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Review Article

AN OVERVIEW OF BIOSIMILARS

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ABSTRACT

Biosimilars are surmounting pharmaceutical market from last three decades and sale increasing progressively. Advances in the biotechnology lead to development and discovery of new biological products to treat various life-threatening diseases. Biosimilars are biological drugs that are produced after expiry of the patent of approved innovator. This review attempt to highlight the differences between biosimilars and chemical generics, development stages, issues of concern with the use of biosimilars and need of appropriate regulations for their approval. Generic approach is not scientifically useful to manufacture biosimilars. Biosimilars have more structural complexity, multi-layered manufacturing or scale-up process and risk of immunogenicity; therefore required unique regulatory pathways to introduce them in the market. Safety and efficacy of biosimilar are essential parameter to increase access in the population. Biosimilars can ensure the cost-effective treatment to invade incurable diseases due to enhanced competition in pharma/biotech industries to manufacture it.

Keywords: Biosimilars, Biologics, Follow-on biologics, Generic drugs, Subsequent-entry biologics.

INTRODUCTION

The advances in cloning of human genetic material and recombinant DNA technology for development of *in vitro* biological production systems have allowed the discovery of new biological substance for the ultimate development of a drug. Hybridoma technology (monoclonal antibody) combined with recombinant DNA technology has smoothed the way for tailor-made and targeted medicines. Recombinant therapeutic proteins are of a complex nature. These proteins are produced in living cells such as bacteria, yeast, plant, viruses, and animal or human cell lines [1,2].

Biosimilars are biological drugs that are produced after the expiry of the patent or data protection of approved innovator bio-therapeutic products or reference drugs. After the expiry of the patent approved recombinant drugs (e.g. insulin, human growth hormone, interferon, erythropoietin, and more) any other biotech company can manufacture and introduce these biological drugs into market as biosimilars [3,4]. The similar biologic drug products are known as similar biotherapeutic product (SBPs) by World Health Organization (WHO), biosimilars by European Medicines Agency (EMA) of the European Union (EU), follow-on biologics (FOBs) by the US Food and Drug Administration (FDA), and subsequent-entry biologics by Health Canada [5].

Biosimilar drugs are proposed to have identical therapeutic activity as the reference product, so as to treat the same ailment as the reference product. Though, they are having numerous similar properties but are not equal to innovators or reference product. This is mainly because the nature of the manufacturing process and the size and complexity of the active substances in biosimilars differ from the generic chemical products [6].

MARKET SCENARIO

Biologics or biopharmaceuticals or biotechnologically produced drugs are key growth enhancers for the world pharmaceutical market. As per market report, world market for biosimilar to be worth $19.4 billion by 2014 and rapidly increasing from 2009 to 2014 with a compound annual growth rate of 89.1% [7]. By 2016, patent of biological products of worth $25 billion are driving to be expired. This will create a new avenue for pharmaceutical producers to enhance their financial status and minimize the medical spending on biosimilar products [4]. Sandoz was the first pharma company to bring one to the market - human growth hormone Omnitrope® in 2006. The first truly complex biosimilar Binocrit®/Epoetinalfa Hexal followed in 2007 and then Zarzio®/Filgrastim Hexal® was launched in several European countries in 2009 [2]. Recently, Biocon an Indian multinational launched the world's first biosimilar (developed in an organism) Trastuzumab injection for the treatment of breast cancer [8].

GENERICS AND BIOSIMILAR

A generic product may be defined as a product that has been produced by chemical synthesis having a same active component as drug and capable of exhibiting therapeutic equivalence as the reference product. A biosimilar defined as an officially approved new version of innovator bio-therapeutic products for which the patent has expired. Biosimilars active ingredient is revealed by proper assessment to have quality characteristics as well as a biological activity to reference protein product [9]. The comparison between generic and biosimilar with respect to product, manufacturing, clinical development, and regulation [10] is highlighted in Table 1.

