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# DEVELOPMENT OF BIOSIMILARS: AN OVERVIEW OF THE REGULATORY FRAMEWORK IN INDIA, USA, EU; MAJOR CHALLENGES AND RELATED CASE STUDIES

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**Keywords:**

Biosimilars, Biosimilar development, Extrapolation of indications, Functional similarity, Harmonization, interchangeability

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**ABSTRACT:** A similar biologic product also called biosimilar, follow-on biologic, is highly similar in terms of quality, safety, efficacy with that of the reference product. These are the pharmaceutical products used as the prime treatment options in many chronic diseases and as substitutes for the primary treatment. For development and approval, each nation has adopted its own regulations, and some countries are adopting WHO guidelines. In India Institutional BioSafety Committee (IBSC), Review Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), CDSCO are the competent authorities involved in the approval process. In EU the legal basis of Article 10(4) of Directive 2001/83/EC lays down the requirements for the Marketing Authorization Applications (MAAs) based on the demonstration of the similar nature of the two biological medicinal products. The US Biologics Price Competition and Innovation Act of 2009 (BPCIA) permits the licensing of biological products. During the development process, the biosimilar developer should consider specific parameters like the manufacturing process, demonstrating analytical similarity, which includes structural and functional similarity, interchangeability, and extrapolation of indications. In addition to these parameters, the other major hurdle for biosimilar development is the lack of harmonization of the regulations. This article covers an overview of the regulatory framework in India, USA, EU and the major challenges associated with biosimilars development with related case studies.

**INTRODUCTION:** Biologics is one of the fastest and booming industries in the pharmaceutical sector. These are complex pharmaceuticals produced by biotechnology using living systems and tissues.

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The use of Biologics started a decade ago, which brought a significant change in treating many life-threatening and chronic diseases like Psoriasis, Rheumatoid arthritis, Ulcerative colitis, and Juvenile idiopathic arthritis, Ankylosing arthritis, and others [6].

A European Commission report identified that the competition among biosimilars leads a path for additional treatment options [28]. Biologics includes different substances and products like recombinant vaccines, recombinant growth hormones, blood and blood products, growth factors, monoclonal

antibody products [7]. The development of biological products includes multiple levels like highly controlled manufacturing processes, analytical similarity assessment, biological assessments, and clinical efficacy and safety, including immunogenicity analyses. Even though biologics are used in the treatment of many diseases, they cannot be afforded by all the patients. Hence the use of these biological therapies can be increased with the development of biosimilars as these are more economical than biologics.

According to FDA, biosimilar is defined as "A biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." EMA described a biosimilar as "A medicine highly similar to another biological medicine already marketed in the EU (reference medicine)." CDSCO describes biosimilar as "A Similar Biologic is the product which is similar with regard to quality, safety and efficacy to an approved Reference Biological product based on comparability."

Biosimilars are becoming more readily accessible worldwide, as various biologic drugs are on the way to lose patent protection and laying down the path for producing the biosimilars for those reference products. The EMA has approved its first biosimilar, omnitrope, in the year 2006 [5].

In the United States, the first biosimilar was filgrastim-sndz approved in 2015. In India, the first biosimilar was approved before the US and Europe, but there was no specific guidance available at that time. Biosimilars cannot be the exact copies of the reference product but are highly similar to the originator because of their complex structure. The objective of the biosimilar development process is to establish a high degree of structural similarity with its reference product. Cutting-edge technologies must be employed to demonstrate a high degree of structural and functional similarity.

The development of a similar biologic consists of different stages namely product development and comparative analysis; process development, scale-up, and validation; clinical trials; regulatory review and approval. The regulatory requirements of these stages vary from nation to nation and have varied timelines. These stages also have an impact on the overall cost of the product [3]. **Fig. 1** represents stages during the development of biosimilars. During the product development and comparative analysis stage, the cell line of interest was created. These cell lines were allowed to reproduce the proteins of interest. The stability of these cell lines and proteins that are produced should also be validated. The manufacturing process should be validated to produce the highest yield.

