Biosimilars 2024

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Abstract: *Biosimilars, a rapidly growing category of medications in The United States of America (US), play a vital role in addressing health conditions. This study provides a comprehensive overview of the distinctions between Biosimilars and Generics, examining the Biosimilar landscape with a focus on approved products and those in the pipeline from key market players. Emphasizing the cost-effectiveness of Biosimilars akin to Generics, the paper outlines the intricate differences between them, highlighting the divergence in The United States Food and Drug Administration (US FDA) approval pathways for Biosimilars and Generics. The paper further explores regulatory frameworks, including the Biologics Price Competition and Innovation Act (BPCIA), offering insights into approved Biosimilar products. Recognizing the challenges in Biosimilar development and evaluating the pros and cons in comparison to Generics are crucial for healthcare professionals and patients navigating this dynamic landscape. As the pharmaceutical industry progresses, this paper aims to elucidate current approaches and key considerations in the field of Biosimilars.*

Keywords: *Biosimilar, Biologics, Regulations, Generics, Biological Products Review*

I. INTRODUCTION:

Biologics (also called Biological Products) are the fastest-growing class of medications in The United States of America (US) and account for a substantial and growing portion of health care costs (24). Biologics refer to a substance obtained from a living organism or its by-products, employed for the purposes of diagnosing, preventing, or treating diseases (3). A variety of Biologics have gained regulatory approval, including Therapeutic Proteins like Filgrastim, Monoclonal Antibodies such as Adalimumab, and Vaccines designed to address conditions like Influenza and Tetanus (2). A Reference product is the sole Biological product already sanctioned by the US FDA, serving as the benchmark for assessing a proposed Biosimilar product. Approval of a Reference product involves comprehensive safety and effectiveness data. The evaluation of a proposed Biosimilar product is centered on comparing it to the Reference product, ensuring a high degree of similarity and the absence of clinically meaningful differences (2). A Biosimilar product is highly similar to an approved Reference product (also known as the Originator or Reference Biologic) (38). Biosimilar product must demonstrate no clinically meaningful differences in terms of safety, purity, and potency compared to the reference product (3). Biosimilar products, like Generic products, provide cost-effective alternatives to brand-name medications. They follow distinct approval pathways from Generics, avoiding redundant clinical trials. However, it's crucial to recognize that while Generics mirror their respective Reference products as exact replicas, Biosimilars achieve a high degree of similarity without attaining structural identity to their Reference products (3). This is due to the fact that the manufacturing process for Biologics is proprietary to each manufacturer and is produced using living organisms and complex biotechnological methods and steps, such as recombinant DNA (Deoxyribonucleic Acid) technology, fermentation, and purification. All of these contribute to the lot to lot variation in Biologic products (both Reference and Biosimilar). Whereas, Generics are manufactured using a wholly reproducible process which is straightforward and involves chemical synthesis (3, 9). Biosimilars are not identical to Generics; significant differences

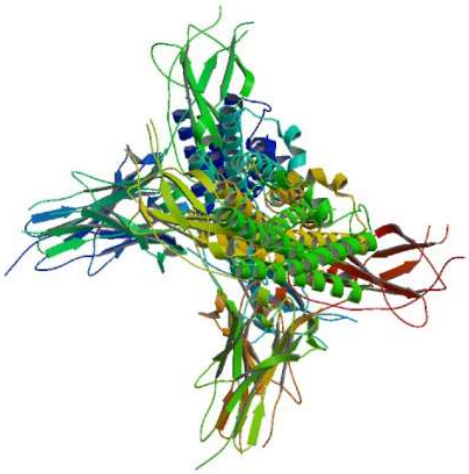
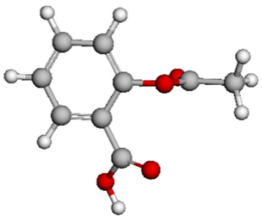
set them apart like molecular size, distinctive structure, and the complexity and elevated costs involved in their development (15, 9). Table 1 summarizes the differences between Reference Product for Biologics, Biosimilars and Generics for better clarity and understating. Figure 1 shows the molecular complexity between Biologics and Generics.

