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Regulatory requirements for approval and Registration Procedure of Biosimilar in US and European Union (EU)

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Abstract

The market for biotechnology-derived medicinal products is evolving rapidly with the imminent entry of biosimilars. The development and approval of biosimilars represent a critical pathway to expanding access to biological therapies while maintaining high standards of safety, efficacy and immunogenicity profile because biosimilars are made in living organisms there may be some minor differences from the reference medicines.

In the US, biosimilars are regulated under the Biologics Price Competition and Innovation Act (BPCIA), which is part of the Affordable Care Act. The regulatory pathway emphasizes a stepwise approach, involving analytical studies, preclinical assessments, and comparative clinical trials to establish biosimilarity with a reference product. The FDA assesses the totality of evidence provided by the biosimilar applicant to make a determination on safety, purity, and potency.

In the EU, the approval process for biosimilars is governed by the European Medicines Agency (EMA). The regulatory framework relies on a robust comparability exercise, emphasizing extensive analytical studies and well-designed clinical trials to establish biosimilarity. The EMA assesses the comprehensive data package submitted by the biosimilar applicant, considering the totality of evidence before granting marketing authorization.

While the overall approach is similar, there are nuanced differences in the regulatory processes. The US typically requires a more prescriptive approach to clinical trials, with the expectation of conducting at least one confirmatory comparative clinical trial. In contrast, the EU may allow for a more tailored approach to clinical development, recognizing that the need for extensive clinical trials may vary depending on the nature of the biosimilar and the reference product.

As the biosimilar landscape continues to evolve, ongoing collaboration and harmonization efforts between regulatory authorities aim to streamline global access to high-quality ,cost-effective biologic therapies.

Keywords: Biosimilar, biologics, Regulatory approval, Biologics License Application (BLA), Investigational New Drug Application (IND), non-clinical studies, clinical studies, US FDA, EMEA, CHMP.

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1. Introduction

1.1 Regulatory Bodies

Regulatory bodies such as the Food and Drugs Administration (FDA) in the US are responsible for approving whether a drug can proceed to clinical trials and whether it should be allowed to come in to the market or not these body has to evaluate the scientific and clinical data to ensure that the drug can be produced with consistently high purity, better therapeutic results and it does not have unaccepted side effects. (1)

Table 1. Regulatory bodies in the World

Country	Regulatory Bodies
US	Food and Drug Administration(FDA)
Canada	Health Canada
India	Central Drug Standard Control Organization (CDSCO)
Japan	Ministry of Health, Labour, Welfare(MHLW)

UK	Medicines and Healthcare Products Regulatory Agency(MHRA)
Australia	Medicines and Healthcare Products Regulatory Agency(MHRA)
Europe	European Medicines Agency
Philippines	Food and Drug Administration(FDA)

1.2 Biological Products

Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. Biological medicines are medicinal products produced with help of biotechnological process that contain proteins derived from DNA technology and hybridoma techniques using living system or organism as source. The small molecule product has significant difference than the biological product illustrated in the below table-2.

The first regulatory guidance for Biosimilars was established by Europe in 2004 while the first Biosimilar named Omnitrope® was authorized in 2006 by Sandoz Biopharmaceuticals in reference to Genotropin (Somatropin®, Pfizer). While Binocrit® is the First European Complex is a recombinant epoetins alpha developed as similar biological product to the reference product Erypro /Eprex (Epoetin alpha, Janssen-Cilag) authorized in 2007. Japan has released the final guidelines on 4th March 2009, while the final draft guideline for Biosimilar in Canada was released in March 2010. The leading biological innovators are the US and Europe market. Biosimilar guidelines and regulations are being developed world wide as shown in figure-1.

