BIOSIMILARS AND IDENTIFICATION OF BIOSIMILARITY

Submitted in the fulfillment of requirements for the degree of

MASTERS OF SCIENCE IN BIOTECHNOLOGY
By:

SHEFALI (197810)

Under the Supervision of
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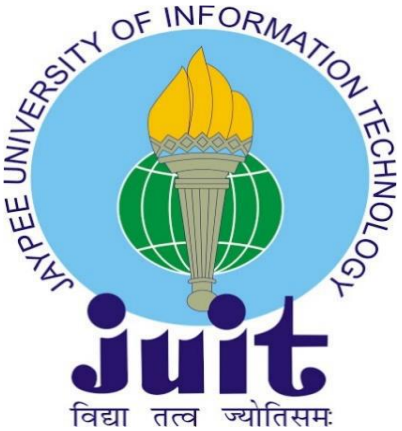

JAYPEE UNIVERSITY OF INFORMATION TECHNOLOGY
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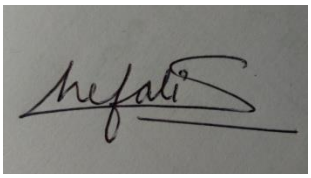
MAY 2021

Tables and figures:

DECLARATION BY STUDENT

I hereby declare that the project work entitled "Biosimilars and Identifying Biosimilarity" submitted to the Department of Biotechnology and bioinformatics, Jaypee University of Information Technology Solan (H.P), is an authentic record of original work done by me. The work was carried out under the guidance of Dr. Udaybanu Malairaman.

Shefali Sharma (197810)



Department of Biotechnology and Bioinformatics

Jaypee University of Information Technology

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Date: 17.06.2021

SUPERVISOR'S CERTIFICATE

This is to certify that the work titled "Biosimilars and Identifying Biosimilarity " by Shefali Sharma during the end semester in June 2021 in fulfilment for the award of degree of Masters of Technology in Biotechnology of Jaypee University of Information Technology, Solan has been carried out under my supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of any degree or appreciation.

Signature of Supervisor

Name of supervisor: Dr Udaybanu Malairaman

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This is to certify that the above statement made by the student is true to the best of my knowledge.

ACKNOWLEDGEMENT

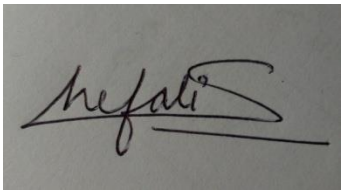
I consider myself particularly lucky in the pursuit of this scholastic goal because inspiration, guidance, direction, cooperation, love, and care all came my way in spades, and it seems nearly difficult for me to adequately thank for the same.

My heartfelt gratitude to Dr. Udayabanu Malairaman, Associate Professor, and Dr. Narendra, (former) Assistant Professor, Department of Biotechnology and Bioinformatics, JUIT Waknaghat, for their expert guidance, unwavering support, inspiration, and constructive criticism throughout my research.

I acknowledge with thanks, the kind of patronage and timely guidance of **Dr. Sudhir Kumar Syal**, Head of Department of Biotechnology and Bioinformatics, Jaypee University of Information Technology, Waknaghat (H.P.).

Also, I'd want to express my gratitude to the entire Department of Biotechnology and Bioinformatics for granting me permission and providing me with the required administrative support during my research.

Date: 17.06.2021



Shefali Sharma _____

1.0. Abstract

Drugs developed by complex molecules of living cells either plants, animals, human cell lines or microorganisms are called biologics. These biologics are specific, patented, approved by FDA and are considered better than generic drugs which are made from chemical synthesis in terms of targeting and side effects, these medications have their fair share of value in the market which makes it difficult to be available for fair prices. In this scenario, biosimilars are the drugs that play vital role by fulfilling the clinical function of its reference drug while being cost effective. Biosimilars are the drugs developed highly similar yet not identical to reference drug such that it plays similar functions as biologic in terms of efficiency and safety. Biosimilars and biologic drugs come in a variety of ways, including monoclonal antibodies and growth factors. Their ability to precisely target signaling pathways and cells is revolutionizing the fight against cancer and inflammation, among other diseases. Biosimilars, as potential substitutes for reference biologics, can help to expand treatment options and meet the increasing demand for biologic therapies. There are certain set of criteria to consider developing a biosimilar. Bio-similarity is identified by a series of analytical techniques with additional orthogonal techniques to test the proposed similarity with the reference. These methodologies are governed by parameters set by FDA to ensure the safety and efficiency of the biosimilar for treatment of purposed disease.

2.0. Introduction

Biologics are the medicines made from complex molecular structures obtained by living organisms through manufacturing under controlled conditions. [3] Medicines such as gene/cell therapies, therapeutic protein, monoclonal antibodies and vaccines are developed by complex biological background. There are drug developed highly similar but not identical to the original patented/FDA approved brand of drug which is called biosimilar. It is a duplication of a known drug to accomplish the same therapeutic and clinical results such that it consist the quality, efficiency and safety of the reference product.

Monoclonal antibodies, which are essential for treating a variety of immunological and malignant disorders, are among the biosimilars available in India. Growth factors such as erythropoietin and granulocyte colony stimulating factor, also known as G-CSF, and human

insulin which is use for the treatment of diabetes are also biosimilars available in India. [2] Biosimilars have been available in Europe for over a decade; the first guidelines for biosimilar development were published in 2005 and have been regularly updated and modified in regard to quality, clinical and non-clinical requirements; there are also product or class-specific guidelines for certain molecules.[1]

Biosimilars have a large market need and are becoming more affordable in both the global and domestic markets. The demand for biological drugs is increasing in today's world. Due to competition in the prices of the drugs biosimilars comes with an advantage as they are available at affordable prices in the market because there is less investment in clinical trial phase I and phase II, which makes biosimilar available at lower prices than the original product, posing a low market risk. [2]

Biologic products have extremely complex molecular structure made from living cells using a variety of techniques. Physical, chemical, biological, or microbiological properties of a biologic are the best way to understand its complexity; we call these properties as quality attributes. [4] The essential quality attributes (CQAs) of these molecules can change due to post-translational modifications in the cell cytoplasm or can also be changed during the drug manufacturing. [3] Variations in these important quality attributes between the reference product and the possible biosimilar to ensure biosimilarity. [3] At any point of the manufacturing process, changes in attributes can occur, and even minor changes in the process can alter and affect the study's bio-similarity, which may cause an impact on clinical efficacy as well as the safety of drug.[3] Bio-similarity must be established first through series of extensive analytical comparability trials, which involves a systematic approach for evaluation of the quality of bio-similar product and similarities within the reference drug and potential biosimilar, using a series of biological, physicochemical, and pharmacological CQAs.

The purpose of this paper is to understand biosimilars, manufacturing of biosimilar drugs and what factors are necessary for the characterizing and evidencing similarity between the reference biologic drug and the potential biosimilar. Moreover, understanding the issues concerning the use of biosimilars and factors affecting them and finally, looking around the current scenario of biosimilars in Indian pharmaceutical industry with respect to other countries.