Table 1: Difference between the Biologics, Biosimilars and Generics (3, 15, 9, 38, 36, 26, 1).

Details	Reference Product for Biologics	Biosimilars	Generics
What are they	A substance derived from living organisms or its products.	A substance derived from living organisms or its products which is highly similar to and has no clinically meaningful differences from an existing US FDA-approved reference product.	A substance produced by the chemical synthesis process and is exact copy of its Reference Product.
Molecular Complexity and Size	Complex, can exceed 150,000 daltons in size		Simple, approximately 180 daltons on average in size.
Immunogenic potential	Could be Immunogenic		Virtually no Immunogenic potential
Manufacturing Process	Proprietary knowledge and therefore different for each manufacturer. Difficult to do reproducibility yielding lot to lot variation. Sensitive to production process changes		Less sensitive to production process changes as compared to Biologics.
Clinical Studies	Extensive clinical studies are required Phase I to IV	Phase I, III studies are required	Often only Phase I studies are required

Prescribing and/or dispensing setting	Prescribed in the Hospital by Doctors (most countries)		Prescribed in day to day healthcare by general physicians and dispensed through community pharmacies primarily in most countries
Regulatory approval Act	Public Health Service Act (PHSA), Biologic License Application (BLA) 351 (a)	Public Health Service Act (PHSA), Biologics Price Competition Innovation Act (BPCIA) 351 (k)	Food, Drug & Cosmetics Act, Abbreviated New Drug Application (ANDA), 505(j)
Development Costs and Timeline	> $ 2 billion, takes 10 years or more	$100 million not including regulatory fees, takes 5 to 9 years to develop	$1-2 million takes, ~2 years to develop

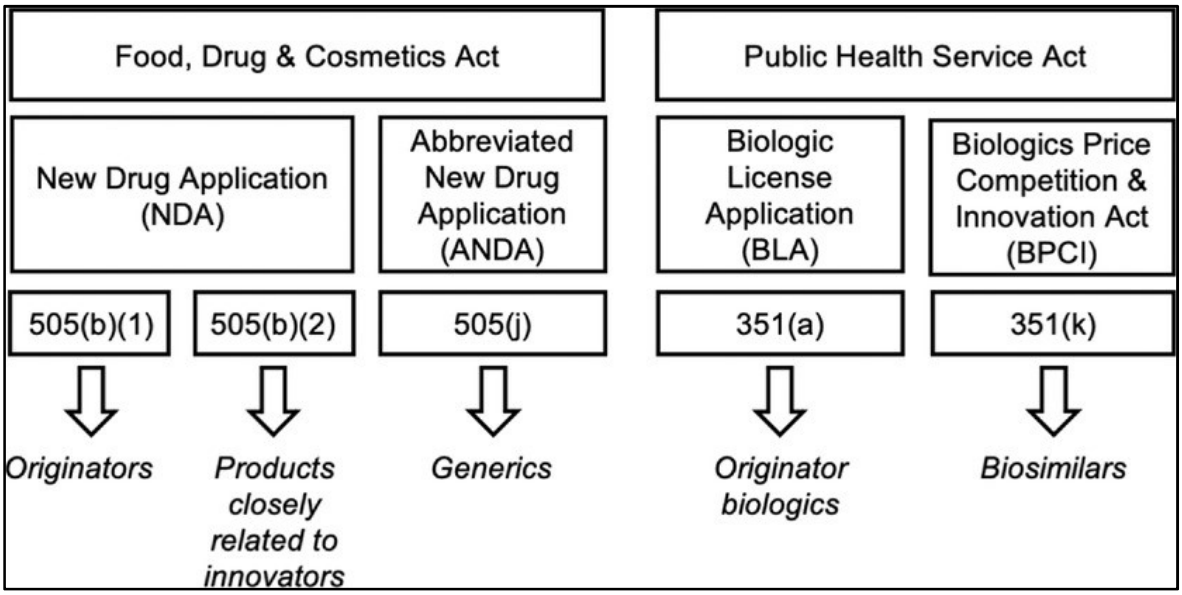
Figure 1: The molecular size and complexity comparison of Biosimilars and Generics (21).