1.3 History of Biosimilar

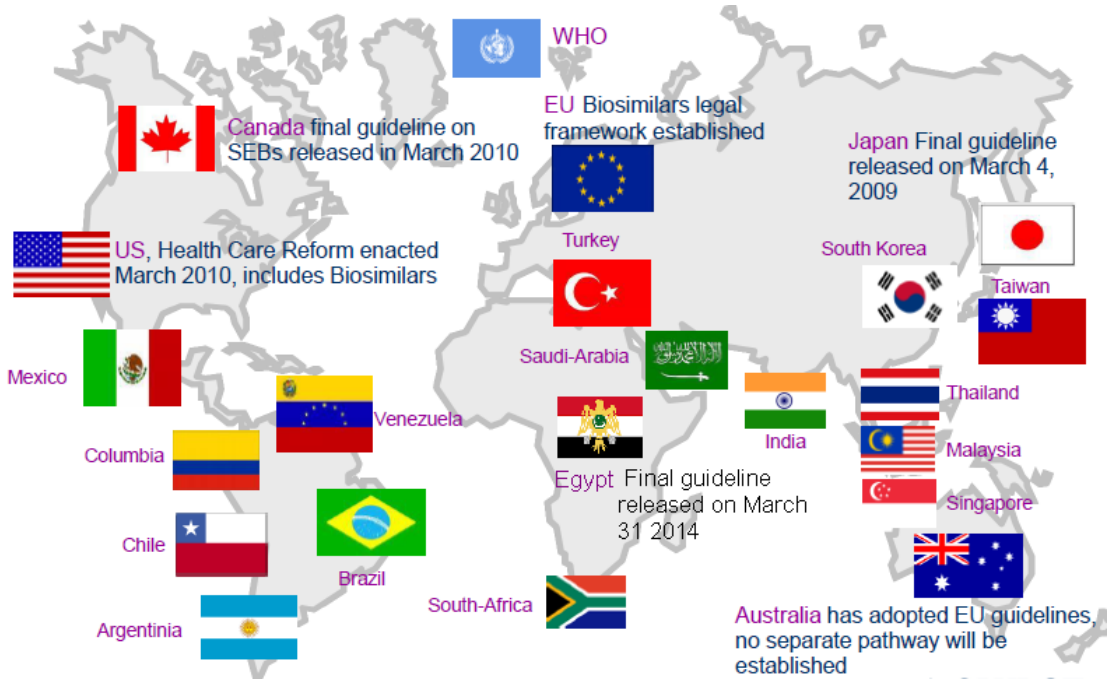

Figure 1. Worldwide established Biosimilar Regulation

1.3.1 History of Biosimilar in US

The US, although it now has a legal pathway (with the approval of the Biologics Price Competition and Innovation Act [BPCI Act], which was signed into law on 23 March 2010 by President Barack Obama), does not yet have a practical pathway with guidance defined by the FDA. The FDA gained the authority to approve Biosimilar (including interchangeable that are substitutable with their reference product) as part of the Patient Protection and Affordable Care Act signed by President Obama on March 23, 2010. The FDA has previously approved biologic products using comparability, for example, Omnitrope in May 2006, but this like Enoxaparin was also to a reference product, Genotropin, originally approved as a biologic drug under the FD&C Act. On March 6, 2015, Zarxio obtained the first approval of FDA. (2) Sandoz's Zarxio is Biosimilar to Amgen's Neupogen (filgrastim), which was originally licensed in 1991. This is the first product to be passed under the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which was passed as part of the Affordable Healthcare Act. But Zarxio was approved as a Biosimilar, not as an interchangeable product, the FDA notes. And under the BPCI Act, only a biologic that has been approved as an ―interchangeable‖ may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. The FDA said its approval of Zarxio is based on review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical

immunogenicity data and other clinical safety and effectiveness data that demonstrates Zarxio is Biosimilar to Neupogen.

1.3.2 History of Biosimilar in EU

The earliest document discussing the possibility of copying a biological product is the concept paper for the comparability guideline that was published in 1998. This concept paper resulted in a guideline in 2003. However, the issue remained very controversial for scientific and legal reasons. The legal uncertainty was removed by the revision of Directive 2001/83/ EC of the European Parliament and of the Council, which came into force in 2005. This directive distinguished the copies of biological products, officially named ‗similar biological medicinal products' with the nickname ‗biosimilars', from the chemically synthesized generics, and contained the basic technical requirements in its Annex 1. The directive says that the applicant for a similar biological product has to provide not only full documentation of quality and evidence for bioequivalence to the reference product, but also results of non-clinical tests and clinical studies that will be defined in scientific guidelines. The reference to guidelines is very useful, because the concept of biosimilarity is evolving and guidelines can be more easily modified according to the advances of science. In contrast to prescribers and patients, EU regulators have a lot of experience in assessing comparability studies, including marketing authorization applications for biosimilars the first biosimilar medicine, Omnitrope® (biosimilar recombinant human growth hormone [rhGH]; Sandoz, Kundl, Austria), was approved in Europe by the EMA in 2006. (3)

1.4 Biosimilar

The biological product is **highly similar to the reference product** notwithstanding minor differences in clinically inactive components; and that there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product. Biosimilar Medicines is intended to have the same mechanism of action as to the original biological medicine, and designed to treat the same diseases as to the innovator's product. Biosimilar are the protein drugs that are **SIMILAR, but not IDENTICAL** to an existing product. But it is difficult to produce the identical or generic of biological drug due to the complex structure of the protein molecule. While name, appearance and packaging of a Biosimilar differs to those of reference biological.

1.5 Reference Product

Reference biological product is defined as ―The product used as comparator for head-to-head comparability studies with the Biosimilar product in order to show similarity in terms of quality, safety and efficacy. Mostly reference product must be authorized based on full quality, safety and efficacy data in the country of origin and marketed for several years without any severe adverse event. Selection of the reference product depends on the commercial opportunities in targeted market and also on the manufacturing site of the reference product. The **single biological product, licensed under section 351(a) of the PHS Act,** against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act. (4)

2. Objective

The regulatory requirements for the approval and registration procedure of biosimilars in the US and the European Union are designed to ensure patient safety, promote competition, and facilitate access to affordable treatments. These regulations aim to verify the safety and efficacy of biosimilars, ensuring they are comparable to their reference biologics in quality, safety, and effectiveness. By establishing clear pathways for biosimilar approval, regulatory agencies foster competition in the biologics market, ultimately increasing access to a wider range of treatment options for patients. Rigorous assessment processes are implemented to protect public health by minimizing the risk of adverse events associated with biosimilars. Additionally, the regulatory frameworks streamline the approval process, enabling biosimilars to enter the market more swiftly and potentially lowering healthcare costs. Adherence to strict quality standards throughout manufacturing, testing, and distribution processes ensures product consistency and minimizes variability. Furthermore, these regulations encourage innovation in biosimilar development while maintaining transparency in communication with stakeholders, including healthcare professionals, patients, and manufacturers. Overall, the regulatory requirements for biosimilars in both regions seek to strike a balance between fostering innovation, ensuring patient safety, and promoting access to affordable treatments.

