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Current State of Regulatory Oversight of Biosimilars in India and Its Implications on the Quality of Drugs: A Comparative Assessment with EU and FDA Regulations

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ABSTRACT

Biosimilars are biologic products that are highly similar to a licensed reference biologic, with no clinically meaningful differences in quality characteristics, biological activity, safety, or efficacy. Biosimilars can help to fulfill unmet medical needs due to their cost effectiveness while at the same time being as efficacious as the innovator drug. They can also improve patient access to otherwise costly innovator biologics. India has the largest number of approved biosimilars as compared to the US and Europe. However, the numbers of clinical studies that are conducted to prove the biosimilarity are lesser than the number of biosimilars approved, which is evident by the number of CTRI registrations done. Some studies have shown the quality of biosimilars approved and marketed in India to be inferior to the innovator drug. This raises concerns regarding the quality of the biosimilars. In this review, the similarities and differences in the guidelines, the approval process, and quality enforcement measures prevailing in the three regulatory regions of USA, Europe and India are discussed. Changes in the approval process and post approval monitoring of drugs and manufacturing facilities are recommended in order to ensure sustained quality standards of drugs entering the market.

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Background

Biosimilars are biologic products that are highly similar to a licensed reference biologic, with no clinically meaningful differences in quality characteristics, biological activity, safety, or efficacy[1-3]. The importance of anti-cancer biosimilars in improving patient access and supporting sustainability to cancer care have been highlighted by reputed oncology societies like The American Society of Clinical Oncology (ASCO) and The European Society for Medical Oncology (ESMO) [4,5].

Vaccines, monoclonal antibodies, and recombinant proteins such as insulin constitute the major class of biosimilar drugs approved and used in India. Despite the large number of biosimilars being manufactured in India, not many clinical studies have been conducted to demonstrate their equivalence with the innovator. The number of CTRI registrations observed are also very few as compared to the number of biosimilars approved [6].In one study by Gota et al comparing the activity of asparaginase in E-coli derived L-asparaginase, the generic formulations screened, demonstrated decreased asparaginase activity. In-vitro analysis for asparaginase activity was done for three generic formulations. It was shown that the asparaginase activity for these varied from 71-75% of the label claim as compared to 94% for the innovator formulation [7]. In another study by Gota et al a biosimilar of Rituximab (Reditux) was compared to the innovator drug (MabThera).The study revealed that the pharmacokinetic profile and B-cell response to Reditux™ was commensurate with those reported for MabThera™ [8]. This has raised concerns regarding the reliability of these drugs. This article mainly describes the overview of US, EU and Indian biosimilar guidelines, how the regulations there evolved over the years, the review carried out for newer biologics, and the implementation of guidelines there to ensure the maintenance of optimal quality of biosimilars after the receipt of regulatory approval. This article also aims to highlight the lacunae in the Indian setup revolving around existent guidelines and to come up with recommendations to improve the current scenario.

Evolution of Guidelines

Zarxio (Filgrastim-sndz) was the first biosimilar to be accorded approval by the US FDA in the year 2015. The regulations for biosimilars were drafted in the year 2009 however, the origin for these regulations dates back to 1996 wherein the FDA provided recommendations concerning, "Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products" [1,2]. This guideline provides recommendations for the sponsor to demonstrate the safety and efficacy of an FDA-