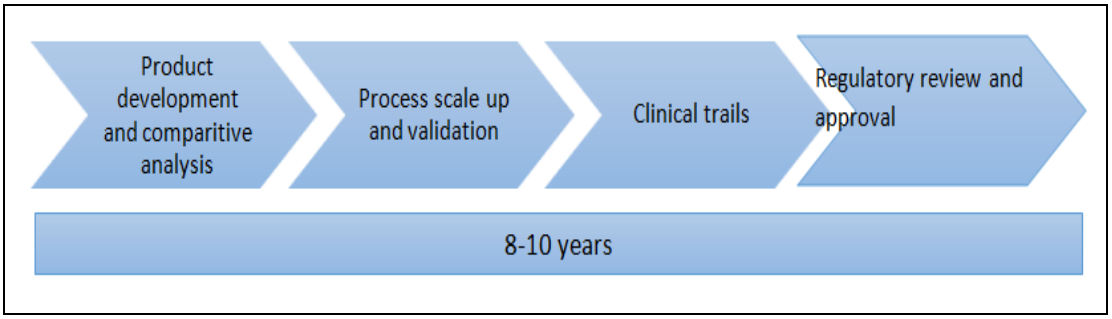


**FIG. 1: STAGES OF DEVELOPMENT OF A BIOSIMILAR**

In the clinical trials phase, the similarity of the biosimilar with the reference product should be shown in terms of clinical efficiency. Sponsors and manufacturers sometimes may face challenges at this stage in establishing the extrapolation of indications, interchangeability, and similarity assessment. After the demonstration of similarity, the product enters into the stage of regulatory review and approval.

Different nations have their own review and approval pathway. EMA issued general and product-specific guidelines. In Europe, most biotechnological products enter the market through a centralized procedure. In the US, the BPCI Act created an abbreviated pathway for the approval of biosimilars. Eight to ten years are required to complete the four stages of the development of biosimilars.

**Overview of the Regulatory Guidelines for the Development of Similar Biologics:**

**Overview of Regulatory Framework in India:** In India, CDSCO is the regulatory authority that is responsible for evaluating the quality, safety, and efficacy of drugs and drug products. As biologics and other biotechnological products are manufactured using living cells and tissues, the Department of Biotechnology (DBT), Review Committee on Genetic Manipulation (RCGM) are responsible for the preclinical development of recombinant DNA derived products.

Institutional Biosafety Committee (IBSC), Review Committee on Genetic Manipulation (RCGM), Genetic Engineering Appraisal Committee (GEAC), and CDSCO are the competent authorities involved in the approval process. CDSCO, in coordination with DBT, furnished guidelines on similar biologics in the year 2016 that addressed various aspects regarding the manufacturing process, clinical safety and efficacy data requirements for preclinical studies, clinical studies, and marketing authorization of similar biologics.

In the development of similar biologics, extensive characterization studies must demonstrate the similarity of molecular and quality attributes regarding reference biologic. If any significant differences are observed in these quality, safety, and efficacy studies, it indicates that the development process requires more extensive preclinical and clinical evaluation studies. Principles involved in the biosimilars development comprises [11]:

• Selection of the reference biologic
• Manufacturing process
• Quality-based considerations for similar biologic
• Quality comparability studies

A Reference biologic is an innovator or original product approved by the regulatory authority only after the critical evaluation of the complete dossier, including details of all the quality, safety, and efficacy aspects. During the selection of the reference biologic, the following factors are to be taken into consideration:

• It should be licensed or approved in India or any other ICH member countries

• The same reference biologic should be used throughout the development process of similar biologic

• The dosage form, strength, and route of administration of reference biologic and similar biologic should be the same

• The active ingredient in the similar biologic should demonstrate similarity with the reference biologic

To illustrate the consistency of the manufacturing process, first three consecutive standardized batches should be used. During the comparison of the similar biologic and the reference biologic, Head-to-head characterization studies are required at both drug and drug product levels. It is essential to compare the critical quality attributes (CQA) and key quality attributes (KQA) of reference biologic and similar biologic as they influence the efficacy of the product. Even 'slight differences' in relevant quality attributes can be detected through extensive analytical methods.

**TABLE 1: CDSCO APPROVED BIOSIMILARS [21]**

| Biosimilar name | Company name | Approved date | Reference product |
|---|---|---|---|
| Acellbia | Biocad | 20 June 2017 | Rituximab |
| Adfrar | Torrent Pharmaceuticals | 11 January 2016 | Adalimubab |
| Bevacirel | Reliance Life Sciences (Lupin) | 10 June 2016 | Bevacizumab |
| Filgrastim | Cadila Pharmaceuticals | 22 October 2013 | Filgrastim |
| Exemptia | Zydus Cadila | 25 September 2014 | Adalimubab |
| Biovac-B | Wockhardt | 2000 | Hepatitis vaccine |

Indian Pharmacopoeia monograph can be followed for establishing analytical similarity. Appropriately qualified assays should be followed for the measurement of quality attributes during characterization.

These qualified assays must be reproducible and reliable. The methods for measuring quality attributes for batch release, stability studies, and in-process controls should be validated following ICH guidelines (ICH Q2, Q5C, Q6B), as appropriate [12].

Some of the CDSCO approved biosimilars between 2013-2017 were included in **Table 1**. Current status of biosimilars at different stages of clinical trials in India are incorporated in **Fig. 2**.