3.0. Methods and Methodologies

3.1. Production framework for biosimilars

Detecting the desired biosimilar's DNA sequence, extracting it, injecting in a vector, and eventually incorporating the vector inside a suitable host cell's genome, which may be a bacterium or a mammalian cell, is the first step in the creation of a biosimilar. [11] Bacterial as a host are cheap and easy to grow, and produce a high yield. However, they are unable to generate huge, complex proteins like MAbs (monoclonal antibodies). [11] Mammalian cells, on the other hand, have low product yield, but however are more fragile and expensive. [11] A master cell colony is synthesized which consists of identical cells which produces protein that is desired, this is done by a series of cell screening and selection. [11] To enhance protein output, this cell culture bank is utilized to develop more cells at a greater scale under well controlled conditions.

Undesired byproducts such as proteins or impurities are separated from the supernatant during downstream processing. To verify for consistency in the 3-D structure and potency of harvested protein, there are numerous analytical methodologies which revolve around biological and physicochemical properties based assays. [11] Finally, additives such as osmotic agents, antioxidants, and buffers are added to the purified medicinal product, which is then contained in external packaging, and kept and supplied under strict conditions. [11]

Some biosimilars uses various kinds of expression systems than their reference pharmaceuticals which may change the posttranslational modifications of a protein, such as glycosylation, altering the product's safety and effectiveness. [11] Different vectors are used to manufacture host cells, where as different systems are used for the screening and selection the cells to make a bank of master culture, various techniques used for the synthesis and purification of the cells, and excipients are all examples of biomanufacturing phases that might affect a product's efficacy and safety. [11] As a result, manufacturers of biosimilar products should analyze the effects of alterations with the help of appropriate analytical techniques, clinical studies, and functional

assays to verify the purity, consistency, identity, efficacy, potency, and effectiveness of their medicines such that they are not jeopardized. [11]

3.2. Reference Standard Selection

The European Medicines Agency (EMA) has developed specific guidelines for the use of reference criteria for biological medicinal products that are identical. [11] To speed up the global production of biosimilars and avoid time consuming clinical trials, an applicant must compare the biosimilar with a reference drug which has not been approved in EEA (European Economic Area) in some clinical tests and in vivo nonclinical animal studies. European Economic Area, is however a regulatory authority with identical science and regulatory requirements should approve the comparator. [11]

If an applicant conducts simultaneous production for Europe and the United States, the EMA biosimilar guidelines state that US reference criteria must be included. [11] Data from empirical investigations, such as structural information and functional information, compare three important aspects that are biosimilar which has been proposed, reference product under EU, and US standard for comparison, that will always be required as bridge data in science. [11] They may also have pharmacodynamic, clinical and pharmacokinetic data for the transitional trials for the three medications. [11]

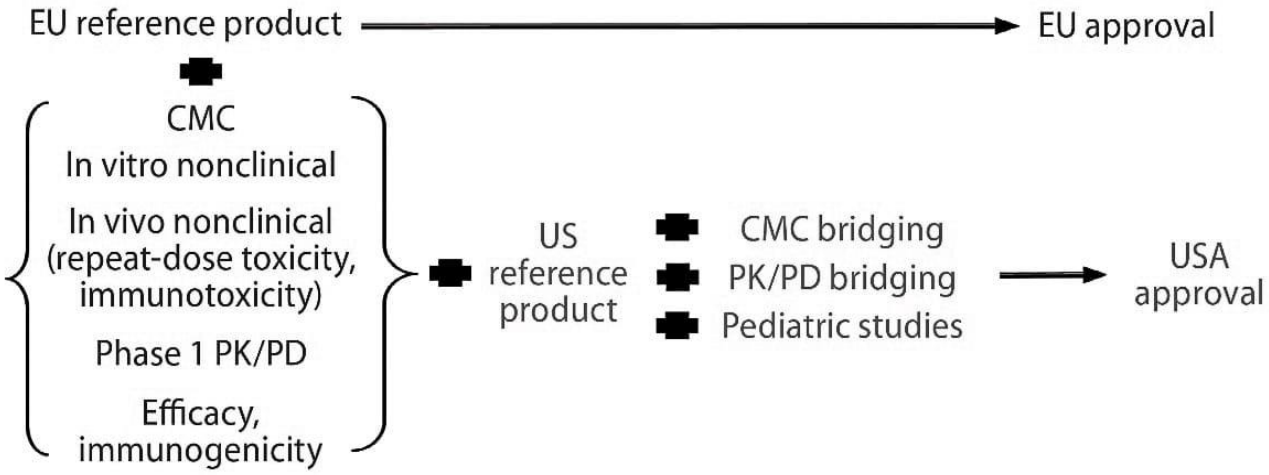


Figure1: Requirements for reference standard [11]

3.3. Attributes in consideration for bio-similarity

Demonstrating similarity between the reference and studied compound first starts with molecular attributes. Because complex biologics may have a lot of essential quality attributes and reference biologics consists of high level of intrinsic variability in the manufacturing phase, the initiation of the biosimilar development is with a detailed characterization of as many of the reference drug's quality attributes as feasible, as well as a list of the variations in each characteristic. [3] The analysis of physicochemical attributes characterizes primary structure, secondary structure, glycosylation and purity and functional attributes which helps us understand the mechanism of action of the molecule and biological activity which is intended. Biological assays supplement structural studies by identifying the possible impact of structural changes between biosimilars and reference biologics on product efficacy or safety. [3] With today's scientific standards, *in vitro* tests and techniques have specified sensitivity to find out differences between closely associated molecules for more precise results. [3] The fingerprint of the reference product is created by combining all of the specified properties of the molecules under test, and it provides

us with a framework to begin detecting bio-similarity of the biologic against which a new biosimilar is identified and manufactured. [3] The following phase in the biosimilar manufacturing is to create a match with the fingerprint obtained by comparing each and every attribute one by one to ensure that the biosimilar can reverse engineer to meet identical standards.

Orthogonality is a key concept for fingerprinting for comparing multiple layers of attributes of the potential biosimilar and its reference drug. [5] With the use of orthogonal statistical methods, which means attribute vectors are viewed as a dot product of vectors, various mapping techniques or fingerprinting is used to construct a big fingerprint algorithm that includes attributes of the product and their relatively high sensitivity and specificity. [5] The patterns that are formed can show undetected structural differences between the products that lead to residual uncertainty regarding biosimilarity. [5]

3.4. Orthogonal and overlapping methods

Physicochemical characterization are performed along with post-translational modifications which forms a complete sequenced fingerprint helping in development of biosimilars and also these characterization helps to evaluate quality as well as purity of different attributes of the products. [8] With the use of several methodologies, a comparison is performed between attributes of reference and suggested biosimilar using substantial information about the primary structure, secondary structure, as well as tertiary structure of both the drug molecules under assessment.[8] To identify an appropriate analytical method for analysis we can obtain guidance from ICH Q6B guideline. [8] The ICH Q6B document is a set of global standards for biotechnology products and biological products generated for new commercial purposes.[8] There are many methods which can be used to collect information of protein structures one such method is SDS–PAGE which characterizes the size, aggregates, and disulfide bond formation variability of the test molecule and can provide information on many protein properties. [8] Isoelectric focusing is another method that provides data on isoform patterns which can also showcase variations in deamidation and glycosylation. The elements that determine the specific

description of the test substance will vary depending on the individual molecule, necessitating procedures that compare the size, shape and charge of the molecules. [8]

Mass spectroscopy is one of the most useful and versatile technique. Mass spectrometry provides information on intact molecular weight, structure confirmation with the help of mass mapping techniques, sequence using MS/MS. [8] MS also offers information on data like posttranslational modification such as glycosylation, disulphide bridging, and heterogeneity information.