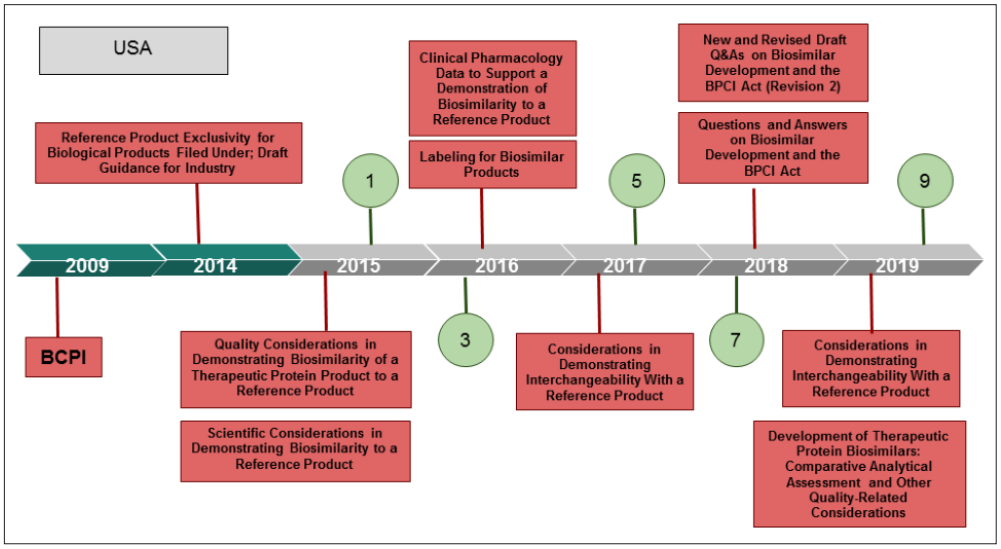
approved product even in case of changes in the manufacturing process. The regulations for biosimilars in the USA started with the Biologics Price Competition and Innovation Act 2010 (BPCI) [9]. The Act was a means to introduce competition and reduction in price of expensive biologics. Over the decade there has been an increase in the number of biosimilars being approved. There have been frequent guidelines being released over the years. The US FDA has approved a total of 23 biosimilars till 2019 [10].

The EU was the first to bring in regulations for biosimilars. The first overarching guidelines were issued in the year 2005. The EU has only three overall guidelines regarding biosimilars. However they have formulated specific guidelines for different kinds of biologics. The EU also follows the ICH (5Q) guidelines. Their first biosimilar Omnitrope was approved in the year 2006.The EU has approved a total of 61biosimilars as of 2019 [10].

In India although biosimilars were manufactured quite early on from the 2000's, there were no regulations or guidelines specific to biosimilars in India until 2012. In 2012, the first guideline, "Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India" was introduced by the joint efforts of The Central Drugs Standard Control Organisation (CDSCO) and The Department of Biotechnology (DBT). These guidelines were amended once in 2016 [11]. These guidelines dealt with the regulation of manufacturing processes, the pre- and post-marketing regulatory requirements as well as safety, efficacy and quality of similar biologics. Previously, the reference biologic had to be licensed and marketed in India, but it has been updated to include all ICH countries as of now. The highest number of biosimilars were approved from 2009-2014 after which there was a decrease in the approval. India has approved a total of 93 biosimilars till 2019 [10].

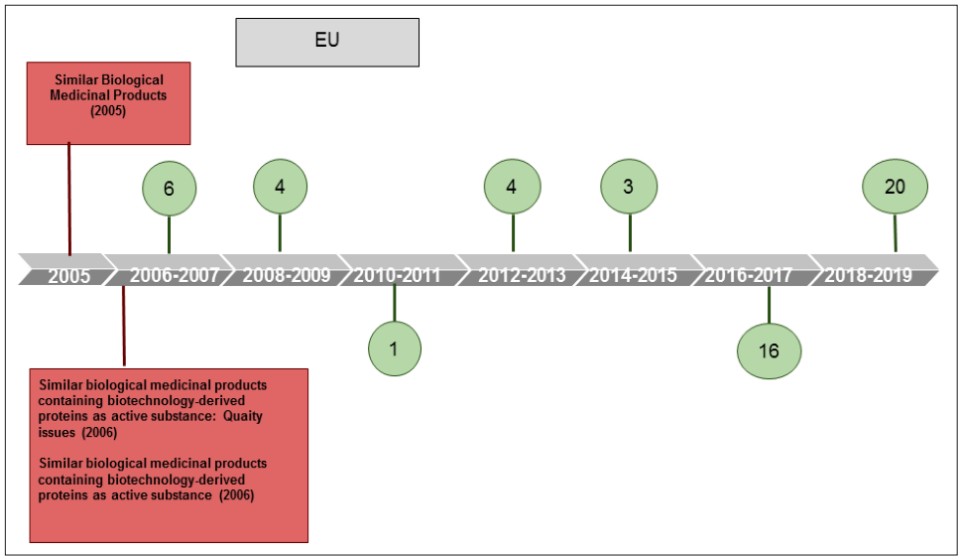
The evolution of the biosimilar guidelines in the US [12], EU [13], and Indian [14] regulatory landscape is shown in Figures 1-3.