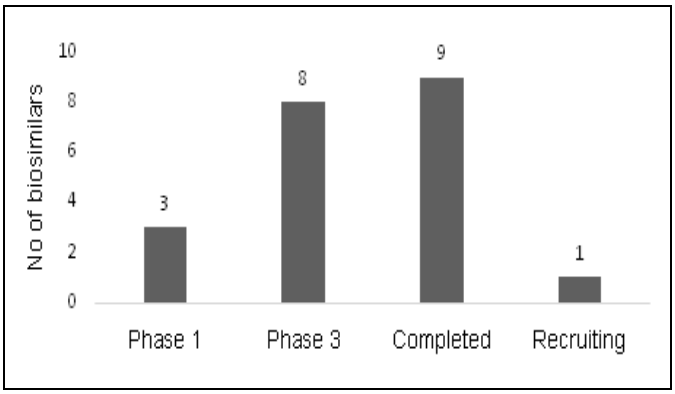


**FIG. 2: CURRENT STATUS OF BIOSIMILARS AT DIFFERENT PHASES OF CLINICAL TRIALS IN INDIA [24]**

**Overview of Regulatory Framework in the United States:** The US President enacted a bill governing the regulation of biosimilars on 23 March 2010. The permission for the licensing of biological products that are similar to licensed reference products is given by the Biologics Price Competition and Innovation Act of 2009 (BPCIA). An application pathway for follow-on biological products is provided by BPCIA and codified in 42 USC 262(k). For this purpose, the FDA established three committees to ensure consistency in the FDA's regulatory approach of follow-on biologics.

Those three committees are the Center for Biologics Evaluation and Research (CBER), CBER Biosimilar Review Committee (BRC), and the Biosimilar Implementation Committee (BIC). The CBERBRC will focus on the cross-center policy issues related to implementing the BPCI Act. To assist the industry in developing follow-on biologic products, the FDA announced three draft guidance documents on 9th Feb 2012 [2].

These documents include "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", and "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product." Some of the FDA-approved biosimilars during 2017-2020 were included in **Table 2**. Current status of biosimilars at different stages of clinical trials in US are incorporated in **Fig. 3**.

**TABLE 2: FDA APPROVED BIOSIMILARS [4]**

| Biosimilar name | Company name | Approval date | Reference product |
|---|---|---|---|
| Hulio (adalimubab-fkjp) | Mylan Pharmaceuticals | July 2020 | Humira (adalimubab) |
| Nyvepria (pegfilgrastim-apgf) | Pfizer | June 2020 | Neulasta (pegfilgrastim) |
| Avsola (infliximab-axxq) | Amgen | December 2019 | Remicade (infliximab) |
| Abrilada (adalimubab-afzb) | Pfizer | November 2019 | Humira (adalimubab) |
| Ruxience (rituximab-pvvr) | Pfizer | July 2019 | Rituxan (rituximab) |
| Zirabev (bevacizumab-bvzr) | Pfizer | June 2019 | Avastin (bevacizumab) |
| Herzuma (trastuzumab-pkrb) | Celltrion | December 2018 | Herceptin (transtuzumab) |
| Retacrit (epoetin alfa-epbx) | Hospira | May 2018 | Epogen (epoetin-alfa) |
| Ixifi (infliximab-qbtx) | Pfizer | December 2017 | Remicade (infliximab) |
| Renflexis (infliximab-abda) | Samsung Bioepis Co., Ltd | May 2017 | Remicade (infliximab) |

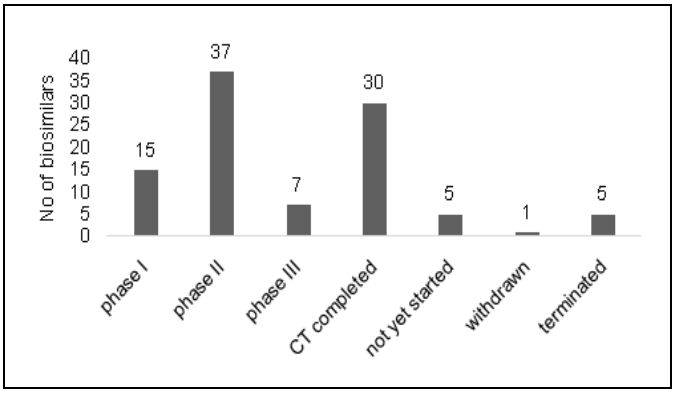


**FIG. 3: CURRENT STATUS OF BIOSIMILARS AT DIFFERENT STAGES OF CLINICAL TRIALS IN US [23]**

**Overview of Regulatory Framework in the European Union:** European Union (EU) is the first to develop a regulatory system for biosimilars. The European Medicines Agency (EMA) began officially considering scientific issues of biosimilars in January 2001. In 2003, an amendment took place in EU legislation phrasing that EC governs the requirements for marketing authorization application for European Commission medicinal products. It also established a new category of applications for biosimilars. EMA issued a general guideline on biosimilars in 2005.