USE OF BIOSIMILARS

Biological medicines play an important role in treatment options for disabling and life-threatening diseases, such as cancer, infectious diseases such as hepatitis, autoimmune disorders, neurodegenerative diseases, and orphan diseases. However, the cost of treatment with a biological medicine can be expensive compared to a "classical" chemical or synthetic medicine [6]. Biosimilar medicines are bringing in the market when patents of the reference medicine have expired. They may supply a cheap alternative to existing biological medicines and enhance competition in Pharma market. Therefore, it may improve access to biological medicines for more patient compliance. Thus, their availability offers potential economic benefit to healthcare systems while supporting patients' access to new treatment options brought about by advances in medical sciences [13].

MERITS OF BIOSIMILARS

1. They are available at cheaper prices than original or reference biological product; hence, there is enhanced demand in the world market for biosimilars.

Table 1: Comparison of generics and biosimilar [10-12]

Specifics	Generics	Biosimilar
Product characteristics	Molecular weight is low Physiochemical properties are well known Chemically highly pure compounds Generic are usually non-antigenic Stability is more than biosimilars They are stored at room temperature	Molecular weight is low high Physiochemical properties are complex Chemically complex compounds which are not easy to purify Biosimilar product may be antigenic in nature Stability is less than generics They are required cold chain for storage
Manufacturing aspects	They are produced by chemical synthesis They are less sensitive to production process change Production process is easy and highly reproducible Purification is simple and well established	They are produced biotechnologically from living cells They are very sensitive to production process changes hence stringent conditions are required Production process is complex and reproducibility is tough to achieve. Purification is complex and time consuming process
Clinical process	Generic is required only phase I clinical studies Enrolment of patient is limited to 20-100 The development costs is less and limited to 5 m$ The time required for approval process is short	They are required broad clinical studies including Phase I, II, and III studies They are required about 100-1500 patients during clinical study The development costs is high as compared to generic about 80-120 m$ They are needed in-depth pharmacovigilance and periodic safety updates after launch
Regulation requirement	They are required to exhibit bioequivalence as a reference drug They are allowed for automatic substitution	As per European Medicines Agency (EMEA) guidelines they are required to ensure "similarity" as an innovator product They are not allowed for automatic substitution yet

2. There is tremendous demand in the market as many biological products are going off-patent.
3. They have less market risk than reference product because of no investment in Phases I-II of clinical trials (CT) [11].

DEMERITS OF BIOSIMILARS

1. The development and production process of a biosimilar is multilayered due to high molecular weight than small molecular weight chemically synthesized the drug.
2. The downstream process of a biosimilar is costly and time consuming.
3. The development process for a biosimilar is lengthy as they are derived from living cells.
4. Biosimilar product can show a similar therapeutic effect but not identical to the innovator product.
5. As compared to chemical drugs, the research and development of biosimilar is a costly, long and risk associated process.
6. Biosimilars are highly sensitive products and require very stringent conditions for production than chemical drugs.
7. To ensure patient's safety regulatory pathways of biosimilar product must include necessary methods or processes [14,15].
8. Clinical studies must be carried out for development biosimilar products to ensure safety and efficacy [16].
9. Automatic substitution of biosimilar product with another one is not allowed [17].
10. As per the economic analysis, the period required to nil the research and development expenditure for biosimilars specifies that data protection should in the ranges of 12.9-16.2 years [18].

DEVELOPMENT STAGES OF BIOSIMILARS

Development of biosimilars is a complex and tedious process that comprises four stages. The overall cost of under development new biosimilar product depends on stages changing with requirement and period involved to finish it. The time period prolongs up to 8 years for development of biosimilar products due to involvement of complex biotechnological process such as preparation of cell banks, replication of host cells, method development, and scale-up for higher batch size and quality control testing [19].

Development of product and relative analysis

This stage contains the manufacturing of targeted protein from defined cell culture and evaluating its stability profile. The newly developed product must be highly similar to innovators product.

Development and optimization of process and validation

This stage can involve complete development and optimization of the process to improve the final yield of the biosimilar product. The scale-up process should follow good manufacturing practice. The production process should be validated for reproducibility of yield.

Clinical studies

This is an important stage for biosimilars product. Clinical studies will be necessary for nearly all biosimilars product so as to validate bioequivalence to reference or innovator product [20].