Table 2. Difference between SMD and Biological Product

Parameters	Small Molecule Drugs	Biological Product
Origin	Chemical Origin	Living System or Organism
Size	Low-weight molecules (typically <1,000 Da)	Relatively Large Size (Generally, 5 to 200 kDa)
Structure	Simple Molecule	Complex Molecule
Manufacturing Method	Using chemical engineering	Biotechnological process like such as recombinant DNA, controlled gene expression, or antibody methods.
Stability	Relatively Stable Molecule	Unstable, sensitive to external conditions.
Administration Route	Oral, IV or Infusion Route	IV or Infusion, as protein are sensitive to enzymatic degradation in GI Tract.
Immunogenicity	Non-immunogenic	Immunogenic

Generic Version	Identical to Innovator Product	Not exact copy of the Innovator.
Examples	Acetylsalicylic Acid	Human Recombinant Insulin, Erythropoietin, Growth Hormones, Monoclonal Antibodies.

Interchangeable or Interchangeability

The biological product is **Biosimilar** to the reference product. It can be expected to produce the **same clinical result** as the reference product **in any given patient.** For a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch. (5)

Table 3. Differences in general requirements between biological, biosimilar and generic products

Criteria	Biologicals	Biosimilars	Generics
Drug Substance	New API	Similar to Reference Product	Identical to reference product
C & M Studies	Full CMC Package	Full CMC Package Extensive comparative analytical studies between Biosimilar and RBD	Full CMC Package
Non-clinical Studies	Full preclinical data as per ICH S6 (R1)	Reduced & comparative to RBD: at least one repeat dose study	Not Required
PK/PD	Standard PK/PD Studies	Comparative PK Profile to RBD	PK equivalence
Clinical Trial	Required for all Indication	Comparative to RBD for at least one indication: one pivotal trial in a representative indication and sensitive population	BA/BE studies are required.
Clinical Trial Design	Superiority, non- inferiority or PK/PD equivalence trial design	Equivalence trial (preferred) or non- inferiority design	Comparative clinical trials are required if the generic drug has narrow therapeutic index
Patient Population	Intended Population	Sensitive in at least one indication	
Study Endpoint	Clinical outcome or validate surrogates	Sensitive and clinically validated	
Efficacy/Safety	Establishing evidence of efficacy and safety/acceptable risk and benefit profile	No meaningful difference to RBD	Therapeutic Equivalence
Indication Extrapolation	Not applicable	Based on set of practical principles: hence case-by-case (clinical trial for more than one use may be needed or required)	All indication of comparator is claimed products are declared bioequivalent
Interchangeability	Not allowed	Case-by-case	Automatic depending on the legislation covering the Health care system
Immunogenicity	Acceptable immunogenicity profile	No meaningful difference to RBD	--
Post-Market	Risk Management Plan	Risk Management Plan	Risk Management Plan

Since biosimilars are a type of biological medicine, all features pertinent to biological medicines apply. Due to the natural variability of the biological source and to the manufacturing process unique to each manufacturer, minor differences can occur between the biosimilar and its reference medicine (table 6 and figure 9). Strict controls are always in place during manufacturing to ensure that minor differences do not affect the way the medicine works or its safety. Thus, these differences are not clinically meaningful in terms of safety or efficacy.

Biosimilars or biologics or biopharmaceuticals are the major magnification driver for the ecumenical pharmaceutical market due to their cost-efficacy, elevating occurrences of various diseases, incrementing number of off-patented drugs, positive outcome in the perpetual clinical tribulations, and elevating demand for biosimilars in different therapeutic applications such as rheumatoid arthritis, oncology and blood disorders.

A biosimilar is not regarded as a generic of a biological

medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular microheterogeneity. Consequently, more studies are needed for regulatory approval of biosimilars than for generics to ensure that minor differences do not affect safety or efficacy. Table 8 compares development and characteristics of generics and biosimilars. (6)

Table 4. Specific features of biosimilar medicines

Parameters	Explanation
Highly similar to the reference medicine	The biosimilar has physical, chemical and biological properties highly similar to the reference medicine. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy.
No clinically meaningful differences compared with the reference medicine`	No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any differences will not have an effect on safety and efficacy.
Variability of biosimilar kept within strict limit	Minor variability is only allowed when scientific evidence shows that it does not affect the safety and efficacy of the biosimilar. The range of variability allowed for a biosimilar is the same as that allowed between batches of the reference medicine.
Same strict standards of quality, safety and efficacy	Biosimilars are approved according to the same strict standards of quality, safety and efficacy that apply to any other medicine.

3. Biosimilar Manufacturing Process

The manufacturing process for Biosimilar should be highly consistent and robust. It is desired to use the same cell line as used by the reference biologics if it has been disclosed in any literature. Alternatively, any cell line that is adequately characterized and appropriate for intended use can be used for development with proper justification, in order to minimize the potential significant change in critical quality attribute and certain impurities that can affect the clinical outcome and immunogenicity of the product. While the manufacturing process for the biosimilar is illustrated in the figure-2