This guideline is revised and published by EMA in 2011. The criteria for approval of biosimilars in EU is that the reference biologic and biosimilar should have same strength, active substance, pharmaceutical form, route of administration, and the demonstration of comparability with scientific justification in terms of quality, nonclinical, clinical efficacy [2]. A company chooses to develop a biosimilar rather than a reference medicinal product in the European Economic Area, based on a complete dossier following Article 8 of Directive 2001/83/EC as amended. In this scenario, the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I to the said Directive lays down marketing authorization application requirements, which is based on similarity demonstration of two biological medicinal products. Comparability studies generate evidence substantiating the similar nature of quality, safety, and efficacy of biosimilar and chosen reference products [26]. Some of the EMA-approved biosimilars during 2017-2020 are included in **Table 3**.Current status of biosimilars at different stages of clinical trials in EU is incorporated in **Fig. 4**.

**TABLE 3: EMA APPROVED BIOSIMILARS [20]**

| Biosimilar name | Company name | Authorization date | The active substance in the Reference product |
|---|---|---|---|
| Amsparity | Pfizer | 13 February 2020 | Adalimubab |
| Cegfila (previously pegfilgrastim) | Mundipharma Biologics | 19 December 2019 | Pegfilgrastim |
| Grasustek | Juta Pharma | 20 June 2019 | Pegfilgrastim |
| Idacio | Fresenius Kabi | 2 April 2019 | Adalimubab |
| Fulphila | Mylan Pharmaceuticals | 20 November 2018 | Pegfilgrastim |
| Herzuma | Celltrion Healthcare | 9 February 2018 | Transtuzumab |
| Mvasi | Amgen | 15 January 2018 | Bevacizumab |
| Blitzima | Celltrion Healthcare | 13 July 2017 | Rituximab |
| Erelzi | Sandoz | 27 June 2017 | Etanercept |

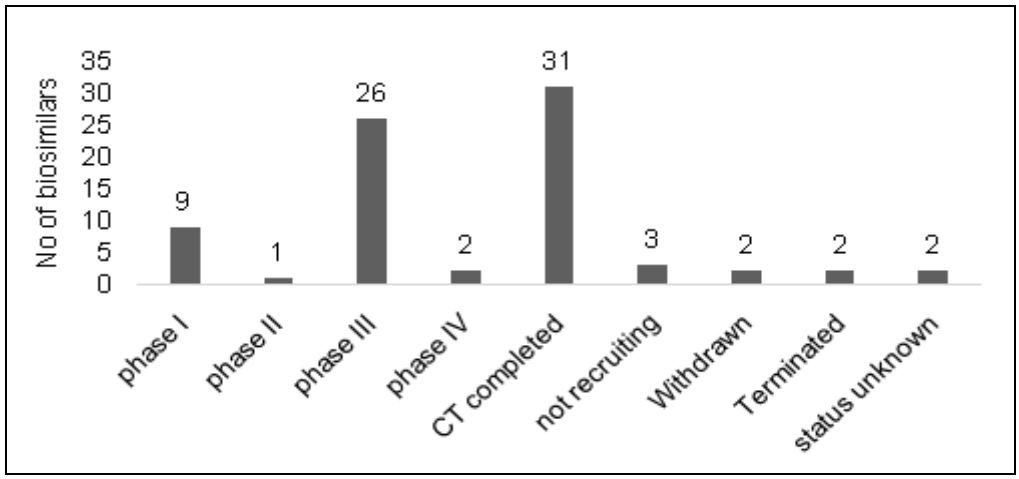


**FIG. 4: CURRENT STATUS OF BIOSIMILARS AT DIFFERENT STAGES OF CLINICAL TRIALS IN EU [22]**

**TABLE 4: COMPARISON OF BIOSIMILAR REGULATIONS IN INDIA, US, EU**

| Parameter | India | US | EU |
|---|---|---|---|
| Definition | A Similar Biologic product is similar in terms of quality, safety, and efficacy to an approved Reference Biological product based on comparability. | A biological product that is highly similar and has no clinically meaningful differences from an existing FDA approved reference product | Medicine is highly similar to other biological medicine already marketed in the EU (reference medicine). |
| Term | Similar biologics | Follow-on biologics | Biosimilars |
| Statutory body | RCGM and GEAC of CDSCO | BPCIA | CHMP of EMA |
| Reference product | Authorized in India or any ICH member countries | Authorized in the US | Authorized in EU |

| | | | |
|---|---|---|---|
| Guidance | Guidelines on similar biologics: Regulatory Requirements for Marketing Authorization in India, 2016 | "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", "Quality Considerations in Demonstrating Biosimilarity | Directive 2001/83/EC |
| Pre-litigation procedure | Absent | Present | Absent |
| Interchangeability | Absent | Present | Absent |
| Data exclusivity | Not specified | 12 Years, A section (k) application may not be filed until four years after reference product approval | 11 Years, comprising ten years for new biologics and a 1-year extension For a further indication |
| Data requirements | Biological activity, preclinical studies, clinical studies, immunogenicity studies, extrapolation of indications, Biosimilarity demonstration | Analytic data that show similar to the reference, animal studies, clinical studies, the identity of the mechanism of action | Purity, Physiochemical properties, Biological activity, Clinical studies, Preclinical, and Immunogenicity studies |
| Stability requirements | Long term and accelerated | Long term and accelerated | Accelerated and under physical stress conditions |