Regulatory process

In Europe, the committee for medicinal products for human use (CHMP), and the European Medicines agency (EMEA) formed a regulatory system for biosimilars, and the first regulatory guidance was delivered in October 2005.

REGULATORY GUIDELINES FOR BIOSIMILARS

European guidelines

The EMA acts as a principal regulatory authority to implement a structure for the marketing authorization of biosimilar products. It has one of the supreme stringent guidelines for emerging biosimilar product (Table 2) [21]. A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). To ensure the similarity with respect to safety, efficacy, and quality of biosimilar product EMA has introduced product specific guidelines [21-23].

As per these regulatory guidelines, the concept of biosimilars is valid for any biological therapeutic product. Also, to enhance pharmacovigilance monitoring the product under investigation specified to the patient should be clearly known. The active ingredient of biosimilar product must be similar to innovator product with respect to molecular and biological terms during the comparability program.

The drug dosage form, dose as well as a way of administration of reference and the biological product should be identical. The safety and efficacy of reference product have to be validated for each indication separately if it has more than one indication. The clinical safety must be observed on current basis after marketing endorsement. The problem of immunogenicity should be reported and its long-term monitoring is required.

Table 2: Evaluating existing regulatory pathways [6]

Criteria	EU/EMEA	WHO	US HR 1427/S.726	US HR 1548
Comparability exercise	Yes	Yes	No	No
Extent of clinical data	Strong	Strong	Weak	Strong
Post-marketing safety studies	Yes	Yes	Yes	Yes
Standard and criteria for interchangeability	National decision (EMEA recommends decision by physician)	None	Present, but weak	Present, strong
Data exclusivity	Unchanged from conventional term 8+2+1 formula	None	Unchanged from conventional 5+3 term	12 years of data exclusivity+ 2 years for new indications
Patent dispute resolution framework	None, occurs at national level	None	Favors biosimilar applicants	Favors owners of the original biologic

WHO: World Health Organization, EMEA: European Medicines Agency

Development of biosimilars as per revised overarching guidelines provides the opportunity for drug manufacturers to employ a comparator official outside the European Economic Area throughout the clinical study of a biosimilar product [24].

US FDA guidelines

US FADA has right to approve biosimilars, plus interchangeable, to retain safety, efficacy, and quality of biosimilars [25,26]. A biological Product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which 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. As per Biologics Price Competition and Innovation Act (BPCI) act of 2009, permission is given to FDA to supervise an "abbreviated pathway" for sanction of biologics that are "biosimilar" to previously approved products. This abbreviated pathway will remove needless and unethical preclinical and clinical testing of the biosimilar product. This ultimately will save time, currency, and human power. Similarly, The Patient Protection and Affordable Care Act of 2010 (USA) is also backing this act [27].

WHO guidelines

WHO has established a structure of overall principles as part of its "Biological Standardization Process." These pursue to manage the scientific characteristics of biosimilars sanction or registration. As per WHO biosimilar defined as a biotherapeutic product claimed to be "similar" in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product, which must have been licensed by national regulatory authorities on the basis of a full registration dossier." As per WHO guidelines label description for biosimilar as a "SBP." The SBP should be undoubtedly recognizable by a single brand name, and its International Nonproprietary Name must also be stated. The WHO recommends that at least one CT will be essential for a biosimilar to be approved. The WHO needs that the applicant should involve the issue of immunogenicity and post-marketing safety assessments in the application form for marketing grant [28].

Guidelines in India

The Department of Biotechnology (DBT) was introduced "Draft Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India," in June 2012. These guidelines state the pre-marketing and post-marketing regulatory requirements as well as necessities to the manufacturing process and quality control of similar biologics. These Indian guidelines are similar to biosimilar guidelines of USA and EU in various aspects. However, India accepted "sequential approach" that is similar to "stepwise approach" (US and EU) to market biosimilar product [29,30].

At present, India is one of the leading contributors in the world biosimilar market. India has demonstrated the greatest acceptance of biosimilars, which is reflected from over 50 biopharmaceutical brands getting marketing approval [31]. Biosimilars have covered their way in India due to the regulatory authorities and regulatory guidelines [32] coming into force.