Biosimilar: Filgrastim	**Generic**: Aspirin
	

US FDA regulatory approval pathways for Biosimilars and Generics are also different. Biologics are reviewed and approved through Public Health Service Act (PHSA) Biologic License Application (BLA) 351a for Reference (also known

as Originator) Biological Product and Biologics Price Competition Act (BPCIA) 351(k) for Biosimilars. While Generics are reviewed and approved through Food, Drug and Cosmetics Act, Abbreviated New Drug Application (ANDA) 505(j)) (35) (Figure 2). It is evident from this information that the regulatory environment acknowledges the unique challenges posed by Biologics and Biosimilars, requiring specialized approaches that differ from the well-established pathways for Generics. US FDA had approved till date 47 Biosimilars (4). The U.S. biologics market has seen rapid growth, comprising 46% of total medicine spending. In 2021, $260 billion was spent on biologics out of a total medicine expenditure of $568 billion. This presents a prime opportunity for Biosimilars, offering cost-effective alternatives and fostering market competition (8).

Figure 2: Regulatory approval pathways for Generics and their Reference Products, and Biosimilars and their Reference Products (adapted from **35**).



As these products continue to evolve, understanding their unique characteristics and regulatory pathways is crucial for healthcare professionals and patients alike. The purpose of this paper is to highlight current approaches within the pharmaceutical industry as they relate to Biosimilars.

II. METHODS:

The information used to write this paper was collected from various sources, including databases such as Google Scholar and Science Direct. Papers were retrieved from these databases using keywords such as 'Biosimilars,' 'Biosimilar review,' 'Biosimilar landscape,' 'Biosimilars regulations,' and 'Biosimilars Vs Generics.' The obtained papers underwent further screening based on publication date (between 2021 and 2024) and by reviewing their abstracts. Subsequently, relevant papers were selected and referred to for the writing of this review paper. Additionally, the reference lists from articles identified in this search were reviewed, and any additional publications considered within the scope of this review were retrieved. All retained articles were qualitatively assessed and described in this review article.

Information from the websites of regulatory health agencies such as the US FDA and EMEA was consulted to explore literature related to the development and approval of Biosimilars products. Furthermore, websites of well-known and reputable companies operating in the field of Biosimilars (for market research, development, and marketing of Biosimilars) were referred to in order to collect additional information.

III. RESULTS AND DISCUSSION:

A. THE BIOSIMILAR LANDSCAPE:

The Biosimilar landscape, situated at the intersection of economic considerations, scientific intricacies, and regulatory nuances, has become a focal point for pharmaceutical companies seeking strategic advantages (30). Biopharmaceuticals stand out as one of the rapidly growing sectors within the Biotechnology industry. Specifically, the Biosimilar segment is experiencing significant expansion, boasting a current global count of over 200 approved Biosimilars (50). Global Biosimilars market is poised for significant growth and is expected to be $66.9 billion by 2028 from estimated to be worth of $29.4 billion in 2023, at a compound annual growth rate (CAGR) of 17.8% (6). According to research conducted by MarketLine and DCAT on the global ranking of countries in biotechnological innovations, the United States holds a dominant position with 48.2% of the biotech market shares. The Asia-Pacific region follows with a 24% share, and Europe holds 18.1% (46). Over the past five years, the US biologics market has exhibited an average annual growth rate of 12.5% based on invoice prices. This growth outpaces that of non-biologics, and currently, biologics account for 46% of total spending. In 2021, the expenditure on medicines in the United States reached $568 billion at ex-manufacturer invoice prices. Within this total, $260 billion was allocated to biologics, constituting 46% of the overall spending on medicines (8). In the wake of the patent expiration of specific innovator products and the increasing endorsement for expedited approval pathways from major regulatory agencies like US FDA and the European Medicines Agency (EMA), there has been a consistent rise in the approval of Biosimilars (50). Though these expedited pathways are not yet not fully optimized for resource optimization, they definitely serves as a robust incentive for pharmaceutical companies wanted to develop Biosimilars (43). The pivotal economic motivation behind Biosimilar development lies in the potential to provide cost-effective alternatives to high-priced reference biologics. The less development costs for the Biosimilars as compared to the Reference products makes them more affordable to patients, which is especially crucial for chronic