Circular dichroism is a valuable tool for measuring protein folding that may also be used to compare the secondary structure as well as tertiary structures of the test compound. [8] Nuclear magnetic resonance (NMR) with high resolution is a vital method for obtaining precise information on protein structure and dynamics. Recent advances in acquisition and analysis have now allowed visualization of whole protein at natural abundance making NMR an ideal technique for similarity assessment of biologics and biosimilars, also it enables evaluation of the structure of therapeutic drugs, without modification, in physiologically relevant conditions.

In different cell lines of a biologic product variability is unavoidable which should have careful comparative studies which is very essential to convince regulators that the biosimilar has bio-similarity, is safe and effective. For such deep analysis multiple orthogonal analytical techniques are performed to both the reference product and the potential biosimilar, these orthogonal techniques including functional studies, fully fledged fingerprint of biosimilarity can give confidence in the test results that patients will not be negatively affected by the biosimilar and i.e. they can be prescribed a biosimilar instead of the original biologic drug.

Stability-indicating characteristics are an important part of structural characterization of biologic products and the development of reliable methodologies for incorporating in the stability program. [6] Other approaches are necessary to verify long-term similarity with the complete molecular fingerprints of the test substances, in addition to the standard stability-indicating method. [6] Assessments of secondary and tertiary fold and epitope availability, likelihood for aggregation by disulfide scrambling and misfolding, post-translational alterations which includes site specific glycosylation, and charge-variant spectra are among the methodologies and properties of particular criteria for stability indication.[6]

3.5. Evidencing bio-similarity

For the determination of bio-similarity both clinical and non-clinical data are considered. The basic approach for the biosimilar fingerprint is the statistical approach which will demonstrate the analytical similarity between the two products. However some attributes has more value than the others.[1] Data with highest importance represents critical quality attributes which includes statistical equivalent tests series to prove comparability, and the FDA recommends that these should include those attributes that pose the highest risk when different. For example protein's glycosylation pattern in some molecules which means the presence of sugars (oligosaccharides) attached to certain protein content (amino acid residues).[1] Next to the most important attributes less critical, and an appropriate quality ranges based on standard deviations. Some quality attributes are less least critical and that's why graphical or raw data are likely to be sufficient enough for bio-similarity analysis. [1]

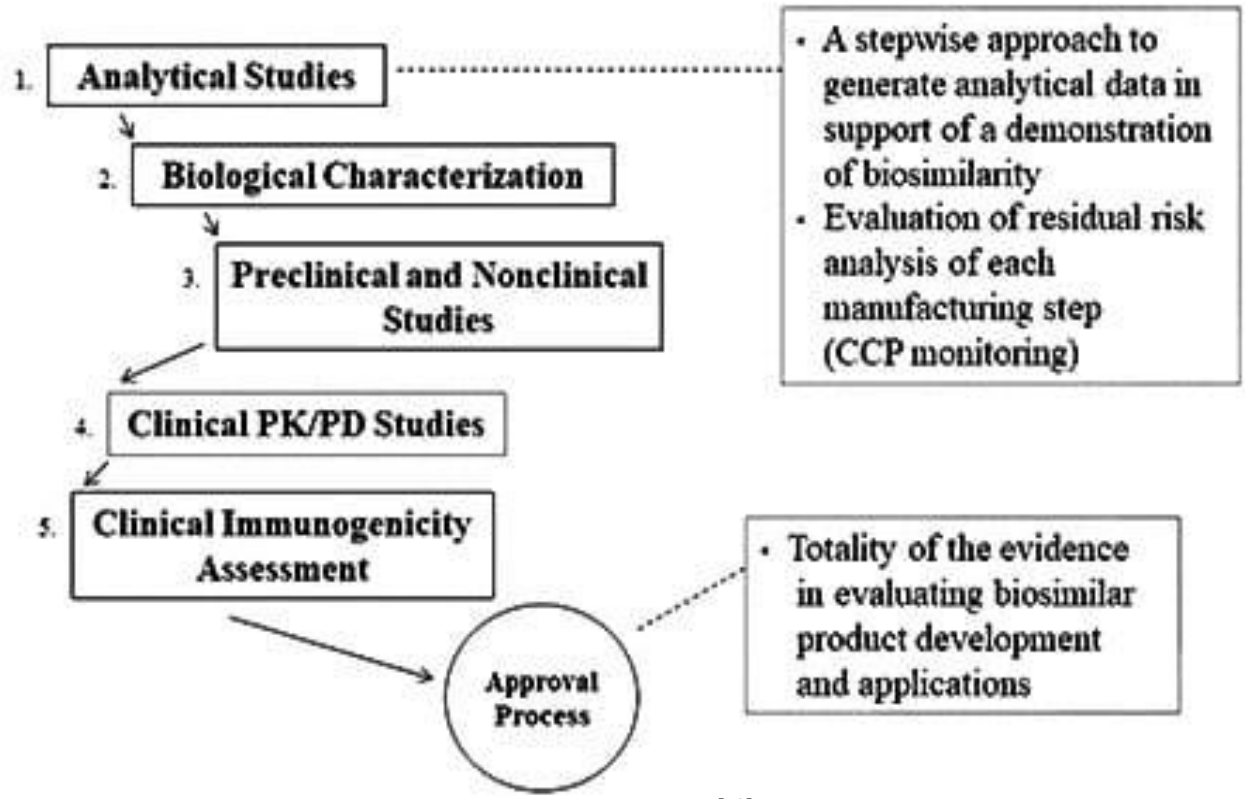


Figure2: Development fof evidence for bio-similarity [10]

Steps to evidence bio-similarity

- The first step in proving biosimilarity between reference and proposed biosimilar is to determine detailed structural information for the molecule, which can then be used as a structural template for the putative biosimilar.[1]
- Studying different batches of the referenced molecule because over time variations may have occurred. Batches may differ according to region as well i.e. the source of the reference product must be taken care especially when biosimilar is developing for a global market. Some countries may require a permit proof of biosimilarity to a batch from another country if appropriate demonstration is made to prove that the product is indeed representative of the authorized product in the country of application [1].
- After all the factors in consideration the attributes are analyzed and fingerprint is developed for a biosimilar involving the use of multiple orthogonal analytical techniques, with appropriate quantitative ranges.[1]
- One element at a time, a similarity comparison within the reference qualities fingerprints the possible biosimilar.[1]

The similarity toolkit

ICH Q6B lays down test protocols for setting quality specifications for biologic drugs. It consists of series of physicochemical and structural assay analyses. [1] It is an excellent starting point for determining strategies for evidencing biosimilarity.