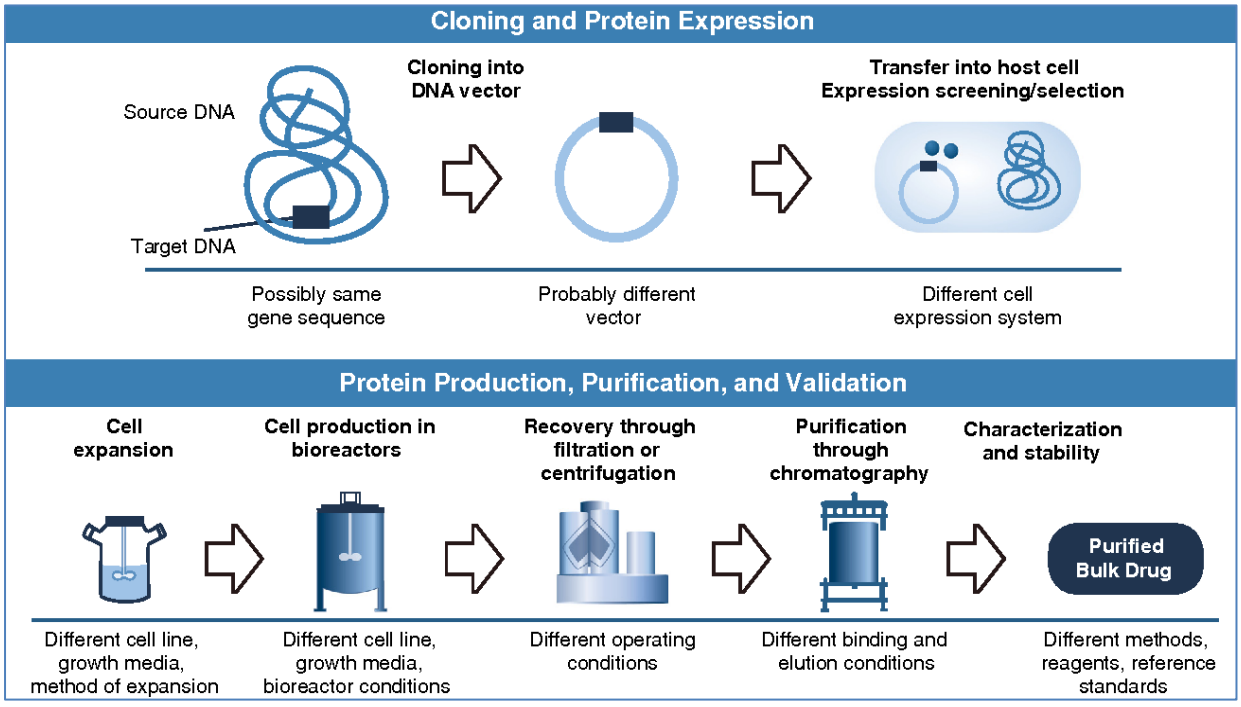

Figure 2. Manufacturing process for Biosimilar Product

Table 5. Comparison of development and characteristics between generics and biosimilars

Generic medicine	Biosimilar medicine
Usually produced by chemical synthesis	Obtained from a biological source
Generally possible to obtain exactly the same molecule	Possible to reproduce the molecule to a high degree of similarity due to unique biomanufacturing methods and natural biological variability
Mostly smaller molecules, easier characterizes	In general, larger, structurally more complex molecules, which require multiple technologies for their characterization

Full data requirements on pharmaceutical quality	Full data requirements on pharmaceutical quality, plus additional quality studies comparing the structure and biological activity of the biosimilar with the reference medicine
Development based on demonstration of bioequivalence (i.e. that the generic and the reference medicine release the active substance into the body at the same rate and to the same extent under similar conditions)	Development based on demonstration of Biosimilarity using comparability studies (comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity)
Clinical data requirements are mainly pharmacokinetic bioequivalence studies	In addition to comparative pharmacokinetic and pharmacodynamic studies, safety and efficacy data may be required, particularly for more complex biological medicine
All indications approved for the reference medicine can be granted based on demonstrated bioequivalence, without the need for further clinical data	Efficacy and safety have to be justified in each indication. However, confirmatory clinical trials with the biosimilar are usually not needed in every indication that has been approved for the reference medicine. After demonstration of biosimilarity, extrapolation of data to other indications is possible if the scientific evidence available addresses all specific aspects of these indications

