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BIOLOGICALS AND BIOSIMILARS: AN OVERVIEW

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Abstract:

Biologics are highly sensitive large molecules with complex structure, difficult to characterize and reproduce, derived from living cells; used for treatment, diagnosis or prevention of disease. . Biosimilars are proteins that are similar to innovator biologics but not the same as they differ slightly in structure however with no clinically significant difference. Biologicals and Biosimilars are core part of modern medicines to manage and treat difficult and rare conditions. They have become an indispensible part of modern pharmacotherapy. The pharmaceutical and regulatory aspects of Biologicals and Biosimilars are reviewed in this article.

Key words: *Biologicals, Biosimilars, Regulatory Approval Process, Indian and WHO guidelines*

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INTRODUCTION:

The beginning of the 21st century saw numerous protein and peptide therapeuticals both on the market and entering the final stages of clinical studies. They represent a new category of biologically originated drugs termed biological or biopharmaceuticals. Their main advantages over conventional drugs can be summarized by their high selectivity and potent therapeutic efficacy coupled with limited side effects. In addition, they exhibit more predictable behaviour under in vivo conditions.

A new class of medicines has evolved with the revolution in biotechnology known as Biologicals (Biopharmaceuticals). Biologicals are large molecules derived using biotechnology for their use in the treatment, diagnosis or prevention of diseases like cancer, diabetes etc. They include proteins such as hormones, vaccines, monoclonal antibodies [1]. Biologicals are beneficial in the management of several health conditions which were once upon a time difficult to manage like cancer, multiple sclerosis, Alzheimer's disease, rheumatoid arthritis, diabetes etc.

Historical Perspectives of Biologicals:

"Virus, therapeutic serum, toxin, vaccine, blood, blood component or derivative, allergenic product, or analogous products, applicable to the prevention treatment, or cure of disease or condition of human beings" are generally considered as biological products. They have been around for nearly two centuries, since the development of first commercial Blutserum therapy (serum therapy) by Behring and Kitasato. Behring's diphtheria serum therapy was first clinically tested in 1891 and by 1894, Faberwerke Hoechst launched the first biological product, antidiptheria serum (e.g., crude polyclonal antibody preparation), to combat a serious diphtheria epidemic in Europe).

One of the next advances in biological products was the introduction of heterologous insulin purified from pigs and cows, marketed as Iletin by Eli Lilly starting in 1923 as life-saving treatment for patients with type 1 diabetes mellitus. While additional animal serum-derived products were developed over the next half century, they increased the use of biologics therapy in incremental stages. The scenario changes last quarter of the 20th century, with the advent of recombinant protein technology. Genentech led the path to production of recombinant therapeutic proteins in the late 1970s by cloning and expressing human somatostatin, insulin growth hormone, and human growth hormone (HGH) in *Escherichia coli [2}*.

Recombinant human insulin, HumulinR, the first recombinant human therapeutic protein was developed by Genentech and Eli Lilly, and the first approved for sale in the US on October 30, 1982[2]. The fully human protein, HumulinR, helped to eliminate the issues with immune responses directed against heterologous insulin from livestock. In the 27 years since Humulin was brought into the market, more than 165 biological products have been marketed for a broad array of therapeutic diseases. While few of these, such as a – antitrypsin and alpha-1-protenaise, are still purifies from human blood, the vast majority of biologics on the market today are from recombinant sources, requiring reliable, and consistent cell-based production platforms.

Classification of Biopharmaceuticals

Biopharmaceuticals are categorized as protein therapeutics which constitutes most of the biological products into four functional groups [3]:

i. Protein therapeutics with enzymatic or regulatory activity (e.g., insulin growth hormone, factor 1x replacement therapies, and beta-gluco-cerebrosidase replacement therapy for Gaucher's diseases.

ii. Protein therapeutics with special targeting activity (e.g., monoclonal antibodies that bind specific therapeutic targets, such as the antitumor necrosis factor-α biologics.

iii. Vaccines (e.g., human papillomavirus (HPV) vaccine made using HPV major virus-like particles containing HPV major capsid protein L 1); and,

iv. Diagnostics (e.g., biomarkers such as glucagon, and imaging agents such as technetium-labeled antibodies).

