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Biosimilars: an Emerging Market Opportunities in India

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Abstract

In recent few years, there are many epic Biological products are going off patent which has generated an abridged route for the Biosimilars products which relies on the extensive comparability testing against Reference Biological Products (RBP) assuring product's quality, safety and efficacy. Biosimilars are product similar to biologics but not indicate to them. Thus they require distinct marketing approval with abounding documentation as they are not generic version of biologics. These made regulatory and administrators of different countries to establish strict balance between the cost benefit and risk management of the product. The first draft guideline for Biosimilars was established by Europe, subsequently Japan and USA has developed the draft guidelines. While recently India has established the biosimilars guideline in June 2012. India has vigorous Pharmaceutical Industry for the generic drug while it can become an emerging market for the Biopharmaceutical drug. The regulatory structure for the biosimilars in India is depicted in this article with comparison of the biosimilars guidelines established by India and WHO. The approval process will be based authenticating a comparability quality between the biosimilars products and original product due to small alteration may lead to intolerable modifications in safety and efficacy. In many cases non-clinical studies are more difficult and potentially expensive to perform where biosimilars are highly species specific. Thus there is need for stringent regulatory guidelines. The biosimilar market will soon be thriving above $ 80 billion price of drugs in next seven years.

Keywords: Genetic engineering; Biosimilars; Bio therapeutics product; Marketing surveillance

Abbreviations

WHO: World Health Organization; ICH: International Conference on Harmonization; USA: United States of America; USFDA: United States Food and Drug Administration; EMEA/EMA: European Medicine Agency; CDSCO: Central Drug Standard Control Organization; DCGI: Drug Controller General of India; RCGM: Review Committee on Genetic Manipulation; GEAC: Genetic Engineering Appraisal Committee; INN: International Nonproprietary Names; RBP: Reference Biologics/Bio therapeutic Product; SEBs : Subsequent Entry Biologics; SBPs: Similar Bio therapeutics Product; PCSK-9: Proprotein Convertase Subtilisin Kexin 9; LMWH: Low Molecular Weight Heparins; LMO: Live Modified Organisms; CAGR: Compound Annual Growth Rate; GMP: Good Manufacturing Practice; CT: Clinical Trials; PK: Pharmacokinetic; PD: Pharmacodynamic; MOA: Mechanism of Action; PMS: Post Marketing Surveillance; CMC : Chemical Manufacturing Control; PSURs: Periodic Safety Update Reports; IBSC: Institutional Biosafety Committee; DBT: Department of Biotechnology; NIB: National Institute of Biologics; DSMB: Data and Safety Monitoring Board

Introduction

Biosimilars or biologics or biopharmaceuticals are the major magnification driver for the ecumenical pharmaceutical market due to their cost-efficacy, elevating occurrences of various diseases, incrementing number of off-patented drugs, positive outcome in the perpetual clinical tribulations, and elevating demand for biosimilars in different therapeutic applications such as rheumatoid arthritis, oncology and blood disorders. Recently, in USA the biosimilars are also developed and approved for lower cholesterol level under class of PCSK-9 inhibitor [1].

At the end of 2015, it is estimated that patent worth $ 80 billion of biosimilars are expected to expired globally. While the global biosimilars market is expected to reach $ 6.22 Billion by 2020 from $ 2.29 Billion in 2015, as it is growing at a CAGR of 22.1% from 2015 [2]. Fundamentally, biosimilars are licitly approved subsequent versions of innovator biopharmaceutical products following patent and exclusivity expiry. Biosimilar products has different therapeutic classes, while the existing biosimilars are erythropoietin's, growth hormones, granulocyte-colony stimulating factors and low molecular weight heparins (LMWH) and emerging biosimilars are Alfa interferon's, Beta interferon's, follicle stimulation hormone, insulin's, monoclonal antibodies (Table 1).

Regulatory Bodies	Terminology used for Biosimilar
US-FDA	Follow on Biologics
WHO	Similar Bio therapeutic Product
India	Similar Biologics
Europe	Biosimilar
Brazil	Follow on Biologics
Canada	Subsequent Entry Biologics

South Africa	Non-Comparable Biologics
Japan	Follow on Biologics

Table 1: Various biosimilars terminologies used by different regulatory bodies.

