases, cancers, and endocrine disorders. While biologics have proven to be effective in treating or managing many diseases, patient access is often limited by high costs. The development of biosimilars is an attempt to reduce treatment costs.

Biosimilars must be nearly identical to their reference biologics in terms of efficacy, side effect risk profile, and immunogenicity. Although the manufacturing process still involves production within living cells, biosimilars undergo fewer clinical trials than do their reference biologics. This ultimately reduces the cost of production and the cost of the biosimilar drug compared to its reference biologic.

Finally, as India has sub optimal pharmacovigilance system, success of biosimilars depends upon the implementation of adequate pharmacovigilance systems and regulatory guidelines.

Biosimilar will expected become a progressively important part of the pharmaceutical Ecosystem. Though, they continue to face barriers to adoption, including questions of interchangeability, a typical lack of approval for all the reference biologic's indications, the need for biosimilar manufacturers to negotiate with payers, the challenge of overcoming unique patent dynamics, and innovators' established positions within the physician community. Biosimilar maker needs to face unusual problems in the development, clinical improvement, manufacturing, registration and product marketing contrasted with customary generics. India's characteristic quality in pharmaceutical

marketing has been the back to end up one of the key player being developed and maker of biosimilar.

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