A comparison of Biosimilar regulations among India, US, EU was made in **Table 4**.

Number of biosimilars approved till 2019 in India, US, EU was represented as a pie diagram in **Fig. 5**.

First approved biosimilars in India, US, EU till 2019 was given in **Table 5**.

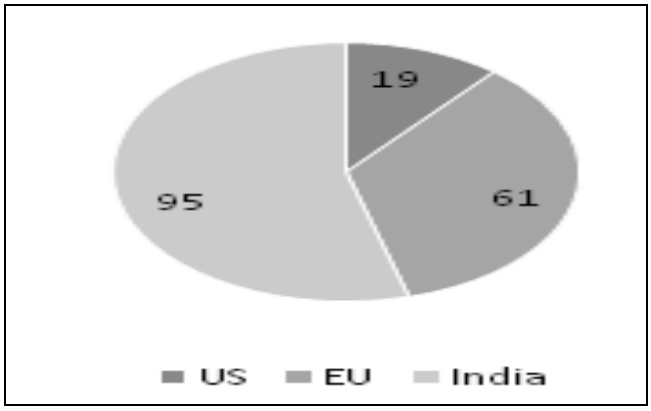


**FIG. 5: NUMBER OF BIOSIMILARS APPROVED IN INDIA, US, EU TILL 2019** [20]

**TABLE 5: FIRST APPROVED BIOSIMILARS IN INDIA, USA, AND EU**

| Country | Company name | Biosimilar | Year |
|---|---|---|---|
| India | Wockhardt | Biovac-D | 2000 |
| US | Sandoz | Zarxio | 2015 |
| EU | Sandoz | Omnitrope | 2006 |

**Major Challenges Associated with the Development of Biosimilars:**

**Manufacturing Process:** Manufacturing techniques should be in compliance with current good manufacturing practices (cGMP), ICH guidelines like Q8 (Pharmaceutical Development) Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality System), Q11 (Development and manufacture of drug substances-chemical entities, biotechnological/ biological drugs). Biologics are manufactured using living organisms like yeast, bacteria, and other mammalian cell lines. The Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/ 49348/ 2005) describes the quality requirements for a biosimilar. One part of this guideline is devoted to the manufacturing process.

Each biosimilar is defined by (a) the physico-chemical characteristics and quality attributes of the reference medicinal product already on the market and (b) the manufacturing process designed to yield the biosimilar medicinal product. This data can serve as a basis for creating the new product's manufacturing process, defining the quality attributes, and predicting how these may affect overall safety and efficacy [9].

Different factors, like appropriate genetic sequence, selection of vector, cell expression systems, quality control, and purification systems, affect the structure of the biological product [8]. Biosimilar developers must demonstrate that their products maintain consistent quality manufacturing through state-of-the-art methods, which are sufficiently similar to the reference product. Three main steps that includes in the manufacturing process of a biological product are as follows [1]:

• Cell expansion and expression
• Protein isolation and purification
• Formulation and drug product packaging

The complete manufacturing process of reference biologic is not unveiled by the innovator. It is the property of the innovator even after the patent expiry. Hence the biosimilar manufacturer must develop his own manufacturing process by reverse-engineering the reference product to produce a highly similar product.

It has been possible to synthesize identical versions of individual small peptides, for which the amino acid sequences have been determined [1]. For example, the glycosylation pattern of granulocyte colony-stimulating factor (G-CSF) and interferon-γ can be different in different expression systems.

Another example is EPO (erythropoietin), a molecule that has immunogenicity issues, in some cases, due to minor changes in the manufacturing process of the final product.

However, this safety issue concerns an originator. Thus, small changes in the manufacturing process may change the product's characteristics, with a drastic impact on clinical outcomes.

A change in the manufacturing process occurs for various reasons, for instance:

• Scaling-up of the process
• Improving the efficiency of the process
• Modernizing the process
• Replacement of the equipment used in the process

Usually, it is not recommended to bring any changes to the biosimilars manufacturing process than their original counterpart. Minor differences are allowed as long as they do not result in clinically meaningful differences concerning safety, purity, and potency compared with the reference product [31]. Sometimes the changes in the manufacturing process may also lead to post-translational modifications [30]. Moreover, modifications can also improve the manufacturing process's quality, efficiency, and reliability or end-product. In these cases, further nonclinical and clinical evaluations might be needed to evaluate the product, depending on the extent of modifications brought [32]. Monitoring and controlling all aspects of the production of biosimilars should give utmost importance [29].