Recombinant hepatitis-B-surface antigen was the first indigenously developed and commercialized biopharmaceutical in the year 1997. Several biopharmaceuticals have been indigenously developed and have received approval the last 13 years.

BIOLOGICALS Vs CHEMICAL DRUGS

Chemical drugs are small in size and can be easily replicated as their chemical structure is known. Whereas Biologics are large molecules, highly sensitive in nature and their structure being complex and heterogeneous; cannot be easily understood.[1.] Biologicals are proteins that are derived using recombinant DNA technology for their use in the treatment, diagnosis or prevention of various diseases like autoimmune disorders, cancers etc. The major differences between the chemical drugs and biologicals are as follows.

Chemical drugs:
- Produced by chemical synthesis.
- Well defined structure and low molecular weight.
- Mostly process independent.
- Completely characterized.
- Stable
- Mostly non-immunogenic

Biologicals:
- Produced by living cell cultures
- High molecular weight
- Complex heterogeneous structure .
- Highly process dependent.
- Impossible to fully characterize molecular complexity and heterogeneity.
- Unstable, sensitive to external conditions.
- Immunogenic [4]

Manufacturing Process of Biologicals:
The manufacturing process involves complex procedures requiring recombinant DNA technology which makes its replication difficul [5]. The complex procedures include various steps that are described as follows:

- **Identification of the genetic code of the protein to be synthesized**
- **Insertion of the identified genetic code into the cell (bacteria, yeast or cultured animal cell)**
- **Isolation of these genetically engineered cell lines**
- **Growth in large bioreactors**
- **Various purification processes are used to isolate protein from the cells**
- **Addition of inactive compounds**
- **Final formulation obtained after filling the desired isolated protein**

Every step in the development of biologics is intricate, sensitive and specific to a particular medicine and therefore, even minor alterations lead to changes in cell behaviour and differences in the structure, stability or other quality aspects of the end product. Any of these differences that occur will have the potential to affect the treatment's safety, efficacy and shelf life, and to increase the risk of an unwanted immune response.
Some Biologicals of Therapeutic Importance are listed in Table 1.

Table 1: Some Biopharmaceuticals of Therapeutic Importance

S.No	Biopharmaceutical	Therapeutic Use	Company Name
1.	Nutropin™ (somatropin)	Growth disorders	Genentech
2.	Abbokinase™ (eudurase urokunase)	Ischemic events	Abbott
3.	Humulin™ (recombinant insulin)	Diabetes	Eli Lilly
4.	Ceredase™ (algucerase)	Gaucher disease	Genzyme
5.	Streptase™ (streptokinase)	Ischemic events	Astra Zeneca
6.	Intron ATM (IFN-alfa-2b)	Hepatitis B and C	Biogen/Roche
7.	Serotim™ (somatropin)	AIDS wasting	Serono
8.	Humatrope™ (somatropin)	Growth disorders	Eli Lilly
9.	Epogen™, Procrit™, Epres™ (erythropoietin)	Anemia	Amgen
10.	NeoRecormon™ (erythropoietin)	Anemia	Roche
11.	TNKase™ (tenecteplase TNK-tPA)	Acute myocardial infarction	Genetech
12.	Actimmune™ (IFN-gamma-Ib)	CGD, malignant obsteopetrosis	Inter Mune
13.	Alteplase™ (tPA)	Acute myocardial infarction	Genetech
14.	Proleukin™ (IL-2)	HIV	Chiron
15.	Neupogen™ (filgrastim G-CSF)	Anemia, leukemia, neutropenia	Amgen

BIOSIMILARS

Biosimilars as defined by the US FDA are biological products that are highly similar to and has no clinically meaningful differences from an existing FDA-approved reference products. Biosimilars are proteins that are similar to innovator biologics but not the same as they differ slightly in structure however with no clinically significant difference. Biosimilars are not the exact replicas of originator biologic and are therefore not generics. Biosimilars though being similar to biologics have naturally occurring minor differences which calls for caution with respect to adverse effects and immunogenicity during their use; signifying the importance of pharmacovigilance. In today's scenario biologicals are core part of modern medicines to manage and treat difficult and rare conditions. They have become an indispensible part of modern pharmacotherapy [6].