Figure 1: Evolution timeline for biosimilars in the US [12].



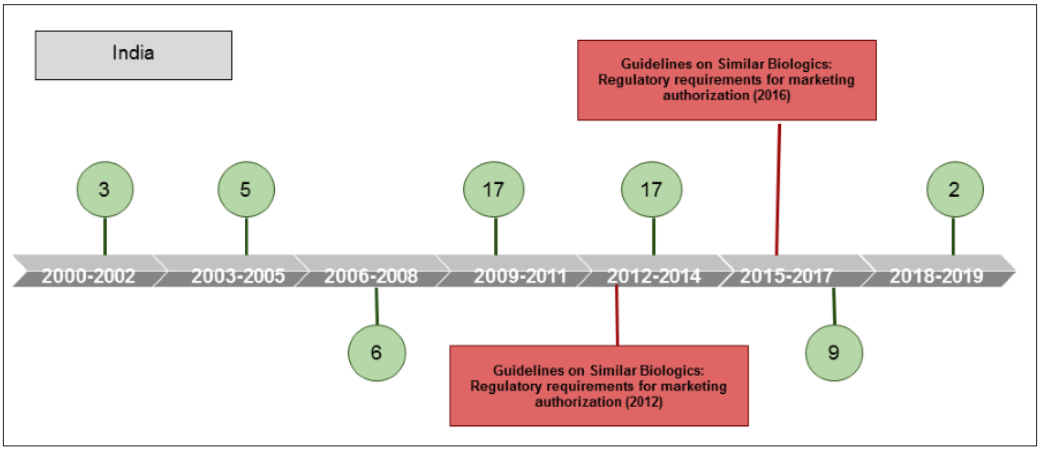
(Numbers are indicative of the number of biosimilars approved during the specified time point]

Figure 2: Evolution timeline for biosimilars in Europe [13].



(Numbers are indicative of the number of biosimilars approved during the specified time point]

Figure 3: Evolution Timeline for Biosimilars in India [14].



Overview of Regulations

Data Required for the Approval of Biosimilars in the USA

In the USA a separate application, the 351(k) needs to be submitted for the approval of biosimilars [1,15]. The application must include all analytical, non clinical and clinical data which provides evidence of biosimilarity between the proposed product and the reference product. The analytical evidence generated should demonstrate a similar amino acid sequence in the proposed biosimilar and the reference product. In case of any modifications or manufacturing changes, additional studies are required to be conducted. Analytical methodologies should be used to detect differences in characteristics such as structure and function of the biomolecule. A comparative stability and degradation study of the proposed biosimilar and the reference product should also be carried out [15]. Animal toxicity data for the proposed biosimilar is also required. The kind of clinical trials required to be conducted depends on the variability between the two products found from analytical studies. Clinical trials should be designed to determine clinically relevant discrepancies between the proposed product and the reference product in terms of safety and efficacy. Clinical studies conducted should provide data on pharmacokinetic and pharmacodynamic profiles in humans. The BPCI Act has a provision for exclusivity to manufactures of biologics. The application for biosimilars will not be authorized until 12 years after the date of authorization of the reference product.