**Recommendation:** By using advanced technologies in the manufacturing process of biosimilars, the extent of post-translational changes can be reduced. As a result, the extent of similarity with the reference biologic can also be increased.

Hence, biosimilars manufacturers, if they use advanced technologies in the manufacturing process compared to reference biologic, may quickly get regulatory approval. Regulatory agencies also expect that the biosimilars developers use advanced technologies in their processes.

**Structural and Functional Similarity:** A high degree of structural and functional similarity between the biosimilar and reference products can be achieved through extensive characterization, which informs an iterative process development. Structural and analytical similarities should be established in terms of isomers and function. Single analytical test or nonclinical/clinical study was not sufficient to demonstrate a high level of similarity of a biosimilar with a reference biologic.

For establishing equivalence at the molecular level, different analytical methods are required. An analytical similarity assessment (structural and functional similarity) investigates structural and functional elements such as primary structure, glycosylation, post-translational modifications, purity, charge heterogeneity, and higher-order structure as bioactivity features impact the clinical properties of the proposed biosimilar [17].

**Case Study:** Structural and functional similarity assessment of Rituximab

**Background:** Rituximab is used for the treatment of cancer (B cell lymphoma), immune-mediated inflammatory disease (Rheumatoid arthritis, Wegener's granulomatosis).Analytical similarity exercise was performed with a chimeric mouse/ human monoclonal antibody biotherapeutic, five biosimilars of rituximab (Ristova, Roche) accessible on the Indian market [18].

The techniques used for the structural and functional characterization of Rituximab were listed in **Table 6**.

**TABLE 6: TECHNIQUES USED FOR STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF RITUXIMAB**

| Structural characterization | | |
|---|---|---|
| **Categories** | **Attributes** | **Technique** |
| Primary structure | Intact mass | ESI-TOF-MS |
| | Peptide mapping | ESI-TOF-MS after trypsin digestion |
| | N-glycan profiling | QTOF-MS after procalnamide digestion |
| High order structure | Secondary structure | CD Spectroscopy |
| | | FTIR Spectroscopy |
| | Tertiary structure | Fluorescence spectroscopy |
| Size heterogeneity | LMWs | SDS-PAGE |
| | Aggregates(HMWs) | SE-HPLC |
| | Particle size distribution | DLS |
| Charge heterogeneity | Acidic and basic variants | CEX-HPLC |
| | Functional characterization | |
| Fab-related functional activity | Binding to CD20 | FACS |
| Fc-related functional activity | Cell-based assay | ADCC |
| | Cell-based assay | CDC |
| | Binding to CD16a | SPR |

ADCC - antibody-dependent cell-mediated cytotoxicity, CD - circular dichroism, CDC - complement-dependent cytotoxicity, CEX-HPLC - cation exchange-high performance liquid chromatography, ESI-TOF-MS -electrospray ionization-Time-of-flight-mass spectrometry, FACS - fluorescence-activated cell sorting, FTIR - Fourier transform infrared, Q-TOF - Quadrupole-Time of Flight, SDS-PAGE - sodium dodecyl sulfate-polyacrylamide gel electrophoresis, SE-HPLC size exclusion-high performance liquid chromatography, SPR surface Plasmon resonance

**Observation:** The evidence states that biosimilars showed similarity for protein structure and function, and there were notable differences for charge heterogeneity, size heterogeneity, and glycosylation pattern.

**Recommendation:** Analytical evaluation is a far more sensitive tool in assessing similarity than clinical studies in the development of biosimilars.

**Interchangeability:** The medical practice of exchanging one medicine for another expected to achieve the same clinical effect is called Inter-changeability. It means that a reference product can be replaced with a biosimilar, or one biosimilar can be replaced with another. Interchangeability can be done through either switching or substitution [14]. Switching is the prescriber's decision to exchange one medicine with another with the same therapeutic intent in a given patient. The practice of dispensing one medication instead of another equivalent and interchangeable medicine done at the pharmacy level without consulting the prescriber is called substitution (automatic). Interchangeable products and biosimilars are distinguished only by the USA, which is laid down in the Biologics Price Competition and Innovation act of 2009. The authority to designate biologics to be interchangeable and thus substitutable is taken by the FDA only if permitted by state laws. In May 2019, FDA released a finalized guidance 15 document describing interchangeability requirements which covers four major topics:

• Data and information required to support interchangeability demonstration

• Design and analysis considerations of a switching study or studies that support interchangeability demonstration

• Comparator product considerations in a switching study

• For proposed interchangeable products, abbreviated considerations for developing presentations, container closure systems, and essential parts of a delivery device.