BIOSIMILARS VERSUS INNOVATOR BIOLOGICALS

Biosimilars are not exact copies of originator biologic and neither these are expected to be the exact replicas of the innovator biologics as the manufacturing process through which a biologic is made cannot be exactly duplicated by another manufacturer. They are similar to their innovator products but there being some minor difference in the structure due to different manufacturing processes involved they are not the same; however, these differences are not clinically significant and so the clinical outcome with innovator biologics and biosimilars is identical. Although both innovator biologics and biosimilars being protein in nature have immunogenic potential, biosimilars tend to produce more adverse drug reactions than reference products, immunogenicity being the most common among them; as biosimilars do not have to go through the same regulatory approval process as innovator product.[5,7]

BIOSIMILARS VERSUS GENERICS

Biosimilars are not generics; there is a difference between the two. Generics are exactly identical to their reference products in all the aspects, as the chemical structure of the small (chemical) drugs is completely known and can be exactly duplicated. Whereas the biosimilars are not the exact copies of the innovator biologics as the biologicals have complex heterogeneous structure which cannot be exactly replicated and also manufacturing process is complex, a slight change in any of the manufacturing steps produces difference in the products, when the difference is clinically insignificant the manufactured product is termed biosimilar [4,5,7-9].

The major differences between generics and biosimilars are as follows

Generics:

- Generics are therapeutically equivalent with their reference products.
- Active ingredient is always the same.
- Generics exhibit same clinical effect as reference products.
- Manufacturing of generics is simple and consistent.
- Cost of developing generic is around $2-3 million.
- For Approval of generics regulatory bodies require bioavailability & bioequivalence studies.
- Product substitution is permitted for generics.

Biosimilars:

- Biosimilars are Clinically identical to their reference products but not the same.
- Active ingredient is likely to have variation.
- Same clinical effect is not seen, there are chances of differences in effects.
- Manufacturing of Biosimilars is complex and variable.
- Cost of developing a biosimilar is approximately $75-250 million.
- For Approval of biosimilars regulatory bodies require clinical trials, manufacturing and post- approval safety monitoring programs similar to that of the original innovator companies.
- They do not accept equivalence.
- Substitution of Biosimilars is not permitted, as the substituted product may not be comparable to prescribed product in terms of safety and efficacy.

REGULATORY APPROVAL PROCESS FOR BIOLOGICAL PRODUCTS

Biological products are considered as NEW DRUGS as per the Indian "Drugs and Cosmetics Act." Products intended to be marketed in India are regulated by either drug Controller General of India or by DCGI or by DCGI and Department of Biotechnology (DBT). The history regulatory related to drug import, manufacture and sale are covered under the Drugs and Cosmetics Act of 1940 and Drugs and Cosmetics Rules of 1945. The Act's main objective is to ensure that available human drugs are safe efficacious and conform to prescribed quality standards, and marketed cosmetics are safe for use. CDSCO office along with the Indian Council of Medical Research have adopted international regulatory guidelines for biomedical research on human subjects in 2000 and Indian GCP guidelines

were released by CDSCO office and Guidance on Common Technical document for the NDA application were other initiatives for streamlining the requirements for conducting clinical trial and new drug approval process in India.

Currently, clinical trials in India are regulated by Schedule Y of the Drug and Cosmetics Rules, 1945. During the amendment of drugs and cosmetics rules, 2005, the Schedule Y was extensively revised to bring the Indian regulations on par with internationally accepted definitions and procedures. Schedule Y defines the requirement and guidelines for and/or manufacture of new drugs for sale of clinical trials.