4. Marketing Authorization in US

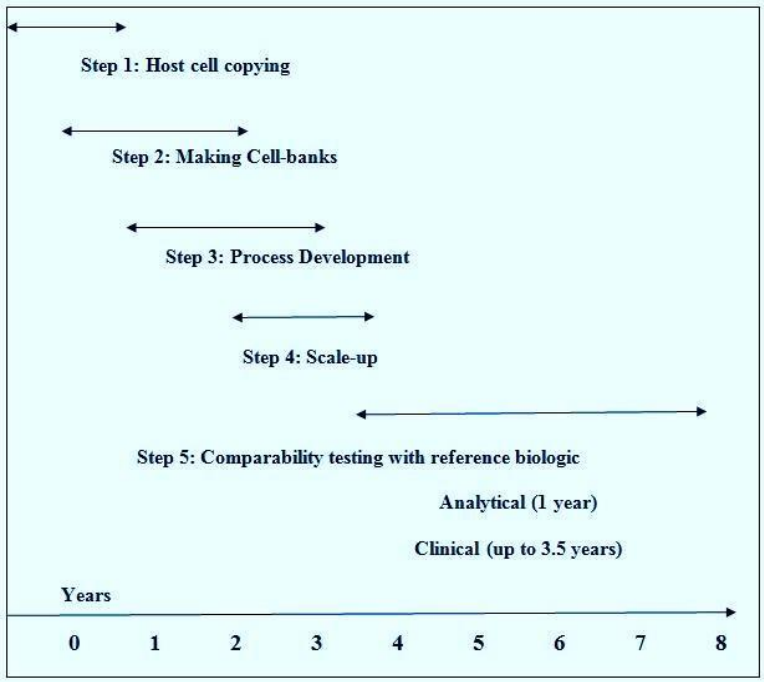

Figure 3. Timeline for Development of Biosimilar

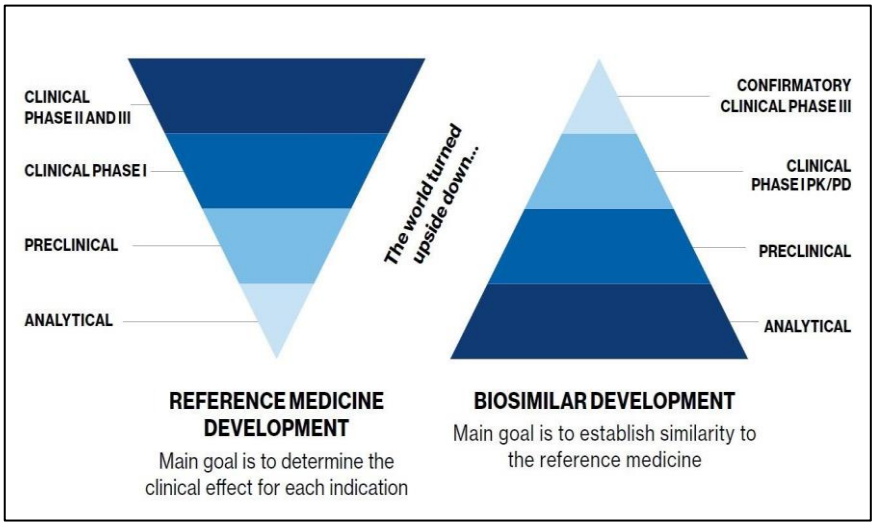

Figure 4. Reference Medicine Development and Biosimilar Development

4.1 Comparability Studies

During the development of the Biosimilar and biopharmaceuticals, comparability exercise plays an important role. The major trigger for the comparability assessment is change in upstream / downstream processing, scale up of manufacturing process, while change in manufacturing facility or equipment change etc. The study data required for the comparability study is illustrated in the figure 5. (7)

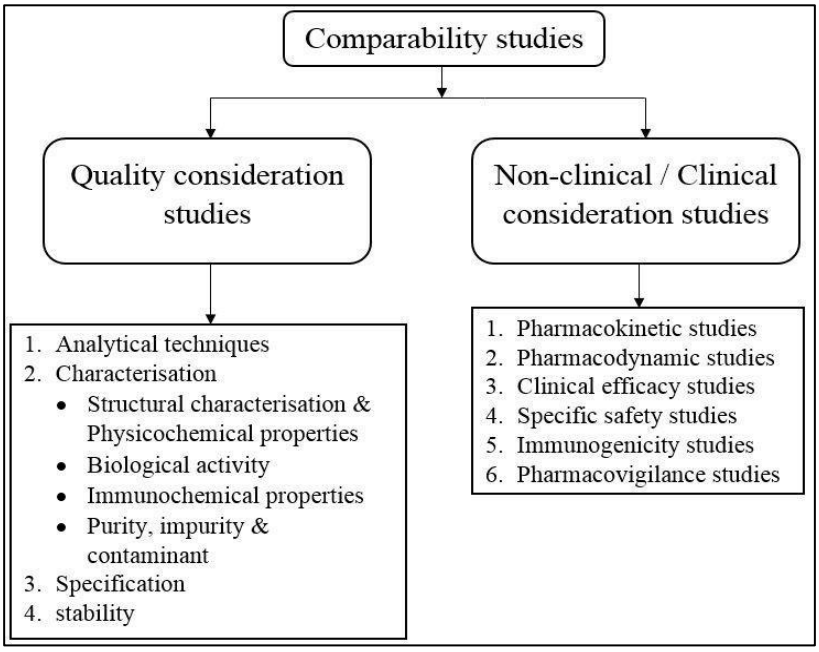

Figure 5. Various studies conducted under comparability studies

4.2 Biologics Regulation

BIOLOGICS -A product highly similar to the reference product without clinically meaningful differences in safety, purity and Potency.

Biological products are approved according to PHS act 1944. As PHS act allows biosimilar to be license under 351(k) based on 'less data of product specific clinical and non-clinical data rather than full complement package listed as abbreviated licensure pathway. RBP must be approved under 351(a) and marketed in the country of origin.

4.2.1 Drug Regulatory Process

The different drug approval processes are regulated by two different regulatory acts stated below:

1. Food Drug and Cosmetic Act (FDCA)
2. Public Health Service Act (PHSA)

4.2.2 Types of Application

The different type of application can be submitted to FDA is listed in table-6 with brief description.

Table 6. Various type of application submitted to FDA

Type of application		Description
Investigational New Drug Application (IND)	Investigator IND	Submitted by a physician who both initiates and conducts an investigation.
	Emergency IND	Authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND.
	Treatment IND	Experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.
New Drug Application (NDA)	505(b)(1)	Application consisting the information which we owned or obtained through research.
	505(b)(2)	Application consisting the information which we do not own or have right of reference to include published literature.
Abbreviated New Drug Application (ANDA) 505(j)(2)(A)(iii)		Approved for the drug having same API, route of administration, the dosage form and strength of the new drug to the ―Reference Listed Drug‖.
Biologics License Application (BLA)	351(a)	Request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce.
	351(k)	Must demonstrate that it is highly similar to 351(a) reference.

Orphan Drug Application	Drugs intended for the safe and effective treatment, diagnosis or prevention of rare disease that affect fewer than 2,00,000 people in the U.S.