In US, no interchangeable products are approved till now [13]. EMA has abstained from taking an official position on biosimilars interchangeability.

It is the responsibility of the member states to guide prescribers and prescribing practices regarding the interchangeable products. It also does not make a distinction between interchangeable products and biosimilars.

**Case study:** Systematic review of efficacy and safety of switching patients between reference and biosimilar infliximab

**Background:** A Biosimilar version of widely prescribed drugs like infliximab, a tumor necrosis factor antagonist, is increasing dramatically. Since biologics and biosimilars are not identical copies, it is necessary to demonstrate that switching between a reference biologic and biosimilars is safe and efficacious through scientific justification. As stated by the US FDA, studies must demonstrate that even after multiple switches between products, biosimilars must remain equivalent or non-inferior to a reference product to establish Interc-hangeability [16].

To collect the evidence evaluating the safety and efficacy of switching between reference and biosimilar infliximab patients with inflammatory disorders including Crohn's disease, rheumatoid arthritis, ulcerative colitis, plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis were chose for this study.

**Methods:** By searching the MEDLINE database, published studies presenting data on switching between reference and biosimilar infliximab were identified. By exploring the EMBASE database, Congress abstracts were identified.

**Observation:** A total of 149 abstracts and 113 journal articles were found. In this analysis, 70, which were considered to be relevant, are included. Most of these publications were uncontrolled, observational studies. Six randomized, controlled trials data were identified. Evidence revealed no clinically significant safety or efficacy signals associated with switching.

**Recommendation:** Based on current evidence, as there is no increase in safety, efficacy, and Immunogenicity between similar biologic and reference biologic so that interchangeability studies can be skipped to an extent.

**Extrapolation of Indications:** When applying for a biologics license, the 351(k) biologics license application (BLA) pathway has a significant advantage when compared to the 351 (a) biologic pathway of the originator, which creates an opportunity for extrapolation of indications beyond those that are directly studied. Pursuing the 351(k) pathway, the sponsor need not conduct clinical studies for every indication proposed for a biosimilar, which is not possible in the case of 351(a). Licensure for additional conditions of use for a proposed product other than which reference product is licensed may be obtained if the sponsor provides "sufficient scientific justification for each indication for which licensure is sought."

The scientific principle that protein structure determines the molecular function and, ultimately, clinical PK/PD, efficacy, and safety of the biological drug is the underlying rationale behind extrapolation [10].

This concept is successfully implemented with biosimilars of EPO, filgrastim, and infliximab in Europe [8]. FDA has provided recommendations related to clinical data extrapolation across indications as a part of guidance for biosimilars development. During phase 3 of a clinical trial, human volunteers should be selected in such a way that clinically meaningful differences in safety and effectiveness between biosimilar and reference products are more likely to be detected. This selection will remain the key consideration for extrapolation [6].

**Case study:** Based on the infliximab biosimilar CT-P13

**Background:** CT-P13 (Remsima, Inflectra) is a biosimilar of infliximab. It is a human–murine, chimeric monoclonal antibody (mAb) against tumor necrosis factor (TNF) that is used in the treatment of several immune-mediated inflammatory diseases (IMIDs) [19].

The EMA approved CT-P13 in September 2013 for all indications held by the infliximab RMP (Remicade), namely rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (PsO), adult and pediatric Crohn’s Disease (CD) and adult and pediatric ulcerative colitis (UC). Health Canada granted approval of CT-P13 only for the treatment of RA, AS, PsA, or PsO but not for inflammatory bowel disease (CD and UC). Such discrepancies in regulatory approaches create uncertainty in the scientific validity of extrapolation in biosimilar development.

**Method:** This case study begins by considering the physicochemical characterization of two infliximab molecules and the role of TNF and TNF antagonists in the pathogenesis and treatment of IMIDs as a means to explain the rationale for extrapolation of the clinical data for CT-P13 to IBD indications.

**Observation:** CT-P13 is effective in approximately 518 patients with IBD; differences between CT-P13 and RMP have been reported from comparing 14 patients treated with CT-P13 and 22 patients treated with RMP in Ireland. Taken together, data from studies that have evaluated the use of CT-P13 in patients with IBD suggest that this biosimilar is effective and generally well tolerated.

In the case of CT-P13, evidence from preclinical MOA (Mechanism of action) studies and clinical PK studies appears to support the use of this biosimilar in IBD. Evidence emerging from studies involving 'real-life' use of CT-P13 in patients with CD and UC is in line with the conclusion that this biosimilar is effective and well-tolerated in these populations.