3.2 Data required for the approval of biosimilars in the EU

According to the EU guidelines, biosimilarity can be demonstrated by analytical tests, biological assays, non-clinical and clinical data which is in conjunction with data required for the US. There is a huge emphasis on analytical studies [16]. However clinical and non clinical studies are not required to be done if extensive analytical studies done can provide enough proof of comparability. Clinical trials are targeted to confirm biosimilarity and to clarify any key questions from previous analytical or functional research. An adequately powered clinical trial should be designed to get comparative data with respect to pharmacokinetics, pharmacodynamics, efficacy, safety and immunogenicity [3].

3.3Data required for the approval of biosimilars in India

The evidence required for proving biosimilarity in India is also similar to the US and EU. However, animal studies should be conducted to study the immunogenicity of the biosimilar and how it compares with the reference biologic. Toxicological studies must be conducted in pharmacologically relevant species. At least one repeat dose toxicity assessment with the expected route of administration must be performed. Clinical studies must evaluate the adverse events due to the proposed biosimilar in comparison with the reference product. Also, Indian regulations allow for the waiver of clinical safety and efficacy studies if physicochemical, in vitro techniques and preclinical studies provide strong evidence for biosimilarity between the biosimilar and the reference product. A post marketing risk management plan must also be in place in such cases [11]. However there seems to be a problem here. Experts have stated that the analytical and preclinical testing requirements in India are not at par with those of US FDA, EU or WHO. Also phase 3 studies are not conducted if there is considerable PK, PD evidence of biosimilarity. This results in faster drug approvals. Statistical validity of the trials are also questionable since the number of participants recruited are also low [17,18].

A comparison of the guidelines in the three regions is given in Table 1[19–21].

Review Process

US FDA

To facilitate efficient development& approval of biosimilar products, the FDA has come up with the Biosimilars Action Plan (BAP). It focuses on enhancing the quality of the production and approval process of biosimilar drugs, maximizing scientific and regulatory transparency for the biosimilar product development community, establishing better communication between patients, clinicians and payers to enhance understanding of biosimilars. A specific committee, i.e Therapeutic Biologics and Biosimilars Staff (TBSS) has also been constituted which supports consistent review and policy development efforts for biosimilar product development and approval. The Biosimilar Product Development Program (BPD) has been designed to provide manufacturers with comprehensive, product-specific assistance [22]. The FDA reviews the entirety of the data and details, including the basis for comprehensive analytical (structural and functional) characterization, animal studies if appropriate, then proceeds on to clinical pharmacology studies and, if necessary, other comparative clinical studies when evaluating the licensing of a biosimilar product [23]. All the information regarding the process of approval of Biosimilars inclusive of the different types of reviews and departments of the FDA involved has been made available by the FDA on their website [1,24].

The EU

The European Medical Association (EMA) has mandated that all medicines produced using biotechnology must be approved through the EMA (centralized procedure). For certain biosimilars, such as low molecular weight heparins derived from porcine mucosa,

exceptions are made. Data is reviewed by the EMA Scientific Committees on Human Medicines and Protection (CHMP and PRAC) as well as by EU Biological Medicines Experts (Biologics Working Group]) and Biosimilars Specialists (Biosimilar Working Party) when a company applies for a marketing licensure at the EMA. The assessment by the EMA leads to a scientific consensus, which is then referred to the European Commission, which eventually offers an EU-wide marketing authorisation. The agency, upon receipt of the application, commences validation at the next deadline for submissions indicated on its website. The validation procedure for biosimilars of centrally authorized medicinal products starts in the same month. For biosimilar applications, whose reference medicinal product was authorized through national procedure of a member country, the EMA shall request the concerned authorities in that member state to confirm that the reference medicinal product is authorized, along with details on the complete composition of the reference medicinal product within a span of one month. The assessment process will however only begin once all the necessary and appropriate information is obtained. If any member of the CHMP (Committee for Medicinal Products for Human Use) has not obtained the parts of the dossier which were requested from the applicant within a month from the start of the evaluation process, the clock will be stopped by the EMA till the resolution of the issue. The opinion of the CHMP will be given within 210 days (clock-stops within the procedure are not counted) which will be ensured by the EMA [25].