For structural analysis there are six specification requirements [1]:

i. Amino-acid compositions

ii. Amino-acid sequences

iii. Terminal-amino acid sequence

iv. Structure of peptide map carbohydrate

v. Sulfhydryl groups and disulfide bridges

vi. peptide map

For physicochemical properties there are 6 specifications as follows [1]:

i. molecular size or molecular weight

ii. isoformic patterns

iii. spectroscopic profile

iv. electrophoretic patterns

v. patterns of liquid chromatographic

vi. extinction coefficient

Property To Be Determined	**Available Methodologies**
Amino acid sequence and modifications	Peptide mapping, Mass spectrometry Chromatography
Glycosylation	Mass spectrometry, anion exchange, capillary electrophoresis, , peptide mapping, mass spectrometry, enzymatic digestion
Folding	Mass spectrometry, fluorescence, hydrogen deuterium exchange and ion mobility mass spectrometry, S-S bridge determination, calorimetry , nuclear magnetic resonance, , circular dichroism Fourier transform spectroscopy
PEGylation and isomerization	Chromatography, peptide mapping
Aggregation	Size-exclusion chromatography, light scattering dynamic, microscopy, transmission electron, ultracentrifugation, microscopy,

	asymmetric field flow fractionation
Proteolysis	Electrophoresis, mass spectrometry, chromatography
Impurities	Immunoassays, proteomics, metal and solvents analysis
Subunit interactions	ion mobility mass spectrometry, chromatography
Heterogeneity of size, charge, hydrophobicity	Chromatography, ion mobility-mass spectrometry, light scattering capillary electrophoresis-mass spectrometry, gel and capillary electrophoresis,

Table1. Potential analytical tools [1]

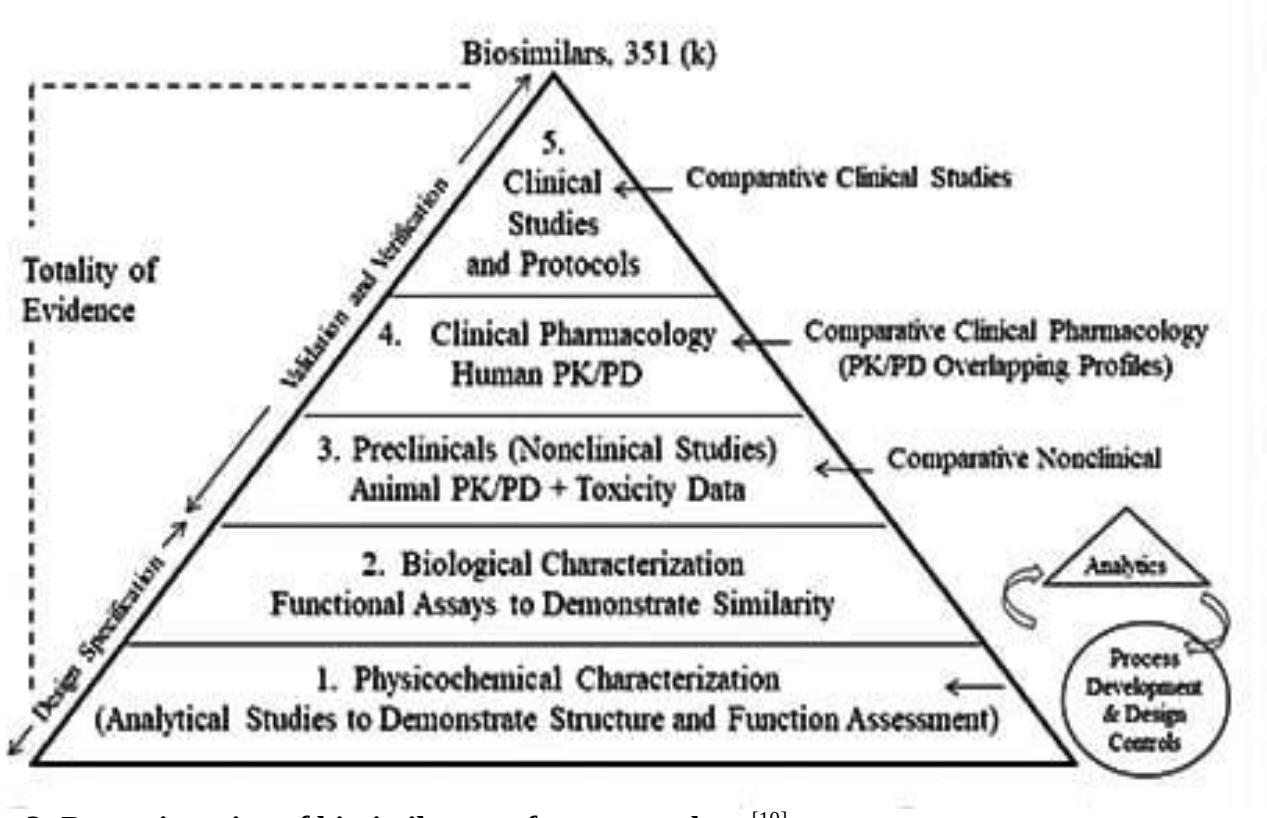


Figure3: Demonistration of biosimilar to reference product [10]

3.6. Higher order structure determination

Determining a biologic has its effects on activity and is another significant factor to consider when creating a biosimilarity fingerprint. To assess higher order structure, multiple methods – both qualitative and quantitative – can be used. Circular dichroism, which is sensitive to helix content and provides one of the most widely used quantitative techniques, is one of the most widely used quantitative techniques which provides information on secondary structure and some tertiary structures as well. [1] Fourier transform infrared spectroscopy (FTIR) is another quantitative method for determination of secondary structure this technique is sensitive to sheet content and less inclined to be influenced by buffer system. [1]

Both intrinsic and extrinsic fluorescence techniques are used, in which intrinsic methods are used to determine local tertiary structure and extrinsic techniques are used to determine surface hydrophobicity, but only qualitative results are obtained.[1] There are other qualitative approaches like differential scanning calorimetry, which examines thermal stability, and UV-vis spectroscopy, which examines local tertiary structure.[1] Hydrogen is a new method that has emerged from research application, Hydrogen–deuterium exchange mass spectrometry is a modern tool that has evolved from research applications. [1] It highlights specifics of dynamics, conformation, and interactions, but it is costly and has substantial data processing requirements. Two-dimensional protein nuclear magnetic resonance is another method that is more commonly used in science. [1]

It's also important to look at how biologics oligomerize and aggregate. Dynamic light scattering (DLS) is a technique that can be used to look for high-molecular weight aggregates, and SDS-PAGE is an inexpensive method however it has low-throughput for measuring aggregates. [1] Both oligomers and aggregates can be studied using quantitative methods such as SV-AUC(sedimentation velocity analytical ultracentrifugation) and SEC-ALS (size-exclusion chromatography using multi-angle light scattering). [1]

Comparative functional assays must also be conducted in addition to assessing comparative structures. To link product attributes with biological properties, suitable quantitative biological assays must be produced and run, and the results for the reference drug and biosimilar must correlate well if regulatory approval is to be granted. [1] The assay must also be able to determine properties that are important to the biosimilar's existence. Biochemical assays, such as ligand binding, immunoassays, enzymatic assays, and radioimmunoassay studies are among the techniques that can be used. Others, such as cytotoxicity, cell uptake, proliferation, secondary messenger, and PCR-based functional assays, are cell culture-based. [1] The structural and functional methods used can differ from one biosimilar to the next. The resulting data, on the other hand, should always cover a broad enough range of parameters to give regulators trust that the proposed biosimilar will have same effect as its reference product when consumed by patients. [1]