**Recommendation:** Extrapolation of clinical data can decrease or omit the need for studies in multiple indications, and hence, may increase access to biosimilars quickly.

**Nomenclature:** The International Nonproprietary Names (INN) has been assigned to biological products for the last 5-6 decades to get global recognition by a unique name. Products are named for their function or structure, and product-specific letter groups, called stems, help health professionals easily recognize the compound. For understanding, the stem for EPO molecule is –poietin, while for synthetic polypeptides with a corticotrophin-like action is -actide.

However, protein structures are increasing in complexity, and also the manufacturing processes may make these molecules structurally, biologically, or even immunologically different from the natural proteins. The system of INN creates complexity in the case of biosimilars. This system of INN is being used only by few regulatory authorities where as other nations consider a distinct nonproprietary identifier for biosimilars. For instance, Japan and Australia add a qualifier that is usually short and separate, and sometimes it can include the name of the manufacturing company [10].

Recently WHO has proposed the Biological Qualifier (BQ) scheme to avoid the proliferation of separate and distinct national qualifier systems [25]. To all biological substances assigned INN's, it is applied retrospectively and prospectively, which can be adopted voluntarily by any Regulatory Authority. BQ scheme will give a code of four letters at random to complement the INN for a biological compound. It will uniquely identify the manufacturing site and manufacturer of the active substance directly or indirectly in a biological product. But this BQ system was suspended.

**Observation:** Giving a unique name to biosimilars internationally will avoid confusion among regulatory authorities, prescribers, and consumers. By providing unique identifier, tracking of the biosimilars can be done effectively during pharmacovigilance.

**Harmonization of Regulations:** Biosimilars are facing a particular challenge regarding interc-hangeability, because it has been addressed in different ways in the US and across the EU. However, the concept of Biosimilarity is well-understood by all major regulatory agencies; rarely differences may arise in the scientific interpretation of a biosimilar development program or application. Regulatory agencies may have different ideas about the adequacy of Biosimilarity margins, one *vs.* two assay approaches, and the need for animal studies, local patient inclusion in clinical trials, or the use of locally-sourced comparator products. Suppose there is not enough communication between the company and the regulator(s), in that case, a company could find it needs to obtain additional data to receive approval in different countries [10].

But the industry has begun to observe movement toward greater alignment among key regulatory agencies. In a theme addressed at the Drug Information Association Biosimilars event in October 2016, the FDA coined the term "scientific alignment" to describe the move toward scientific unification amongst regulators. The FDA avoids using the word "harmonization" because this would

imply that guidelines and regulatory documents are identical amongst all nations, which is highly unlikely to occur. One strategy established to strengthen consensus among agencies is "The Biosimilars Cluster" launched in 2011; Health Canada, FDA, EMA, and the PMDA are included in this cluster [27]. This group meets several times a year to discuss development challenges and the scientific and regulatory issues that may arise as agencies are receiving the same candidate's applications.

In addition to the cluster, the FDA and EMA have established a program to provide parallel scientific advice to sponsors. Through this program, a sponsor can request a parallel review between the agencies to address a specific question or issue that may arise within a development program (EMA and FDA 2017). Many of these questions may appear because there are no existing guidelines or differences between the two agencies' policies (EMA & FDA). This program aims to encourage communication between the FDA and EMA and promote sharing information and perspectives. It is also expected to provide the requirements clearly to the sponsor and understand any differences in opinion about moving the development process forward.

**Recommendation:** By bringing harmonization in regulations across the world helps the manufacturers to get approval quickly. If the biosimilar is approved in one country and need not conduct clinical trials in other countries, this results in cost reduction. By this, biosimilars can quickly enter the market, and their availability to patients also increases.

**CONCLUSION:** Biosimilars are one of the essential pharmaceutical products that have a wide range of applications. The patent expiration of many biologic drugs has led to a pathway for biosimilars' evolution, and many biologics are on the line to lose their patent protection in the coming years. The critical consideration for the approval of biosimilars is the demonstration of Biosimilarity with the reference product. The Biosimilarity should be established based on the totality of evidence throughout the development stage. FDA states that the Biosimilarity with the reference product should be in a range of 80-120%. Compared with biological products, these biosimilars are less expensive because there is no necessity to conduct complete clinical trials by the biosimilar developer. Different nations have adopted country-specific guidelines for the development of biosimilars. Biosimilar developers are facing many obstacles due to a lack of harmonization. The harmonization of regulations internationally helps the biosimilar developer to overcome regulatory challenges like Inter-changeability, extrapolation of indications, and the cost reduction of biosimilars. The disclosure of some steps in the manufacturing process by the reference product manufacturer may also help the biosimilar developer. Using advanced technology in the manufacturing process, limiting the patent litigations, and creating awareness among the patients and physicians regarding the switching from biologics to biosimilars leads to more market for biosimilars.

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