The leading challenges faced by biosimilar drug developers is proving the equipollence or similar attribute of their biological drug to the reference product because of great variation in properties and even miniature alterations can lead to unacceptable deviations in safety and efficacy resulting into the prerequisite of class-concrete guidelines for several intricate molecules of biological [3]. There are different terms used for biosimilar by different regulatory bodies as shown in Table 1 [4-7].

The different definitions of biosimilars are:

Europe (EMEA) Definition: A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise [8].

USA (USFDA) Definition: The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and "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 [9].

Canada (Health Canada) Definition: A SEB is defined by Health Canada as "a biologic product that would enter the market subsequent to, and similar to, an innovator product authorized for sale in Canada [10].

India (CDSCO) Definition: Similar biologics- A biological product/ drug produced by genetic engineering techniques and claimed to be "similar" in terms of safety, efficacy and quality to a reference biologic, 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 [7,11].

Regulatory Framework of India

India is one of the significant givers in world bio generic market alongside the china. In 2012, India has issued the Similar Biologics Guideline by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology. The important features of the guidelines are summarized below:

Applicable Regulations and Guidelines: Drug and Cosmetics Act 1945 and various rules for hazardous microorganisms/genetically engineered organisms or cells, 1989 regulate Similar Biologics for the manufacture, use, import, export and storage. The list of various guidelines help in development of Similar Biologics are shown in below Figure 1 [7,11].

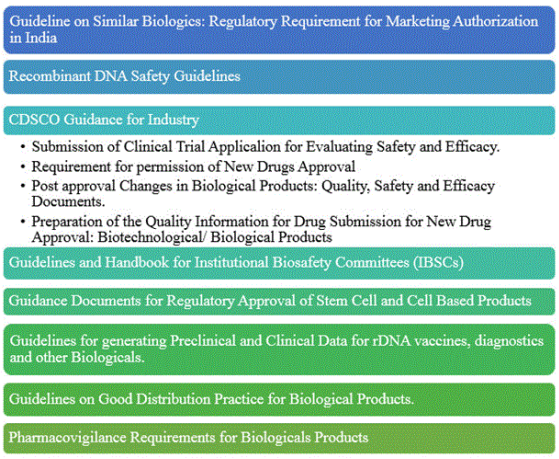

Figure 1: Various guideline for biosimilar in India.

Selection of Reference Biologic: The following factors should be considered for selection of the reference biologic [7,11].

- Active Ingredient and strength of reference product must be same with the biosimilar product.
- Same reference product must be used throughout study of quality, safety and efficacy.
- Must be approved and marketed in India with all Quality, Safety and Efficacy data.
- If not authorized in the India, than it must be licensed and marketed for 4yrs. Post approval in Innovators jurisdiction.

Regulatory pathway for biosimilars in India

The decision time period taken by Regulatory Committee/ Competent Authorities is as per below Table 2.

Procedure	Time Period
RCGM approval for pre-clinical animal studies	45 days
DCGI approval for Human Clinical Trials protocol	45 days
DCGI examination of clinical trial data and response	90 days
DCGI & GEAC decisions (simultaneous)	45 days

Table 2: Timeline taken by regulatory committee/competent authorities.

The general regulatory pathway for the approval of the biosimilar in India is as per below Figure 3 [7,11].

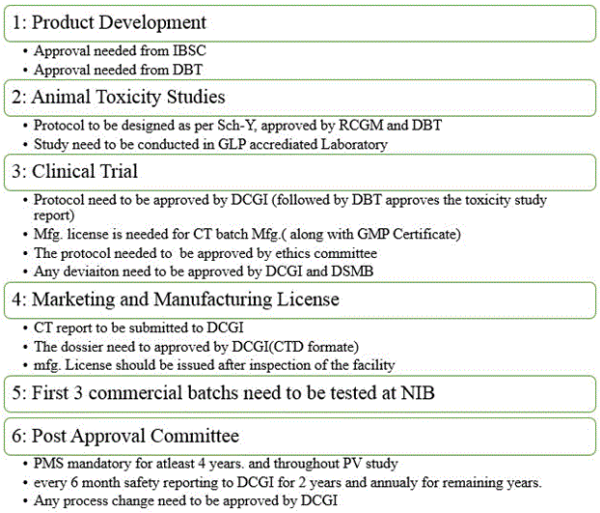

Figure 3: Biosimilars approval pathway in India.