3.7. Extensive Comparability Data

Since biological systems are fundamentally complex, expression processes may cause a major impact on the structural and functional attributes of proteins they produce. [11] Biological product variability is thus well defined, among even the different batches of the same product. The FDA and EMA need detailed functional and structural analytical comparable database to showcase the comparability before starting clinical PK/PD and preclinical trials. [11]

Physicochemical, immunological, and biological assays are the three types of biomolecular tests. A protein's structural elements and modifications should all be tested with the ability to identify variations where biosimilar's quality target product profile will be defined on based on observed attributes of the reference standard. [11]

Characteristics	Attributes	Analytical methods
Primary structure	Amino acid sequence	RP-HPLC, peptide mapping, LC-ESI-MS
High-order structure	Disulfide structure, secondary and tertiary structure free thiol analysis	CD spectroscopy, LC-EST-MS peptide mapping, X-ray crystallography, Elman assay, antibody conformational array, FTIR
Purity, change heterogeneity, amino acid modification	Thermal stability, charged isoforms, monomer content	HPLC , SEC-MALS, DSC, CE-SDS, IEF, SEC, SV-AUC, IEC-HPLC
Glycosylation	Deamidation/oxidation/C-terminal variants, HPLC, LC-MS, CE-SDS , analysis, glycosylation, oligosaccharide profile, sialic acid analysis, N-glycan LC-MS peptide mapping monosaccharide content	HPAEC-PAD , LC-MS peptide mapping, HPLC, LC-MS, CE-SDS
Potency	Antigen and C1q binding, CDC, antigen neutralization assay, FcRn binding	ELISA, SPR, cell based CDC, neutralization and apoptosis assay

Table 2: Physicochemical and biological characterization methods [11]

3.8. Strategies for biosimilar control

A control strategy is a set of supply, operational, and monitoring controls being used to guarantee that a bioprocess delivers products with the necessary quality characteristics consistently. [11] The degree of control required is determined by the criticality of all the quality attributes and the capacity of a system to consistently produce output which meets quality standards. [11]

Input materials testing, in-process control (IPC) checks, product data monitoring, process control, release design checking, stability testing, quality control, characterization testing, quality assurance control, and responsive testing are all part of the integrated control strategy.[11]

For a biosimilar integrated control strategy, establishing requirements is a major source of uncertainty. Commercial requirements, on the other hand, are subject to a variety of regulatory guidelines. [11] According to EU guidelines, the selection of tests which is used in requirements or control strategies is specific to the product for both drug product and is substrates, and these guidelines must be defined in accordance with ICH Q6B. [11] The US guidelines, on the other hand, make no mention of expectations for developing a biosimilar control strategies. [11]

3.9. Concerning issues with biosimilars

3.9.1. Efficacy

Bioactivity variations between biosimilars and their innovator products have been demonstrated in previous studies. [12] The isoform distribution was diverse with a study conducted, evaluating four different countries for 11 epoetin alfa products, these countries includes India, China, South

Korea and Argentina, and there were considerable variations from in vivo bioactivity requirements. For example, in a 71 to 226 %, in-vivo bioactivity ranged, there were five product failures to satisfy their own requirements. [12] When switching epoetins, this difference in efficacy would not be a concern if hemoglobin levels are properly controlled. In the case of monoclonal antibody therapy, transplant rejection, or cancer treatment, however, such variability would be inappropriate. A parallel study examined the quality attributes of several biosimilar brands available in India to those of originator drug products, such as identification, purity, material, and efficacy. [12] The study looked at 16 commercial brands of biopharmaceuticals such as human recombinant G-CSF, recombinant erythropoietin and human recombinant pegylated G-CSF. Furthermore, there exists purity difference between different brands of erythropoietin and G-CSF biosimilars. [12]

3.9.2. Concerns of safety

Concerns regarding immunogenicity have been posed as a result of an increase in reports of pure red cell aplasia linked to a specific formulation of epoetin alfa. [12] This incident has caused the world to be wary of biosimilars. The formation of neutralizing antibodies against endogenous epoetin caused pure red cell aplasia to take on an immunological aspect. [12] In the vast majority of cases, a drug called Eprex which is biosimilar to epoetin alfa is manufactured outside US, was used. A slight improvement in the production process is the most likely cause. [12] In the Eprex formula, polysorbate 80 and glycine have been used to substitute the human albumin stabilizer. [12] Polysorbate 80 is considered to boost Eprex immunogenicity by inducing the development of epoetin-containing micelles or interfering with leachates formed by prefilled syringes with unprotected rubber syringe stoppers.[12] Many patients treated with recombinant interferons developed neutralizing antibodies that greatly reduced their own production in another study for example, in one such study, out of 325 healthy individuals 13 had their clinical studies for pegylated thrombopoietin which is a megakarocyte growth and development factor, which was stopped due to treatment related to thrombocytopenia. [12]

Preclinical evidence may be inadequate to show immunologic protection of certain biosimilars, according to recent EMEA (European Medicines Agency) recommendations on biosimilar comparability. [12] In these cases, the only samples of patients participating in clinical trials and

surveillance done after the marketing can demonstrate immunological protection. The double antigen bridging ELISA assay and radio immune precipitation assay can both detect high affinity antibodies. These analyses, however, must be validated and standardized. [12]

3.9.3. Pharmacovigilance

Since a biosimilar's clinical database is small at the time of approval, strict pharmacovigilance is needed. With biosimilars, immunogenicity is a unique safety concern. On the other hand, the absence of validity and uniformity of technique for identifying immune responses emphasizes the value of rigorous pharmacovigilance. [12] The monitoring data for adverse drug events must be detailed, including information on the drug, like its patented name, its international nonproprietary name (INN), and the dosage it's been issued. [12]

3.9.4. Substitution of biosimilar market

Generic drugs may be prescribed instead of innovator medications thanks to substitution. The original and generic drugs are identical and have the same therapeutic effect, which is why chemical drug replacement is used. Automatic substitution is sufficient for the vast majority of chemical generics and may result in cost savings. [12] Biosimilars, on the other hand, should not be subjected to the same substitution guidelines, as this may compromise therapy protection or result in therapeutic failure. [12] Biosimilar substitution is also a cause of drug safety misunderstanding. In any instance, if an unanticipated occurrence occurs after shifting from a reference biologic to a biosimilar despite documentation of the shift, the event will either be traceable to a specific product or will be assigned to the incorrect product during drug safety analysis.[12] The pharmacists and drug prescribers must be mindful of this in order to avoid making inappropriate substitutions.