THE APPROVAL PROCESS OF BIOSIMILARS IN INDIA [4]

The regulatory pathway for approval of biosimilars in India is a very extensive process. In the approval process, numerous departments and committees are involved. The Indian regulatory organizations reflected biosimilars as new biotechnological products. In product development process, there is approval needed from Institutional Bio-safety Committee and DBT. The DBT gives approval to preclinical study protocol designed by the applicant as per schedule Y. The animal study must be performed in good laboratory practices recognized laboratory. The final report of the animal study is required to be approved by DBT.

A further step is a clinical study of a biosimilar, in this step clinical study protocol needs to be approved by drug controller general of India (DCGI) after that DBT approves the toxicity study report. Manufacturing licenses is required for a CT batch production beside with WHO-GMP certificate. The protocol must be approved by Institutional Ethics Committee. If there is any deviation in the protocol, then it must be sanctioned by DCGI and data safety and monitoring board.

After completion of the clinical study detailed reports should be submitted to DCGI. The dossier should be in CTD format that must be approved by DCGI. The DCGI recommends license for manufacturing after inspection of the facility. After approval of biosimilar for the market, post-marketing surveillance (PMS) is essential for at least 4 months and pharmacovigilance monitoring throughout the study. In addition to that periodic safety update report should be reported to DCGI in every 6 months for first 2 years. Any change in process must to be authorized by DCGI [4].

ANALYSIS OF BIOSIMILARS

To registration of biosimilars drugs, "biosimilarity" want to be validated between the physiochemical parameters of biosimilar and originator batches. To confirm safety and efficacy of biosimilars as compared with reference or originator, preclinical and, clinical studies must be conducted as per regulatory guidelines from the EMA and the FDA. Also developing and validating bioanalytical methods to support these requirements is very essential [33]. ICH guidelines, ICH Q5E [34], and Q6B [35] provide well-defined regulation on physiochemical and structural features that could be considered appropriate in the assessment of comparability as listed below:

- Amino acid sequence;
- Amino acid composition;
- Terminal amino acid sequence;
- Peptide map;
- Sulfhydryl groups and disulfide bridges;
- Carbohydrate structure;
- Molecular weight;
- Isoform pattern;

- Extinction coefficient;
- Electrophoretic pattern;
- Liquid chromatographic patterns;
- Spectroscopic patterns.

The advanced analytical technique such as mass spectrometers employed in the assessment of physiochemical parameters extremely sensitive to concentration and sample matrix. Isolation or purification of an active constituent from the reference formulation is carried out by extraction method, therefore, there could be possibility to a change in physiochemical or structural properties of active constituent and ultimately offers influence on comparability. Along with to physiochemical and structural elucidation, quantification of product and process related impurities should also include in the evaluation of biosimilars [36].

Pharmacovigilance

Pharmacovigilance is an integral part in the approval process of biosimilars. More attention should be given on pharmacovigilance as less number of patients studied throughout approval process of biosimilars [37]. Many biosimilar producing companies therefore set risk management or pharmacovigilance plan for biosimilar product. The risk management activities should be identical as that of reference product.

Pharmacovigilance plan [38] includes:

- Safety assessment of rare and serious adverse events described and predicted as per biological action of the reference product.
- The plan should confirm that any new safety indication is reported.
- Immunogenicity is the main concern in biosimilar product so proper monitoring system of the patient must be needed for accurate assessment of immunogenicity data.
- Full recognition of drug (reference or biosimilar) accompanying an adverse event.

CONCLUSION

Biological products are in market from last three decades and growing rapidly due to mainly intended in the treatment of incurable diseases. Biosimilar products are not a synthetic chemical drug or generic; biologics are high molecular weight and complex than chemical drugs because they are derived biotechnologically from living cells. The generic method is technically not correct for biosimilar products to bring them into the market. The EMA, WHO, and US FDA guidelines are the reference standard for many countries, 16 countries adopted these guidelines and 3 countries filled draft as the basis of their own regulations. There is a need to use well-designed CT to establish biosimilarity for patients safety.

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