According to the recent update applicant can file the application for animal toxicity studies and clinical trial to RCGM and DCGI simultaneously to reduce the time frame of approval. Additional only after the approval of animal toxicity study reports, the applicant can conduct the clinical trial.

Competent Authorities: Major three competent authorities are involved in the approval process are as per below Figure 2 with their major functions [7,11].

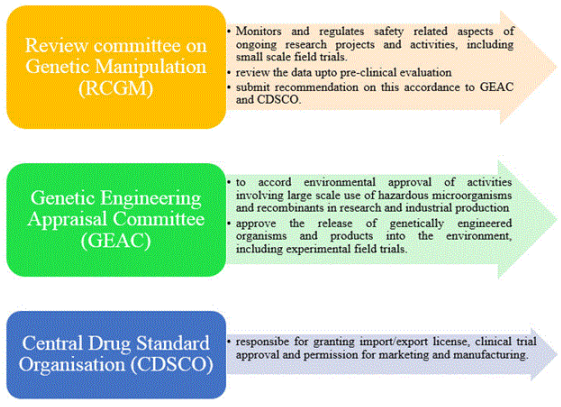

Figure 2: Major competent authorities with their function.

In Guidelines by CDSCO have established five different protocols for approval of biosimilars. These protocols are as follow [12]:

Protocol I: Indigenous product development, manufacture and marketing of pharmaceutical products derived from live modified organisms (LMOs), where the end product is not an LMO (Figure 4).

Protocol II: Indigenous product development, manufacture and marketing of pharmaceutical products where the end product is not an LMO (Figure 5).

Protocol III: Import and marketing of pharmaceutical products in finished formulations where the end product is an LMO (Figure 6).

Protocol IV: Import and marketing of pharmaceutical products in bulk for making finished formulations where the end product is an LMO (Figure 7).

Protocol V: Import and marketing of pharmaceutical products derived from LMOs in bulk and/or finished formulations where the end product is not an LMO (Figure 8).

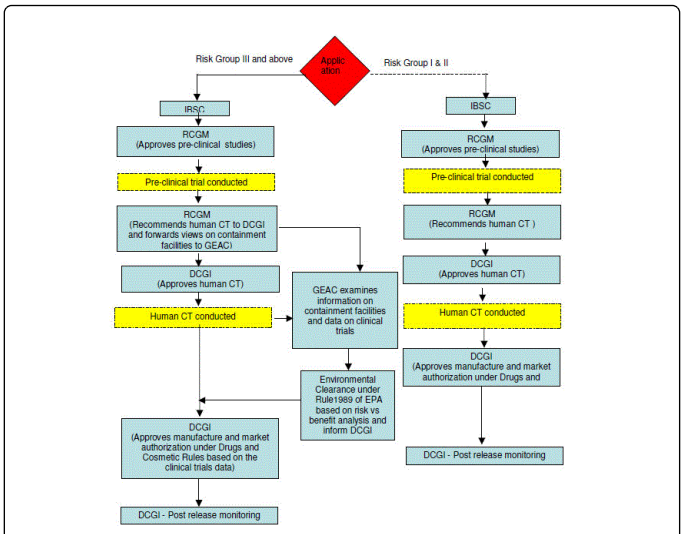

Figure 4: Approval pathway for biosimilars under protocol-I.

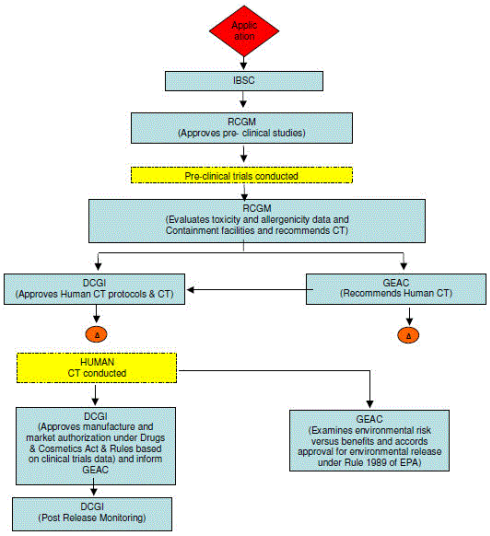

Figure 5: Approval pathway for biosimilars under protocol II.