3.9.5. Labeling and naming

In technical terms, the medicinal products are referred to as INN. Generic adaption for chemical therapies is given the same name for identification as reference pharmaceuticals since they are the perfect reproductions. Biosimilars, on the other hand, require specific INNs in order to allow biopharmaceutical prescribing and dispensing, as well as precise pharmacovigilance. To assist physicians and pharmacists in making informed decisions, biosimilars should provide comprehensive labeling that includes variations from the reference product as well as unique safety and efficacy details. [12]

3.9.6. Regulatory approval

Unlike chemical generics, biosimilars are subject to more stringent accuracy, safety, and efficacy testing criteria. The European Parliament released guidelines for biosimilar regulatory approval in May 2004. [12] EMEA published guidelines in February 2006 that detailed clinical, nonclinical, and quality standards for biosimilars. [12] Based on these guidelines, the EMEA has approved biosimilars of somatropin which are valtropin, omnitrope, for epoietin namely retacrit, binacrit, silapo, hexal and abseamed, and biosimilars for G-CSF namely tevagrastim, biograstim, and ratiograstim. [12] The EMEA has also declined marketing plan for drugs like aplheon, an interferon biogeneric, due to concerns about production methodology and quality control. The application of biosimilar Marvel Insulin was also denied due to a lack of evidence to prove bio-similarity between biosimilar under trail and its reference. [12]

French legislation and Spanish Ministry of Health and Consumer Affairs also comprise of laws banning replacement of one biological drug for another. [12] Many regulatory authorities, including US-FDA (Food and Drug Administration), are working to set rules for biosimilar marketing clearance. There are no specific criteria for biosimilar approval in India. [12] As a result, biosimilars are entering the Indian market unchecked.

3.10. Manufacturing Challenges

In order to boost product growth and quantity, comply with revised regulatory policies, or improve the effectiveness and durability of the integrated manufacturing system, certain biosimilar producers may need to modify or replace their production methods. Manufacturing modifications to any biological product, whether it's the original or a biosimilar, are subject to stringent regulatory controls and limitations.

Development Stage	**Expected Changes**	**Regulatory Recommendations**
Early stage (preclinical)	Change in cell line, fermentation process, raw materials; steps order of purification steps or replacement of purification steps	Comparability testing generally not as extensive as for an approved product
Late Stage (Clinical)	Change in cell line, fermentation process, raw materials used during (clinical)fermentation; steps of purification steps or purification steps; development and manufacture of drug product; new drug substance or new drug product	Extensive comparability studies are performed to support the pre- and post change products for similarity in quality, safety, and efficacy; data as per ICH Q11 (25)
After Market authorization (post approval changes)	Change in cell line, fermentation process/scale-up, raw materials; steps of authorization purification steps or replacement purification steps; manufacturing site	The product is not expected to change at this time. Any adjustments must be thoroughly investigated and justified in terms of their safety and efficacy; follow

		the variation guideline.

Table 3: Manufacturing changes and regulatory recommendations [11]

3.11. Biosimilars approval

The approval of biosimilars by FDA is largely based on the approved reference product. Any biosimilar producer typically relies on FDA assessments of a standard drug, this is done by demonstrating that the biosimilar drug which has been proposed is highly comparable to the standard drugs and that there are no clinical differences between the two. For such determinations, quality data from the reference standard has been used, and manufacturers of biosimilars must produce full fledge samples of administrative and clinical data from multiple attributes to identify and confirm bio-similarity between the standard drugs and the potential biosimilar. Biosimilar manufacturing companies designing and implementing a quality management system which improves the time of biosimilar arrival in the market.

The FDA's draught guidance framework includes a feature that allows for fingerprint-like protein recognition. [8] This is monitored by comparing a series of parameters using orthogonal methods which can be used to classify a protein and can hence show similarities between reference drug and biosimilar.[8] Approval of enoxaparin in July 2010, which is a generic heparin drug with low molecular weight, this idea was recognized and put into practice. Enoxaparin was successfully licensed without the need for any clinical test trials, this approval was termed on five strict parameters established by the FDA as adequate proof that enoxaparin contained the same properties of action as its reference standard which is Lovenox. [8] The characteristics for the approval were:

1. Chemical attributes and physical attributes of enoxaparin [8]
2. The chemical processes used to break down the chemical structure of heparin into fragments and the nature of the heparin compound. [8]
3. The activity and organization of the enoxaparin components[8]
4. Anticoagulant behavior of the substance was tested in the lab. [8]

5. The manner in which the drug is effective on human body. [8]

INN Name	Brand Name	Company Name	Approval Date
Adalimumab	Amjevita	Amgen	September 23, 2016
Insulin glargine	Basaglar	Eli lilly and Boehringer Ingelheim	December 16, 2015
Etanercept	Erelzi	Sandoz	August 30,2016
Infliximab	Inflectra	Pfizer (Hospira)	April 5,2016
Filgrastim	Zarxio	Sandoz	March 6,2015

Table 4: Biosimilars approved on the US market [11]

INN Names	Brand Names	Company Name	Approval Dates
Filgrastim	Accofil, Biograstim, Filgrastim Hexal, GrastofilNivestim, RatiograstimTevagrastim, Zarzio	Accord Healthcare, CTArzneimittel, Hexal,Apotex, Hospira,Ratiograstim TevaGenerics, Sandoz	Sep 18, 2014; Sep 15, 2008; Feb 06, 2009; Oct 18, 2013; Jun 08, 2010; Sep 15,2008; Sep 15, 2008; Feb 06, 2009
Adalimumab	Amgevita, solymbic	Amgen	Jan 26, 2017, Jan 26, 2017
Etanercept	Benepali	Samsung Bioepis	Jan 14, 2016
Infliximab	Remsima, flixabi, inflectra	Celltrion, Samsung Bioepis, Hospira	Sep 10, 2013; May 26, 2016; Sep 10, 2013

Rituximab	Truxima	Celltrion	Dec 15, 2016
Epoetin zeta	Retacrit, Silapo	Hospira, STADA R&D	Dec 18, 2007; Dec 18, 2007
Epoetin alfa	Binocrit, Abseamed, Epoetin alfa	Sandoz, Medice Arzneimittel, Hexal	Aug 28, 2007; Aug 28, 2007; Aug 28, 2007
Follitropin alfa	Ovaleap	Teva Pharma	Sep 27, 2013
Somatropin	Omnitrope	Sandoz	April 12, 2006
Insulin	Abasaglar, Lusduna	Eli Lilly/Boehringer Ingelheim, Merck (MSD)	Sep 9, 2014; Jan 4, 2017
Enoxaparin sodium	Inhixa	Techdow Europe	Sep 15,2016
Teriparatide	Movymia	STADA Arzneimitte	Nov 10, 2016*

Table 5: Biosimilars approved on the European market [11]

3.11.1. Extrapolation

Extrapolation is a biopharmaceutical concept that refers to biosimilar clearance for indications that the reference drug which has not been specifically evaluated in a biosimilar clinical trial. [15] If a robust comparability program has demonstrated biosimilarity to the reference product, including safe operation, effectiveness, and pharmacokinetics which are key indication suitable for identifying possible clinical relevant variations, and there is sample scientific support for the extrapolation, where evidence on safety and effectiveness can be extrapolated from one application to another [15] Data extrapolation has been around for a long time and is a well-established science and regulatory concept. [15]

Biosimilar development needs extrapolation Extrapolation not only speeds up the approval process, but it also allows for the omission of studies that aren't needed for board authorities and the redirection of resources in the fields where research is far more

beneficial. [15] In this way manufacturing costs can indeed be reduced, lowering the cost of effective drugs for patients. [15]

Extrapolation regulatory clearance hinges on the entirety of proof showing biosimilarity and empirical rationale. While clinical studies are important, analytical studies are crucial for evaluating biosimilarity and are typically more sensitive in this regard than traditional clinical datasets. The sensitivity of some analytics has increased by a factor of ten million in the last 20 years. As a result, several structural elements and roles of monoclonal antibodies, as well as structure-function relationships, can still be established with high sensitivity. Extrapolation is supported by data from the entirety of evidence as well as familiarity with the reference biologic.

