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Regulatory Comparison, Requirements and Approval process of Biosimilars in United States of America and India

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ABSTRACT
The term Biosimilars also known as biopharmaceuticals became a huge success in the developing countries due to their efficacy towards treatment of certain chronic diseases like cancer, diabetes, arthritis etc., Current scenario estimates that $60 billion worth of smash hit on biological drugs going off-patent in the United States of America. This creates an abbreviated route for biosimilar product development and approval. In contrast to generics, biosimilars are comparable to yet not indistinguishable from their reference product, because their compound qualities are straightforwardly identified with the assembling procedure which cannot be closely duplicated. Regulatory authorities require extensive characterization and comparability data to demonstrate biosimilarity to the reference biological product. Following European Medicines Agency's general guideline, the World Health Organisation (WHO) published a rule to introduce internationally adequate standards in 2009. Food and Drug Administration (FDA) published first guidance on biosimilars in 2012. India released draft regulatory guidelines for similar biologics on 19th June 2012, and finalized guidelines were implemented on 15th September 2012. The global biosimilars market is likely to reach 10.90 Billion US dollars by 2021 from 3.39 Billion US dollars in 2016, at a Compounded Annual Growth Rate (CAGR) of 26.3%. Regulatory functions and approval process of biosimilars among two major countries are discussed in this review.

Keywords: Biosimilars, Regulatory activity, Approval process, United States America, India.

INTRODUCTION

Biosimilars are biological based medical products whose active drug substances are made by a living organism by recombinant DNA or controlled gene expression methods[1, 2]. Like generics, biosimilars are similar but not exact to their reference product, because their chemical nature are directly proportional to their manufacturing process which cannot be as such duplicated[3, 4]. Biosimilars expected to have a similar component of activity for indistinguishable infections from the pioneer biopharmaceutical drugs[5]. Biosimilars are high molecular density in nature and might be very difficult to change in assembling forms, beginning material and technique for control[6]. Even minor changes in the process can lead to fatal outcomes, safety and efficacy issues. So the regulatory authorities require extensive characterization and comparability data to demonstrate bio similarity to the reference biologic product[7, 8]. Various region-specific, product-specific biosimilar guidelines were published by the respective regulatory authorities of a particular country to aid the manufacturers in biosimilar development and approval[9]. The global biosimilars market is expected to reach USD 10.90 Billion by 2021 from USD 3.39 billion in 2016, at a CAGR of 26%[10, 11] The central point driving the development of this market is the expanding interest for biosimilar products because of their cost-adequacy, developing strain to shorten social insurance consumption, rising geriatric population, vital coordinated efforts bringing about the improved efficiency and clinical preliminary exercises for biosimilars, expanding government sponsorship and activities to create advance biosimilars in future[12, 13].

Table 1: Various terminologies and Definitions used for Biosimilars by different Regulatory authorities[14, 15]

Regulatory agency	Naming	Definition
USFDA	Follow-on Biologics or Biosimilars	"A biosimilar is a biological product that is highly similar and has no clinically meaningful differences from an existing FDA-approved reference item as far as safety, purity and an intensity of the product"
CDCSO	Similar Biologics	''An organic medicate delivered by hereditary designing procedures and professed to be "comparable" regarding adequacy and quality to a reference biologic, which has been allowed promoting approval in India by DCGI with safe use in India''

The FDA principles define Biosimilars sponsors follow a stepwise approach:

1. Analytical investigations of the proposed biosimilar and reference item to evaluate physical, chemical, and functional similarity
2. Nonclinical (animal) studies to evaluate toxicities
3. Comparative clinical examinations to assess pharmacokinetics (PK) and pharmacodynamic (PD) profile of the proposed biosimilar and reference item, and to look at clinical immunogenicity and
4. Potentially, additional clinical examinations if residual uncertainty remains[16].

Because of the idea of biologics, contrasts between the biosimilar and reference biologic will quite often be found, yet the key is deciding the clinical importance of those varieties. The measure of clinical information mentioned is needy upon the degree of vulnerability that remaining parts following diagnostic and nonclinical examination[17]. Following the accommodation of the total 351(k), if FDA affirms that the item is without a doubt biosimilar to or tradable with the reference item and if the office where the biosimilar is fabricated if consents to the Appropriate FDA examination, at that point the proposed biosimilar can be endorsed[18].