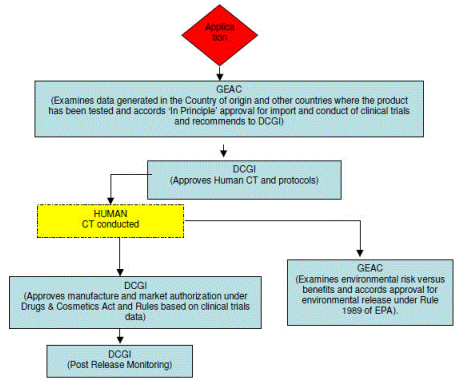

Figure 6: Approval pathway for biosimilars under protocol III.

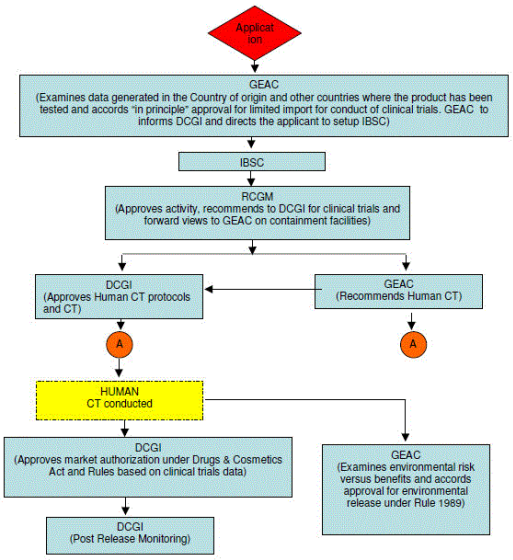

Figure 7: Approval pathway for biosimilars under protocol IV.

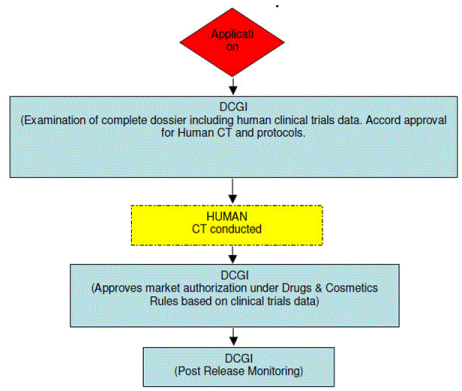

Figure 8: Approval pathway for biosimilars under protocol V.

WHO

Guideline on Evaluation of Similar biotherapeutics products was developed by WHO in 2009 after recognition of need for similar biotherapeutics product evaluation and overall regulation in 2007.

It gives worldwide worthy standards to authorizing biotherapeutic items that asserted to be like innovator result of guaranteed quality, safety, and efficacy that has been authorized on the premise of full dossier.

The key principles of WHO guidelines are (WHO):

The permitting of SBPs will depend on the demonstrated comparability, to some degree, on non-clinical and clinical information created with an officially Licensed Reference Biotherapeutic Product (RBP).

The product won't likely qualify as biosimilar, if the applicable contrasts are found in the quality, non-clinical, or clinical studies.

It is connected to the all-around described and entrenched biotherapeutic product, for example, recombinant DNA-inferred restorative proteins, Vaccines, plasma determined product and their recombinant analogs.

It additionally states "International Nonproprietary Names (INNs)" served as helpful instrument for pharmacovigilance for biologicals.

Debates like compatibility or substitution and licensed innovation are unaddressed by WHO as these are not inside of its command as a consultant.

There is key distinction between the drafted guideline by India and WHO for endorsement of biosimilars which has been shown in Table 3 [4,12].