Table 7. Application Review Period by FDA

Review approaches	Period
Standard Review	Approx. 10 months
Priority Review	6 months
Fast Track Review	60 days

4.3 Registration Requirements for Biosimilar in US

4.3.1 General requirements:

A 351(k) application must include information demonstrating that the biological product:

- Is biosimilar to a reference product.
- Utilizes the same mechanism(s) of action for the proposed condition(s) of use but only to the extent the mechanism(s) are known for the reference product.
- Condition(s) of use proposed in labeling have been previously approved for the reference product.
- Has the same route of administration, dosage form, and strength as the reference product?
- Is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent.

4.3.2 General requirements: 351(k) applications:

- The PHS Act requires that a 351(k) application include, among other things, information demonstrating biosimilarity based upon data derived from:
- Analytical studies demonstrating that the biological product is ―highly similar‖ to the reference product notwithstanding minor differences in clinically inactive components.
- Animal studies (including the assessment of toxicity); and
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product. (8)

Table 8. Registration Requirements for Biosimilar in US

Sr. No.	Criteria	US
1	Approval procedure	Biologics License Application (BLA)
2	Form used	351(k)
3	Application fees	w clinical-$ 1,746,745 w/o clinical -$ 873,373
4	Submission Format	eCTD
5	Language	English
6	Submission method	Prepared in common format with specific regional information and submitted to the regulatory body
7	1	Module 1: Administrative Information
8	2	Module 2: Quality overall summary
9	3	Module 3: Quality
10	4	Module 4: Nonclinical study report
11	5	Module 5: Clinical study report

4.3.3 Approval Process for Biosimilar Products in US

All FDA-approved biological products, including reference products and biosimilar products, undergo a rigorous evaluation so that patients can be assured of the efficacy, safety, and quality of these products.

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved in a ―standalone‖ application that must contain all data and information necessary to demonstrate its safety and effectiveness. Generally, the data and information necessary to demonstrate the safety and effectiveness of a reference product will include clinical trials for the disease indications being sought by the manufacturer.

A biosimilar is highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from, an existing FDA-approved reference product. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety and effectiveness of the proposed product. The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity. The

comparative data are generated and evaluated in a stepwise fashion that begins with a foundation of detailed analytical (structural and functional) characterization and comparison of the products, moving on to animal studies if necessary and then to comparative clinical studies.

Consequently, rather than generating the same full profile of nonclinical and clinical data as the reference product, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on FDA's previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients. (9)

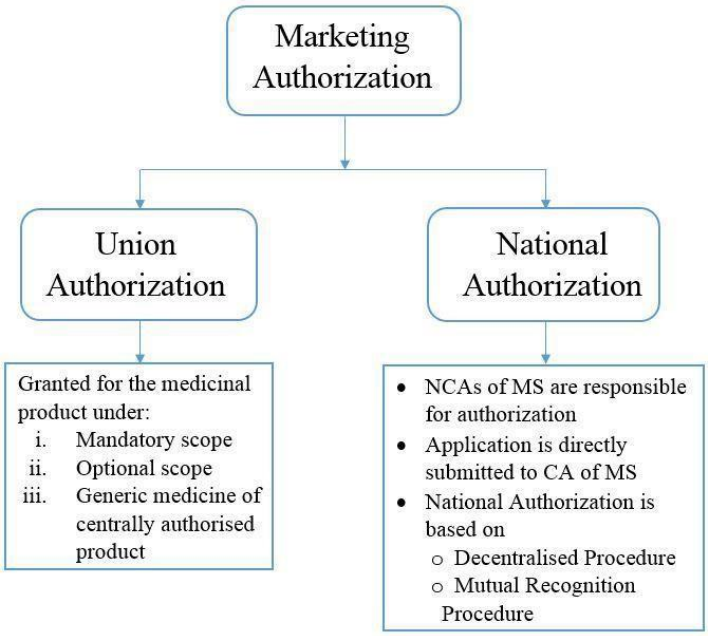

Figure 6. Category of Marketing Authorisation in EU

5. Marketing Authorization in EU

Marketing authorisation for the medicines in EU region are classified in 2 major categories shown in figure-6

The review process of drug approval depends on the authorization procedure listed in below table: 9

Table 9. Registration review period in EU

Submission Procedure	Review Period
Centralized Procedure	210 days
Decentralized Procedure	210 days
Mutual Recognition Procedure	390 days
National Procedure	210 days

5.1 Development and approval of biosimilars in EU

Approval of medicines in the EU relies on a solid legal framework, which in 2004 introduced a dedicated route for the approval of biosimilars. The EU has pioneered the regulation of biosimilars since the approval of the first one (the growth hormone somatropin) in 2006. Since then, the EU has approved the highest number of biosimilars worldwide, and consequently has the most extensive experience of their use and safety. Over the years, EMA has issued scientific guidelines to help developers conform to the strict regulatory requirements for approving biosimilars. The guidelines have evolved to keep pace with rapid advances in biotechnology and analytical sciences, and they take on board increasing experience of clinical use.

5.2 Process for approval of biosimilars in the EU

All medicines produced using biotechnology and those for specific indications (e.g. for cancer, neurodegeneration and auto-immune diseases) must be approved in the EU through EMA (via the so-called centralised procedure'). Nearly all biosimilars approved for use in the EU have been approved centrally, as they use biotechnology for their production. Some biosimilars may be approved at national level, such as some low- molecular weight heparins derived from porcine intestinal mucosa. When a company applies for marketing authorisation at EMA, data are evaluated by EMA's scientific committees on human medicines and on safety (the CHMP and PRAC), as well as by EU experts on biological medicines (Biologics Working Party) and specialists in biosimilars (Biosimilar Working Party). The review by EMA results in a scientific opinion, which is then sent to the European Commission, which ultimately grants an EU-wide marketing authorisation.