BIOLOGICS APPROVAL PROCESS

IND process

- Vaccines and biologics follow the same general pathway as for drugs.
- Sponsor shall submit all the non-clinical data in case of IND to FDA, FDA inaction in 30 days triggers the study under the IND to proceed
- The sponsor can initiate the clinical trials and process and review remains the same as of small molecules
- For every phase of a clinical trial, the sponsor has to review and continue to the next phase of the trial
- Once the clinical trial data is ready, the sponsor has to perform a pre-approval meeting.

NDA process

- After a sponsor submits a BLA, the FDA assembles a review team and then evaluates, within the first 60 days after submission, whether it can file the application or refuse
- For NDA the manufacturer shall submit an application to the Director, **Center for Biologics Evaluation and Research (CBER)** of FDA on forms prescribed for such purposes, and shall submit data derived from nonclinical laboratory and clinical studies to prove **safety, purity, and potency**
- Examination of biologics license application by USFDA:
  - Examination
  - Availability of product
  - Manufacturing process

PATENT EXCLUSIVITY TERM FOR BIOSIMILARS IN THE USA

Area 351(k) (7) of the PHS Act portrays the particularity of reference biologics communicating that biosimilars may not be approved before 12 years of the underwriting of the reference item[19].

Table 2: Fee for registration as per Biosimilar User Fee 2021Amendments (BSUFA)[20]

User Fee Type		FY	FY 2022
Biosimilar Biological Product Development (BPD) Fee	Initial BPD	$ 102,494	$ 57,184
	Annual BPD	$ 102,494	$ 57,184
	Reactivation	$ 204,988	$ 114,368
Application Fee	Clinical Data Required	$ 1,746,745	$ 1,746,745
	Clinical Data not Required	$ 873,373	$ 873,373
Program Fee		$ 304,162	$ 304,162

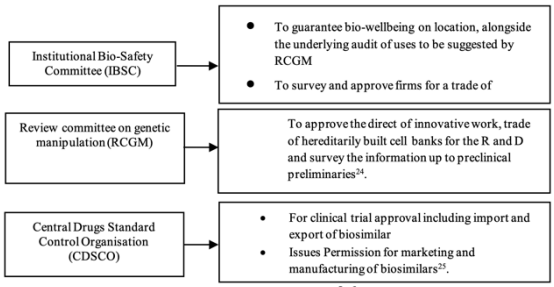
Regulatory aspects of Biosimilars in India:

In India, the import, manufacture, distribution, sale of biosimilars is governed under the Drugs and Cosmetics act and rules 1945[22].

Institutions and committees responsible for Biosimilars approval in India:

- Institutional Bio-safety Committee (IBSC)
- Central Drugs Standard Control Organization (CDSCO)
- Review Committee on Genetic Manipulation (RCGM)
- Genetic Engineering Approval Committee (GEAC)
- Recombinant DNA Advisory Committee (RDAC)
- Indian Council for Medical Research (ICMR)

Functions of various authorities involved in biosimilar approval:



Biosimilar guidelines in India[26]:

As of late Indian Drug administrative power, the Central Drug Standard Control Organization (CDSCO) proposed modified rules for Similar Biologics 2016 (Proposed Guidelines) which may supplant the past Guidelines on Similar Biologics 2012, which tends to the administrative pathway concerning producing procedure and wellbeing, adequacy and quality angles, pre-market managerial necessities including proportionality practice for quality, preclinical and clinical examinations and post exhibit regulatory essentials for similar biologics[27].

FDA approved Biosimilars

Table 3: FDA approved Biosimilars and follow on Biologics (2015-2022)[21]

Product name	Active substance	Authorization date	Manufacturer/ Company name
Zarxio (filgrastim-sndz)	Filgrastim	6 Mar 2015	Sandoz
Basaglar	Insulin glargine	16 Dec 2015	EliLilly/Boehringer Ingelheim
Inflectra (infliximab-dyyb)	Infliximab	5 Apr 2016	Pfizer (Hospira)
Erelzi (etanerceptszzs)	Etanercept	30 Aug 2016	Sandoz
Amjevita (adalimumab-atto)	Adalimumab	23 Sep 2017	Amgen
Renflexis (infliximab-abda)	Infliximab	21 Apr 2018	Samsung Bioepis
Cyltezo (adalimumab-adbm)	Adalimumab	25 Aug 2019	Boehringer Ingelheim
Nyvepria (pegfilgrastim-apgf)	Neulasta (pegfilgrastim)	Apr 2020	Pfizer (Hospira)
Semglee (Insulin glargine-yfgn)	Lantus (Insulin glargine)	July 2021	Mylan Pharmaceuticals Inc
Fylnetra (pegfilgrastim-pbbk)	Neulasta (pegfilgrastim)	May 2022	Kashiv BioSciences, LLC