Clinical trial requirements for biosimilars or follow-on biologics

The demonstration of bioequivalence of the generic non-biologic medicine with reference products usually appropriate and sufficient to infer therapeutic equivalence between the generic non-biologic medicine and the reference product. However, the approach established for generic non-biologic medicines is not suitable for development, evaluation and licensing of biosimilars (terminology used in Europe) or "follow-on biologics" (terminology used in the USA). To understand the clinical trial requirements, a brief outline of the dossier requirement for the approval for biosimilar with the reference from WHO guidelines is mentioned here. The office of DCGI has circulated draft biosimilar guidelines for India for comments from the stakeholders. The amount of data required evaluates the safety and efficacy of biosimilars is highly variable and is driven largely by the molecule evaluated and decided by the National Regulatory Authority, DCGI in India. Comparability to the innovator product is one of the most important requirements for a biosimilar product and includes an evaluation of physiochemical properties, biological pre-clinical and clinical comparability. The requirement for comparability data from a quality standpoint is significantly higher for biosimilar development compared to the development of a new and independent biological product. However, this extensive quality evaluation from a physiochemical, pharmaceutical, and biologic perspective reduces the amount of non-clinical and clinical data required for an approval of a biosimilar product. The requirement for biosimilar is organized and explained as shown in Table 1.

Manufacturing and quality

The administrative information summary should include details on the biosimilar product, its substance, raw materials, and manufacturing process. Differences with relevant attributes of the reference medicinal product should also be included. Any other changes introduced during the development which could affect the comparability should be highlighted. A full quality dossier is required for biosimilars. This should be supplemented by the demonstration of comparability (the exercise that will provide the two products have a similar profile in terms of quality safety efficacy).

Non-clinical studies

Before initiating non-clinical studies, results from the quality comparability studies including physiochemical and biological characterization studies should be reviewed from the point of view of the potential impact on efficacy and safety.

Clinical studies

The clinical comparability exercises is a stepwise approach that should ideally start with the pharmacokinetics and pharmacodynamics studies followed by the efficacy and clinical safety and clinical efficacy trials will be required, the clinical studies and nature of a biosimilar trial are likely to depend on the product class. All the clinical studies should address the immunogenicity characteristics.

INDIAN GUIDELINES

The New India Guidelines "Draft Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India," were announced in June 2012, by DBT. The Indian Guidelines on similar biologics address the premarketing and post marketing regulatory requirement (i.e., "comparability exercises"), and also address the requirements related to manufacturing process and quality control. As such these Indian guidelines on similar biologics are comparable in many respects to biosimilar guidelines of USA and EU. India has adopted a "sequential approach" (like "stepwise approach" US and EU) to market biosimilar products [10]. The Review Committee on genetic manipulation of the Genetic Engineering Approval Committee with the permission of DCGI, approves clinical trials to be conducted in India related to biosimilar therapeutic products. The biosimilar has to demonstrate comparable of 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 [11].

Biosimilars in India[12] 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 (GCSF–Grastim, Neukine), streptokinase (indikinase, shankinase, STPase), interferon alpha 2B (shanferon), Rituxinab (MAb), epidermal growth factor receptor (anti-EGFR) MAb–(reditux, bioMABEGFR) [13-15].

There are about 100 biopharmaceutical companies actively involved in research and development, manufacturing and marketing of biosimilar therapeutic products in India. There were 14 therapeutic drugs (similar biologics) available in 50 brands in 2005; The number has increased to 20 therapeutic drugs in 250 brands in 2011. Biosimilar therapeutic products include insulin, erythropoietin, chorionic gonadotropin, streptokinase, interferon, and heparin. The growing biosimilars market offers huge potential for companies involved in manufacturing, research, and development.