5.3 Data requirements for approval: a scientifically tailored package

Medicines are approved when studies on their pharmaceutical quality, safety and efficacy convincingly demonstrate that the medicine's benefits outweigh the risks (positive benefit-risk balance'). For any biological medicine with a new active substance, a positive benefit-risk balance is determined mainly from evidence of safety and efficacy in pivotal trials in humans (figure 7), supported by solid pharmaceutical quality data and non-clinical data. For biosimilars, a positive benefit-risk balance is based on demonstrating biosimilarity, i.e. that the active substance is highly similar to the reference medicine (figure 7). This is achieved via comprehensive comparability studies with the reference medicine (figure 7), and on the basis of solid pharmaceutical quality data. By demonstrating high similarity with the reference medicine, the biosimilar can largely rely on the efficacy and safety experience gained with the reference medicine. An overview of biosimilar development compared with the development of reference medicines is provided in table 10. (10)

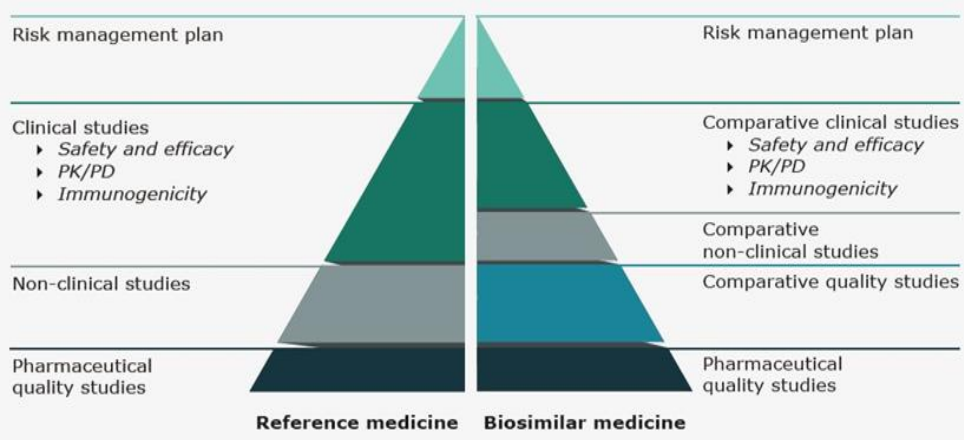

Figure 7. Comparison of data requirements for approval of biosimilar versus the reference medicine

Table 10. Overview of biosimilar development compared with a reference medicine

Biological medicine with new active substance (e.g. reference medicine)	Biosimilar medicine
No previous knowledge of safety and efficacy	Builds on knowledge of safety and efficacy from years of clinical use with reference medicine
Development aims at demonstrating safety and efficacy directly in patients	Development aims at demonstrating comparable safety and efficacy by establishing biosimilarity
Comparability studies only for manufacturing changes during development (e.g. producing larger batches for clinical trials)	Comprehensive comparability studies with the reference medicine
Full non-clinical data (pharmacology and toxicology)	Amount of non-clinical data determined by the outcome of quality studies
Conventional clinical trials to demonstrate efficacy and safety in all claimed therapeutic indications	Comparative clinical trials to exclude clinically meaningful differences
Trials designed mainly to compare with placebo or current standard of therapy using hard endpoints (e.g. long-term outcome, mortality, structural damage) and a relevant patient population to demonstrate benefit	Trials designed mainly to show clinical equivalence with the reference medicine using sensitive endpoints in a population where product-related differences in clinical performance can be detected
Positive benefit-risk mainly established on the basis of safety and efficacy studies in the intended population	Positive benefit-risk based on demonstrating biosimilarity (using comparability studies)

5.4 Evaluation of Similar Biological Medicinal Product

Application for biosimilar is according to the Article 10 of directive 2001/83/EC. The registration workflow for similar biological product is shown in table 11 (2)

Table 11. Evaluation of similar biological medicinal product

Application Submitted to CHMP	
DAY-1	Start of Procedure
DAY-80	Receipt of the Assessment Reports from CHMP Rapporteur and (Co) Rapporteur by CHMP members and EMA. Assessment Reports by Rapporteur and (Co) Rapporteur: Overview(Conclusion on risk benefits) Quality Clinical

	Non-Clinical The so-called Day 80 Assessment Reports and sent to the Applicant for information only.
DAY-100	Rapporteur, (Co) Rapporteur, other CHMP members and EMA receive comments
CHMP peer review →	Preparation of list Of Question ← Report of BWP to CHMP (Quality Part)
DAY-120	CHMP adopts the List of Question and sent to the Applicant by EMA Clock stop, At the latest by Day 120, adoption by CHMP of request for GMP/GLP/GCP inspection, if necessary CHMP.
DAY-121	Submission of the responses, including labelling and package leaflet texts in English.
	Restart of the clock. After receipt of responses, the CHMP will adopt a timetable for the evaluation of the responses.
DAY-180	Submission of **final inspection** report to the EMA, Rapporteur and Co- Rapporteur by the inspection team (at the latest by day 180).
DAY-210	Adoption of CHMP Opinion + CHMP Assessment Report **Accepted or rejected**

6. Comparability Studies: The Cornerstone of Biosimilar Development

Biosimilar development relies heavily on comparability studies' to establish biosimilarity to the reference medicine. This involves a comprehensive head-to-head comparison of the biosimilar and the reference medicine (figure 8).Comparability is conceived as a step-wise process that is tailor-made for each product (figure 8); knowledge from the initial quality comparability studies1 (step 1) is used to determine the extent and type of non-clinical (step 2) and clinical studies2 (step 3) required in the next step of development, always with the aim of ruling out differences in clinical performance between the biosimilar and the reference medicine.