The comprehensive day-wise review process can be found in the EMA's "Procedural advice for users of the centralized procedure for similar biological medicinal products applications" [26].

India (CDSCO)

In the Indian scenario, five committees play a key role in the review and approval process for biosimilars, namely The Institutional Bio-safety Committee (IBSC) Review Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), and the CDSCO. The IBSC ensures on site biosafety as well as reviews applications which could be recommended to the RCGM. The RCGM authorizes the conduct of research and development, permits the exchange of genetically engineered cell banks for research and development as well as reviews the preclinical data. The GEAC reviews and is also involved in approval of all applications wherein the final drug product includes genetically modified organisms/living modified organisms. The CDSCO is the apex regulatory body which is involved in the approval of clinical trials [11]. It constitutes Subject Expert Committees (SECs) which reviews the clinical trial data and provides expert advice to the CDSCO. The CDSCO after due consideration and analysis provides marketing authorization [27].

India has approved the largest number of biosimilars as compared to the US and EU [10]. Although the domestic market for biosimilars in India may be on the rise, international business for these biosimilars may be impeded due to non-compliance to the regulations. Currently, very few biosimilars that are approved in India have managed to enter the European or The US markets. Experts comment that this could be attributed to the non-stringent regulatory framework [17,18].

Implementation

US FDA

In the USA, the FDA routinely conducts unannounced inspections to ensure the quality of drugs manufactured since post approval changes occur in all biologics including biosimilars, so a system to ensure the quality of these drugs should be in place. The FDA maintains a list known as "FDA watch list" which contains information regarding potential signals of serious risks or new safety information of a particular drug. This list is updated quarterly. The Office of Regulatory Affairs and CBER (The Center for Biologics Evaluation and Research] have established "Team Biologics' ' to conduct inspections of biologic drug manufacturers. To assess an establishment's compliance with the relevant cGMP guidelines, there are two levels of inspection coverage. Such inspections reduce the risk of counterfeit or adulterated biologics reaching the consumer by providing a timely feedback to improve the industry's compliance with cGMP. This increased industry-agency communication ensures safeguarding of public health. The frequency of unannounced inspections may increase if any safety issues had been encountered in the past or in case of a complaint received or recall of a particular drug. They can also be planned to oversee the necessary changes being implemented during a follow up inspection or if the site is unresponsive after reasonable contact attempts have been made [28,29]. The FDA has sufficient manpower and resources to manage all these activities i.e there are specialized departments which have been designated to carry out all the necessary activities [30,31]. The FDA maintains their website in a transparent manner that provides information. Likewise, any new guideline which is released is open to the public for comments so that even the public can participate. This transparency enforces the trust of the physicians who are prescribing the drug and also the public who receive the drug. A PADER (Periodic Adverse Drug Experience Report) has to be submitted every 3 months for the first 3 years and then annually thereafter [32].

EU

In the EU, the EQDM certification department is the authority for conducting inspections. The EQDM inspections are conducted to evaluate conformity with the GMP as well as the CEP application (and updates if any]) at the manufacturing and distribution sites. The inspection team normally consists of an inspector from EQDM and an official from the EU/EEA authorities (or countries which have a Mutual Recognition Agreement (MRA) with the EU in GMP sector for API's). These inspections usually last for 3 days. The number of inspections annually is about 40 which also include re-inspections. Local official inspectors are requested as observers in inspections which are carried out in non-EU/EEA/MRA member states. In certain countries (ex. China), the EQDM may hire interpreters to join the inspection team so as to ensure efficient communication with the local site staff [33]. The authorities after inspection, issue either a GMP certificate or a non compliance statement which is then entered in the publicly available database, EudraGMP. In the EU a Periodic Benefit Risk Evaluation Reports (PBRER) should be submitted every 6 monthly for the first two years, annually for the next two years and every 3 years thereafter [26,34]. Sometimes, regulators can require a Post Authorization Safety Study (PASS) to be conducted. If such a study has been imposed on the reference medicine then it would also be imposed on the biosimilar. An addition in the EU all the biologics approved after 1st Jan 2011 are subjected to additional monitoring. These drugs are closely monitored for the first year after approval. A black triangle symbol on the package insert identifies such drugs [3].