The Biosimilars launched in India are given in Table 2

Table 2: Biosimilars Launched in India

S.NO	Product name	Active substance	Company
1.	Basalog	Insulin glargine	Biocon
2.	Biovac-B	Hepatitis B vaccine	Wockhardt
3.	Ceriton	Epoetin alfa	Ranbaxy
4.	Choriorel	Chorionic gonadotrophin	Reliance Life Sciences
5.	Cresp	Darbopoetin alfa	Dr. Reddy's Laboratories
6.	Epofer	Epoetin alfa	Emcure
7.	Erykine	Epoetin alfa	Intas Biopharmaceuticals
8.	Epotin	Epoetin alfa	Claris Life Sciences
9.	Erypro	Epoetin alfa	Biocon
10.	Fegrast	Filgrastim	Claris Life Sciences
11.	FostiRel	Follitropin beta	Reliance Life Sciences
12.	Glaritus	Insulin glargine	Wockhardt
13.	Grafeel	Filgrastim	Dr. Reddy's Laboratories
14.	Insugen	Human insulin	Biocon
15.	Intalfa	Interferon alpha-2b	Intas Biopharmaceuticals
16.	Mirel	Reteplase	Reliance Life Sciences
17.	Myokinase	Streptokinase	Biocon
18.	Neukine	Filgrastim	Intas Biopharmaceuticals
19.	Neupeg	Peg-filgrastim	Intas Biopharmaceuticals
20.	Nufil	Filgrastim	Biocon
21.	Peg-grafeel	Peg-filgrastim	Dr. Reddy's Laboratories
22.	Reditux	Rituximab	Dr. Reddy's Laboratories
23.	Relibeta	Interferon beta-1a	Reliance Life Sciences
24.	Reliferon	Interferon α2b	Reliance Life Sciences
25.	Religrast	Filgrastim	Reliance Life Sciences
26.	Relipoietin	Epoetin alpha	Reliance Life Sciences
27.	Shankinase	Streptokinase	SB/Merieux Alliance
28.	Shanferon	Interferon α2b	SB/Merieux Alliance
29.	Shanpoietin	Erythropoetin	SB/Merieux Alliance
30.	Wepox	Epoetin alfa	Wockhardt
31.	Wosulin	Human insulin	Wockhardt

SB: Shantha biotechnics

A comparison of biosimilar approval guideline of India and WHO is given in Table 3

Table 3: Comparison of biosimilar approval guideline of India and WHO

Area	CDSCO: Indian Regulatory Guidelines	WHO Guidelines
Process	GMP Certified Facility	GMP Certified Facility
	Full cell Bank Characterization as per ICH Guidelines.	Full cell Bank Characterization as per ICH Guidelines
	Post Approval changes warrant comparability study.	Post Approval changes warrant comparability study
	Extractable studies are needed.	Extractable studies are needed.
	Viral validation studies are not needed	Viral validation studies are mandatory.
Analytical	Detailed characterization is expected.	Detailed characterization is mandatory
	Specification needed to be justified.	Specification needed to be justified.
	CMC requirement as per DCGI guidelines	CMC requirement as per ICH M4
Non-clinical	In vitro cell based assay is needed	In vitro cell based assay or receptor based assay is needed.
	In vivo evaluation may be dispensable if in vitro assay are available	In vivo evaluation is needed.
Clinical	Comparative PK/PD is required.	Comparative PK/PD is required.
	Phase III Comparative CT is not mandatory.	Comparative CT is required
	Scientific advice process is done by SEC, Apex committee, Technical Committee	Scientific advice process is not in place all WHO countries but it is for EMA
	Exploration to other indication can be obtained	Exploration to other indication can only be approved if clinical MOA is similar.
	PMS is mandatory for 4 years with 6 months PSURs for first 2yrs	PMS is mandatory
	Immunogenicity is not mandatory but expected.	Immunogenicity is mandatory.

CONCLUSION:

Biologics are highly sensitive large molecules with complex structure, difficult to characterize and reproduce, derived from living cells; used for treatment, diagnosis or prevention of disease. . Biosimilars are proteins that are similar to innovator biologics but not the same as they differ slightly in structure however with no clinically significant difference. Biologicals and Biosimilars are core part of modern medicines to manage and treat difficult and rare conditions. They have become an indispensible part of modern pharmacotherapy.

Biosimilars require 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, Detailed characterization is expected, Specification needed to be justified, CMC requirement as per DCGI guidelines, In vitro cell based assay is needed, *In vivo* evaluation may be dispensable if in vitro assay are available, 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 2yrs, Immunogenicity is not mandatory but expected.

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