Step 1 Comparative quality studies: In vitro studies compare the protein structure and biological function using sensitive techniques capable of detecting minor differences with clinical relevance between the biosimilar and its reference medicine. These studies are much more sensitive than clinical trials for detecting such differences, as there is often variability among human subjects participating in trials. Differences that may affect clinical safety, efficacy or immunogenicity need to be further studied (e.g. in comparative non-clinical or clinical studies, step 2 and 3).

Step 2 Comparative non-clinical studies:

These studies include pharmacodynamic studies in vitro, which look at binding and activation (or inhibition) of physiological targets and immediate physiological effects in cells. Pharmacodynamic studies in vivo (animal models) are only done if no suitable in vitro model exists. In vivo toxicological studies are only required in certain cases, for example when the biosimilar is produced in a new type of cell or organism, or when the formulation includes new excipients not used previously.

Step 3 Comparative clinical studies:

The aim of studies in humans is not to demonstrate safety and efficacy in patients, as these have already been established for the reference medicine. Clinical trials are tailored to confirm biosimilarity and to address any questions that may remain from previous analytical or functional studies. (11)

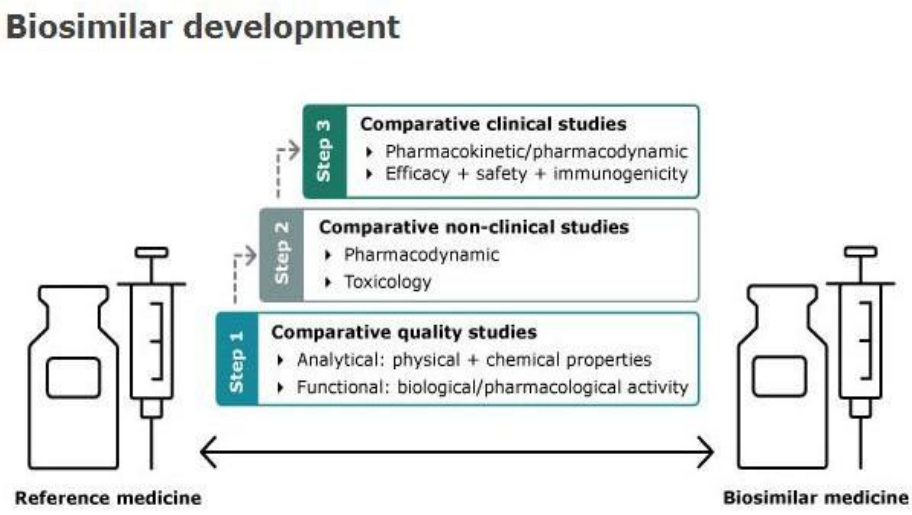

Figure 8. Biosimilar development is comparative and progresses in a step-wise manner

7. Current Legislation with future Perspective

The rising pressure of cost-containment in all major markets is driving the uptake of generics and also creates a demand for biosimilars. However, the cost and duration of development for biosimilars are much greater than for

small-molecule generics, and presents a significant barrier to entry and a resistor of biosimilars market growth. The possible savings achievable through biosimilar products have been estimated very differently in various studies – e.g., estimations of U.S. savings achievable from follow- on biologics vary between $378 billion over the 20- year period 2010–2029 and $2.0–2.8 billion over 10 years [68] or $3.6 billion in 2008– 2017. A recent estimation by the Congressional Budget Office estimates that enactment of biosimilars legislation would reduce total U.S. expenditures on biologicals by $25 billion (thereof federal savings $5.9 billion plus increased revenues of $0.8 billion) over the 2009–2018 period, with competition beginning for most products not before the second half of this period. This would equal about 0.5% of national spending on all prescribed medicines. The study assumes a 35% sales-weighted average market share for biosimilars by the fourth year after launch. Biosimilars are a reality and, as conventional generics, is part of the rules of the gamel in pharma industry. In this context, it has even been considered that competition in future indeed might not primarily be between innovators and price-cutting copiers, but rather with second generation biopharmaceuticals based on improved formulation or delivery systems, or derivatized biologics with improved performance. Thus the ultimate benefit of the emergence of biosimilars, in the end, may be in stimulating innovative research resulting in new options to treat serious diseases. It will be essential that the regulations introduced in various parts of the world do not hinder, but promote pharmaceutical innovation to the benefit of patients, healthcare systems, and industry. (12)

8. Conclusion

Biosimilars are approved under the PHS act in US. Biosimilar is licensed under 351(k) based on the minimal data of clinical and non-clinical studies. Applicant has to inform the innovator manufacturer regarding the biosimilar application according to BPICA in US. Interchangeability is allowed by US-FDA based on the submission of the more data depicting the comparability between the biosimilar and innovator product.

The market for biotechnology-derived medicinal products is evolving rapidly with the imminent entry of biosimilars. EMEA has forged ahead in providing guidance for national regulatory bodies in Europe. The EMEA guidelines are, however, a work in progress, and readers should consult the EMEA web site (www.emea.eu.int) for the latest updates. Development of the biosimilar drug is not easy, as there are various challenging prerequisite which should be taken care during development process. EU biosimilar portfolio and related guidelines continue to grow. EU experience important reference for others. This document contain the framework of EMA which hold the department of CHMP and PRAC under which biosimilar is work. The guideline of EMEA has its own specification regarding the process of its Evaluation, Filling and Registration procedure apart from common process. (13)

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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