INDIA

In India, there is a Risk Based PV program, as a part of the condition of the marketing authorization. A PSUR has to be submitted by the marketing authorization holder (MAH) post licensure of the product The periodicity of submission of the PSUR is half- yearly for the first two years and annually for the next

two years [35]. The national level pharmacovigilance inspection programs will fulfill the need for routine inspections. However, based on recommendations from SECs and various government and statutory bodies like DTAB, DCC, ICMR, NACO, RNTCP, targeted or triggered inspections may replace the need for routine inspections. The CDSCO can ensure compliance with the legal requirements governing medicinal products by means of repeated inspections and, where required, unannounced inspections. It can also inspect the premises; oversee records and documents of MAH or any firms employed by the MAH to perform such other activities [36]. However no data is available regarding the inspections carried out by the CDSCO.

Recommendations

Therefore in order to improve the present scenario the regulatory authorities must ensure that a plan is in place to check whether all MAHs are compliant to existing regulations. Also the analytical and preclinical testing requirements can be ramped up so that Indian biosimilars can meet international standards. The CDSCO affiliated laboratories can be encouraged to conduct quality checks of the various biosimilars on a timely basis so that the quality of these biosimilars can be ensured. Academic institutions can be roped in to support the cause. Also inspection SOPs specific to biologics can be created and drug inspectors can be trained on the same. Physicians and pharmacists can also be trained on a periodic basis and they can be encouraged to report cases of drug inactivity, etc to the CDSCO. The official website of the CDSCO can be upgraded so as to make more information readily available and ensure transparency in the dissemination of data.

Table I: Comparison of US, EU and Indian guidelines

	US GUIDELINE	EU GUIDELINE	INDIAN GUIDELINE
Approval pathway	351 (k) Biologics License application	1. For similar biological applications - legal basis of Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC[19,20] 2. Dossier requirements - Part II, Section 4 of the Annex I and Article 8 of Directive 2001/83/EC[21]. 3. For marketing authorization - the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I. [21]	Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India
Authorities involved	US FDA	EMA and Committee for Medicinal Products for Human Use (CHMP)	1) Institutional BioSafety Committee (IBSC) 2) Review Committee on Genetic Manipulation (RCGM) 3) Genetic Engineering Appraisal Committee (GEAC) 4) Central Drugs Standard Control Organization (CDSCO)
The kind of studies that need to be conducted	a. Analytical Studies b. Animal toxicity studies c. At Least one comparative clinical study that includes immunogenicity.	a. Comparative quality studies b. Comparative non clinical studies c. Comparative clinical studies. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product are not warranted.	a. Analytical Studies b. Preclinical Studies (Pharmacodynamic and Toxicological Studies) c. Comparative Clinical studies (Comparative PK studies)
Interchangeability guidelines	Interc Interchangeability guidelines given along with biosimilar guidelines.	Inter II Interchangeability is left to the member states of EU	Interchangeability is not mentioned in the guidelines.
Reference product guideline	a. The reference product should be a US – licensed reference product. b. For Non US licensed comparator products- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used.	a. Must be authorised in the European economic area. b. In case of a non-EEA authorised comparator, bridging data comparing all three products including analytical studies with clinical and non-clinical data should be submitted (proposed biosimilar, EEA-authorized reference product and not EEA-authorized comparator.	Reference biologic should be licensed in India or the ICH countries and should be an innovator product.

Conclusions

The emergence of biosimilars has ensured that the availability of economical drugs to every section of the Indian population. This is a good thing as it makes drugs more accessible to the deprived sections of our society. However the reduction in price should not compromise the quality of these drugs.

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