For scientifically justifying extrapolation, consider the mechanism of action in each instance, PK and biodistribution, prediction of toxicities, and any other feature. As a consequence, extrapolation analysis isn't really automatic and has only been considered after all available data has been used to establish biosimilarity.

Aspects that should be taken into account when extrapolating are:

1. In each condition, the mechanism of action is binding and molecular signaling, as well as the position and expression of the target or receptor. [15]
2. Pharmacokinetics, pharmacodynamics, and biodistribution measurements can also be useful in determining the mechanism of action. [15]
3. Expected toxicity is a distinction that can occur in each use condition and patient population. [15]
4. Other factors may also include comorbidities or concomitant medications. [15]

3.11.2. Process of Biosimilar approval

The approval of biosimilar includes a detailed analysis of molecular structure and function in relation to the proposed biosimilar product's safety and efficacy, as well as clinically relevant evidence. [10] The following are the most well-known development and implementation concepts:

1. Validation and verification studies, as well as design controls (Analytical Similarity, Manufacturing and Effective CMC Strategy)[10]

2. Biosimilar Creation and Applications on the basis of QbD [10]

3. Considerations in statistics for demonstrating analytical similarity [10]

4. Interchangeability, Extrapolations, Immunogenicity Assessment and Study Design, all components of the proposed biosimilar product's clinical trials are covered by FDA Guidance on Biosimilar Labeling.[10]

Regulatory Requirements	**Applicant's Biosimilar Data requirements**
Analytical studies	Physicochemical and functional analytical data.
Nonclinical studies	Animal tests and trials, comparisons, and confirmations of candidate biosimilar and reference product pharmacologic and toxicological profiles.
Clinical studies	Clinical studies evaluating PK/PD and safety.
Mechanism of action and Receptor binding assays	Selective binding to the G-CSF receptor which is consistent throughout all the labelled indications for usage.

Route of administration	Dosage strength and form of the biosimilar product in comparison with licensed reference product.

Table 6: Biosimilar essentials for approval [10]

3.12. Biosimilar Interchangeability

An interchangeable drug is really a biosimilar that satisfies additional criteria. A biosimilar may be designated as interchangeable according to US Biologics Price Competition and Innovation which allows it to become a substitute for the reference standard where the cooperation of the medical practitioner is not required. In reality, if the biosimilar is marked as interchangeable, it can be used as a substitute for the reference product in several states.

Immunogenicity studies are an additional factor to consider which are specific for interchangeable, even though change in manufacturing process is not really necessary. [11] However, if a biosimilar is designated as interchangeable, pharmacists may use it instead of the original. [11] To be considered an interchangeable in United States, 2009 Act of Biologics Price Competition and Innovation states that for any given patient biosimilars is required to achieve the equivalent clinical results as its reference counterpart. [11] Developers must also demonstrate that a patient can switch between original and biosimilar drugs without experiencing any negative side effects. [11] Biosimilars and interchangeable drugs, according to FDA guidelines, cannot have clinically significant variations in safety as compared to the originator products. The United States is presently just one country that allows biologic medications to be classified in this way. According to a recent FDA draught guidance, sponsors must demonstrate that a new medicine is a biosimilar of the reference. [11] When a medicine is originally approved as a

biosimilar, it can be utilized to support the legal requirement of establishing interchangeability through a swapping study or testing. [11]

According to FDA guidelines published in May 2019, for a biologic to be an interchangeable:

- The biological is a biosimilar to its reference when produce the equivalent results for any given patient as the reference drug. [16]

- The risks of alternating and switching between the bio-product and the primary component for a biologic product delivered to any individual more than once is not bigger than the risk of consuming the reference product without any kind of substitution or switching in terms of reliability or efficacy.[16]

3.13. Biosimilar status in India

In contrast with other countries, India consists of a very vibrant biosimilar market, and as a result, pharmaceutical industries of India have risen to become leaders in biosimilar's global market.[13] India became the first country to authorize a biosimilar, well ahead of the European countries and USA. [13] India licensed its first biosimilar for hepatitis B in 2000, despite the fact that there was really not any specified guideline for manufacturing or marketing of biosimilars available at the time. [13] A number of biosimilars have been manufactured and marketed by variety of Indian biopharmaceutical industry since then. The USFDA recently approved the marketing of a novel biologic developed by an Indian biopharmaceutical company. [13] Herceptin (trantuzumab) was the first biologic to be licensed by the FDA, and it is used to treat many types of stomach cancer and breast cancer. [13] It was also the first biosimilar approved for sale in the United States of America, created by an Indian business.

Today over 100 pharmaceutical companies from India are involved in the production and marketing of biosimilars. [13] Biosimilars are referred to as related biologics by Indian regulatory agencies. India was among the first few countries to accept biosimilars, there was no clear guidelines for similar biologics, and the permitting process for biosimilar takes more time and needs more evidence than other generic drugs. DBT (Department of Biotechnology) and the Central Drugs Standard Control Organization has worked together to create a guideline system based on marketing clearance requirements regulation and relevant biologics in 2012, which were updated and changed in 2016. [13] These guidelines cover development procedure control, the consistency, protection, and efficacy of the biosimilar. It moreover includes the regulatory criteria for similar biologics before and after they hit the market. DBT's Review Panel on Genetic Manipulation monitors the discovery and preclinical analysis of biologics. [13] Biosimilars regulated in India under the Drug and Cosmetic Act of 1940, 1945's the Drug and Cosmetic Rules, and the Rules regarding the Manufacture, Export/ Import, Usage, Hazardous Microbes and GMO safe containment had to be notified under the Act of Environmental Protection, 1986. [13]

Central Drugs Standard Control Organization has made several significant changes to its previous guidelines, such as reference biologic whereby a biosimilar manufactured is authorized and sold in India, has been replaced with the requirement that the reference biologic be approved and marketed in India or some other country like Europe, United States of America, Canada, Japan and Switzerland. [13] Other international organizations with which it collaborates include World Health Organization and European Medicines Agency. Biologics are generated utilizing a systematic procedure to demonstrate the molecular and consistency attributes of proposed biosimilar with original products, according to Indian guidelines. Further distinction between the 2012 and 2016 guidelines has concentrated on studies regarding post-marketing, which according to CDSCO will help to mitigate biosimilar risks. [13] Pharmaceutical companies must conduct Phase-IV trials along with maximum of 200 subjects between two years of getting a clearance for marketing the product, according to the CDSCO. [13] The FDA has included a special feature on non-comparative efficacy and safety research, which states that if two materials are recognized identical under pre-clinical trials, evaluation may proceed with in-vitro analysis using pharmacokinetic approaches and a pharmacodynamic marker that can be used in

place of efficacy.[13] In Phase I study, the residual risk is greatly reduced. To eliminate any residual confusion, phase III drug trial for a biosimilar drug may be used to perform a single handed study of at least 100 quantified subjects in the most vulnerable indication. [13]

"If the health safety and efficacy examinations are relaxed, According to CDSCO, all indications will be accepted for reference product can be given in terms of product's consistency, nonclinical, and convincing PK and PD data," according to CDSCO. [13] Data on immunogenicity could have been collected during the PK and PD analysis, and it would be required after the approval of Phase IV study only if the Phase III trials were successful. [13]

Harnessing this enormous potential, pharmaceutical companies in India are taking a various steps for the betterment of manufacturing process and marketing schemes. Some Vaccines, human insulin, monoclonal antibodies and recombinant proteins are some of the biosimilars which are licensed and used in India. [13] India has now become the largest producer of vaccine and has given its approval to a number of biosimilars for use in different diseases.