Area	CDSCO: Indian Regulatory Guidelines	WHO 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	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 mandatory.
Analytical	Detailed characterization is expected. Specification needed to be justified. CMC requirement as per DCGI guidelines	Detailed characterization is mandatory Specification needed to be justified. CMC requirement as per ICH M4
Non-clinical	In vitro cell based assay is needed In vivo evaluation may be dispensable if in vitro assay are available	In vitro cell based assay or receptor based assay is needed. In vivo evaluation is needed.
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.	Comparative PK/PD is required. Comparative CT is required Scientific advice process is not in place all WHO countries but it is for EMA Exploration to other indication can only be approved if clinical MOA is similar. PMS is mandatory Immunogenicity is mandatory.

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

Biosimilars market in India

India shares 75% of biosimilar market, in which 30 biosimilar products are marketed out of 40 biological products. First biosimilar was approved and marketed in India for a hepatitis B in 2000. In recent years more than 50 biopharmaceutical products have been approved for marketing in India, with more than half of them being biosimilars [13].

Company Name	Biosimilar	Product Description
Torrent Pharmaceutical Ltd.	Adfrar	biosimilar adalimumab for the treatment of auto immune disorders
	Toritz RA	Biosimilar rituximab
Dr Reddy's Laboratories	Reditux	Biosimilar rituximab (mAb targeting CD20)
	Grafeel	Filgrastim (recombinant granulocyte-macrophage colony-stimulating factor, G-CSF)
	Cresp	Darbepoetin alfa (recombinant erythropoietin)
	Peg-grafeel	(pelfilgrastim)
Roche	Actorise	darbepoetin alfa in collaboration with Cipla
Intas Biopharmaceutical Ltd.	Neukine	Filgrastim (recombinant G-CSF)
	Neupeg	PEGylated G-CSF
	Intalfa	Recombinant human interferon alpha-2b
	Epofit	Recombinant erythropoietin
	Mbtas	Rituximab
Shantha Biotech/Merieux Alliance (Hyderabad)	Shanferon	Recombinant interferon alpha-2b
	Shankinase	Recombinant streptokinase

	Shanpoietin	Recombinant erythropoietin
Reliance Life Sciences (Mumbai)	ReliPoietin	Recombinant erythropoietin
	ReliGrast	Recombinant G-CSF
	ReliFeron	Recombinant interferon alpha-2b
	Relibeta	Interferon beta-la
	MIRel	Recombinant reteplase (tissue plasminogen activator)
Wockhardt (Mumbai)	Wepox	Recombinant erythropoietin
	Wosulin	Recombinant insulin
Biocon (Bangalore)	Eripro	Recombinant human erythropoietin
	Biomab	Biosimilar nimotuzumab (humanized mAb targeting epidermal growth factor receptor)
	Nufil	Filgrastim, recombinant G-CSF
	Myokinase	Recombinant streptokinase biosimilar
	Insugen	Recombinant human insulin
	Alzumab	Itolizumab
	Basalog	Insulin glargine

Table 4: Examples of biosimilars marketed in India.

The path forward for biosimilars in Indian pharmaceutical markets is shown in Figure 9.

Figure 9: Forward path for Indian biosimilar.

The examples of the approved biosimilars are listed in Table 4 [14].

Conclusion

With lapse of the patent of biological product will made accessibility of the biosimilar product in the business sector with cost reduction as it is the worldwide need instead of the economy improvement. Biosimilars are bigger and more intricate than the chemical drugs. As they are not the generics, the generic approach won't be suitable for the biosimilar product. Biosimilars are like inventor yet not indistinguishable to the inventor product, prompting prerequisite of the comparability testing. Biosimilar maker needs to face extraordinary difficulties in the development, clinical improvement, manufacturing, registration and product marketing contrasted with customary generics. India's characteristic quality in pharmaceutical marketing has been the spine to end up one of the key player being developed and maker of biosimilars. Accomplishment of biosimilar relies on upon the satisfactory execution of the pharmacovigilance framework and administrative rule while India's pharmacovigilance framework is under upgradation. India needs to create particular enactment administering biosimilar, with stringent administrative guideline and compelling collaboration in the middle of originator and biosimilar producer. Along these lines India has long approach to go especially in connection to legitimate edge work.

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