CDSCO Biosimilar approval process:

1. Product development:
   - Approval needed from IBSC and DBT
2. Animal toxicity studies:
   - As per schedule-Y protocol should be designed, approved by RCGM and DBT
   - Study needed to be conducted in GLP accredited laboratory
3. Clinical trial:
   - DCGI approval for the protocol used and followed by that toxicity study report approval by DBT
   - Manufacturing license is necessary for clinical trial batch manufacturing along with GMP certificate
   - Protocol approval by the ethics committee[28].
4. Manufacturing and marketing license:
   - Submission of clinical trial report to DCGI
   - The dossier needs to be approved by DCGI (CTD format)
   - Manufacturing license will be issued after inspection of a facility
   - First 3 commercial batches need to be tested at National Institute of Biologicals[29].
5. Post-approval committee:
   - PMS mandatory for at least 4 years and throughout Pharmacovigilance study study
   - Safety report to be submitted to DCGI on every 6-month for 2 years and annually for remaining years
   - Any changes in the process need to be approved by DCGI[30].

Timeline for approval:

Table 4: Timeline for Biosimilar approval[31]

Procedure	Period
Pre-clinical animal studies approval by RCGM	45 days
Human clinical trial protocol approval by DCGI	45 days
Clinical trial data and response examination by DCGI	90 days
Final decisions of DCGI & GEAC	45 days

Application forms for Biologicals:

Different types of Application forms used in various stages of development and manufacturing are mentioned below in table 5.

Table 5: Application forms for Biologicals[32]

Stage of development or manufacturing	Regulatory agencies involved	Application format	Approval format
Test manufacturing license, Analysis and Examination	State FDA/CDCSO	Form 30	Form 29
Preclinical studies permission	RCGM	Form C3	Form C4
Submission of preclinical study report	RCGM	Form C5	Form C6
Clinical trial	CDCSO	Form 44	Permission letter
Manufacturing and marketing permission	CDCSO	Form 44	Form 46 (bulk product) Form 45/46 (finished product)
Form 46A (bulk product)	CDCSO	Form 44	Form 46
Commercial manufacturing license	FDA/CDCSO	Form 27D	Form 28D
Registration and import license	CDCSO	Form 40/ Form 8	Form 41 Form 8

Biosimilars approved in India:

Table 6: Recently approved Biosimilars in India: (2012-2019)[33, 34]

Product name	Active substance	India launch year	Manufacturer/ Company name
Actorise	Darbepoetin alfa	2014	Cipla/hetero
Exemptia	Adalimumab	2014	Zydus cadila
Rituxirel	Rituximab	2015	Reliance life sciences
Razumab	Ranibizumab	2015	Intas pharmaceuticals
Bevacirel	Bevacizumab	2016	Lupin
Cizumab	Bevacizumab	2017	Hetero
Adfrar	Adalimumab	2018	Torrent pharmaceuticals
Acelibia	Rituximab	2019	Cipla/hetero

CONCLUSION

Worldwide biosimilars showcase is relied upon to reach $26,551 million by 2020, upheld by a CAGR of 49% in the estimated time frame 2015 to 2020. As many biologic blockbuster drugs are going off-patent, it creates greater opportunities for the pharmaceutical manufacturers to develop the biosimilars of many best-seller biologics. Every country has unique regulations in place to oversee the development and approval of biosimilars. On comparing the regulatory aspects of biosimilars in the USA and India, it has been a path in front of different countries remembering that the way of creating biosimilars. Administrative necessities for the endorsement of similar biologics are comparative however marginally extraordinary in terms of bio comparability, the extent of the rules, the decision of the reference item, the information required for product development and some different aspects of regulations were involved. Recently India has proposed revision for the biosimilar guidelines with intent to streamline the regulation according to the international standards. Even though the emerging growth of biosimilars is high, there are serious consequences also were involved by not monitoring process controls and audit trials during manufacturing.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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