In India, unlike the United States, has no connection between patent protection and marketing. Intellectual property rights for biosimilars are not contingent on or have no link with marketing approval. [17] However, if the biologic is unique, a biologic can be patented, for that biologic must be necessitates a creative measure, must have industrial application, and is not simply a natural discovery of a living organism. [17] When a biologic has already been patented, then a biosimilars of the same reference biologic cannot be protected by the product patent law, however it can be protected by a process patent which satisfy the established criteria. [17]

Some examples of some patents granted are as follows:

- On April 24, 2020, Millenium Pharmaceuticals (a Takeda Pharmaceuticals subsidiary) obtained a patent (IN335696) for its Vedolizumab composition. [17]
- Eli Lilly was recently granted IN336474 for Tibulizumab, Tibulizumab (LY-3090106) is a tetravalent bispecific antibody for the treatment of autoimmune disease. [17]

- In 2015, Genentech received a patent IN268632 titled pharmaceutical formulation comprising HER2 antibody for a pertuzumab antibody formulation containing histidine-acetate buffer. [17]
- Patents for the preparation of insulin compounds have been issued to Biocon (IN257450). [17]

Name of Product	**Active drug**	**Therapeutic Area**
Glaritus	Insulin glargine	Diabetes mellitus
Grafeel	Filgrastim	Neutropenia
Epofer	Epoetin alfa	Anemia
Adfar	Adalimumab	RA, Crohn's disease
Erbitux	Cetuximab	Colorectal carcinoma
Krabeva	Bevacizumab	Colorectal cancer
Herceptin	Trastuzumab	Breast cancer
Intacept	Etanercept	RA
Abcixirel	Abciximab	Autoimmune disease
Relibeta	Interferon beta-1a	Multiple sclerosis
Relipoietin	Epoetin alfa	Anemia, chronic kidney failure, autologous blood transfusion ,

		HIV
Shankinase	Streptokinase	Arterial occlusions, pulmonary embolism, deep vein thrombosis
Razumab	Ranibizumab	Wet macular degeneration, macular edema, degenerative myopia
Terifrac	Teriparatide -parathyroid hormone	Postmenopausal women at high risk of osteoporosis

Table 7 : Some biosimilars approved in India [13]

Name of Product	**Drug name**	**Therapeutic Area**	**Year Of Approval In India**	**Company name**
Acellbia	Rituximab	Non-hodgkin lymphoma chronic B-cell leukarmia	2017	Biocad
Bevacirel	Bevacizumab	Colorectal cancer	2016	Lupin - Reliance life sciences
Cizumab	Bevacizumab	Colorectal cancer	2016	Hetero
Etacept	Etanercept	Juveniler heumatoid arthritis, Psoriatic arthritis Rheumatoid arthritis, Ankylosing spondylitis, Psoriasis	2013	Cipla
Filgrastim	Filgrastim	Neutropenia	2013	Lupin
Insugen	Human insulin	Diabetes mellitus	NR	Biocon
Krabeva	Bevacizumab	Metastatic colorectal	2017	Krabeva

		cancer, brain cancers, ovarian cancer, kidney cancer, cervical cancer , lung cancer		
Maball	Rituximab	Non-Hodgkin's Lymphoma, Lymphoma	2015	Hetero group
MabTas	Rituximab	Non-Hodgkin's Lymphoma, Lymphoma	2013	Intas pharmaceuticals
Peg-filgrastim	Pegfilgrastim	Cancer,Neutropenia	2015	Hetero Group
Zyrop	Erythropoietin	Chronic kidney failure	2010	Cedilla Healthcare

Table 8: List of approved biosimilars product launched by Indian companies [14]

3.13.1. Future Perspectives

Many companies' patents will expire in the coming year, providing an incentive to other pharma industries to investigate the probability of developing new biosimilar drugs. The biosimilar market was estimated to grow by $10 billion by 2020. [13] While biosimilars use in the United States is still rising and expanding, India has become major industry of the world when it comes to manufacturing and using biosimilars. In 2015, the Indian biosimilar market was worth around $300 million. [13] Domestic revenues are close to $250 million, and they're rising at a 14 percent compound annual growth rate India exports a whopping US$51 million worth of biosimilar or similar biologics. [13] According to a 2016 ASSOCHAM-Sathguru survey, biosimilars offer the Indian biopharmaceutical industry a US$240 billion global opportunity, with the domestic market projected to expand to US$40 billion by 2030. [13] According to the Institute of Medical Sciences' health-care research, Indian biopharmaceutical industries involved in the production and marketing of biosimilars would have a similar opportunity.

4.0. Result and discussion

Biosimilars are good potential replacements for reference biologics, which have high costs and limited availability in the market worldwide. These bio base drugs have successfully extended treatment options for a variety of diseases, both simple and complex. Biosimilar creation is a time-consuming process that necessitates a great deal of study and numerous attributes to showcase the biosimilarity towards the reference product. Organizing these methods to assess bio-similarity is a time-consuming method that involves using orthogonal techniques to create a molecular fingerprint of the biologic through a series of clinical and non-clinical experiments, as well as physiochemical factors and post-translational modifications. The developed fingerprint of the critical quality attributes is compared attribute by attribute with the proposed biosimilar to evaluate the bio-similarity between the two molecules. ICH Q6B holds the guideline to identify the appropriate analyticl methodology to be used for similarity comparison. Techniques like NMR, Mass spectroscopy, Circular dichroism, SDS-PAGE, FTIR and more are used to provide information of the test molecule on the basis of size, charge, shape, weight, abundance of the molecule. ICH Q6B also specifies test protocols for determining biologic drug quality requirements based on defined parameters. Biosimilar products continue to have problems with efficieny, protection, pharmacovigilance, substitution, and naming, all of which must be addressed throughout the multiple phases of the manufacturing process and must be reviewed, adjusted, and updated during the process. The FDA would eventually approve biosimilars, mostly approval is based on the approval of its reference counterpart. According to FDA guidelines, any biosimilar would be accepted much quicker if it can demonstrate a higher level of bio-similarity to its reference drug, indicating that it would be safe to use in medical treatments with similar efficacy.

Biosimilars have the potential to make both malignant and nonmalignant diseases more accessible to patients by lowering care costs. From the time biosimilar was first introduced the production and use of biosimilar products have increased exponentially. India has solidified its role as a global player in the production of related biologics. Because of its growing population, it has become a huge market for biosimilars. Though India's potential is enormous and

aspirations are high, retaining leadership poses enormous and overwhelming challenges. Indian biotech firms must modernize their technologies and enhance their workforce skills in order to realize their full potential and maintain their position as a leading industry for biosimilars globally.

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