diseases (26). Additionally, Biosimilars strategically position pharmaceutical companies for market share expansion, particularly in the aftermath of expiring patents for innovator biologics**.** Around 71 biologic patents are expected to expire by 2023, presenting a sales opportunity of approximately $55 billion for competitors interested in manufacturing and selling Biosimilars (28). Biosimilars are viewed as potent tools for global market penetration and companies can strategically embrace Biosimilar development to establish a foothold in diverse markets, thereby catering to varied healthcare needs and contributing to global health equity. This approach not only consolidates the company's market presence but also enhances competitiveness in an industry characterized by rapid scientific advancements and evolving market dynamics (14). Due to this competition more and more products become available in the forcing manufacturers to reduce the prices of their products to maintain or increase market share. Additionally, recognizing the scientific and logistical complexities inherent in Biosimilar development, pharmaceutical companies often opt for strategic partnerships and collaborations. These synergies allow companies to leverage specialized expertise, share resources, and navigate the intricacies of Biosimilar development collaboratively, thereby mitigating risks and optimizing efficiency. This provides a significant opportunity for Biosimilars to enter into market (28).

Biosimilars development process starts with the characterization and understanding of the Reference Product. As the Reference Products actives are synthesised from living organisms they are big in molecular size (can exceed 150,000 Daltons) and have complex structure it is difficult to characterise their molecular structure requiring resource intensive exercise (37). Additionally, the manufacturing processes of the Reference products are proprietary to its manufacturers therefore Biosimilar manufacturers don’t get access them making it more difficult for them and they have to find a new manufacturing process to achieve the same (36). Further, post-translational adjustments and slight change in manufacturing process could affect the functional and physiochemical characteristics of the drug therefore it is not possible to create exact copy of

Reference product (27, 41). Achieving a high degree of similarity without complete structural identity poses a substantial scientific challenge in Biosimilar development. Due to these reasons to identify and characterize the intricate molecular structures of biologics it demand sophisticated technologies, including advanced analytical techniques and innovative methodologies (37). Summary of the Critical Quality Attributes (CQAs) and different analytical platforms used for the same are summarized in Table 2.

Table 2: Critical Quality Attributes (COAs) and Analytical Platforms used for the characterization (37):

Critical Quality Attributes (CQAs)	Analysis	Analytical Platforms used
Primary structure/ identity	Intact mass	▪ LC-UV/ESI-TOF-MS ▪ MALDI-TOF-MS ▪ CE-ESI-TOF-MS ▪ LC-ESI-[Native]MS
	Peptide mapping/ Amino acid sequence	▪ MALDI-TOF-MS ▪ RP-UV/ESI-QTOF-MS ▪ LC-Orbitrap MS ▪ LC-Iontrap MS ▪ 2D-LC-MS
Higher order structure	Secondary structure	▪ Far UV CD ▪ FTIR
	Tertiary structure	▪ Near UV CD ▪ IT-FLR ▪ 1D/2D NMR ▪ IM-MS ▪ HDX-MS ▪ NMR ▪ XRC
	Conformational stability	▪ DSC ▪ VT-CD ▪ TCSPC ▪ NanoDSF ▪ IM-MS (Collision induced unfolding) ▪ NMR
Glycosylation	Oligosaccharide pattern	▪ HILIC-FLD/QTOF-MS ▪ RP-ESI-QTOF-MS ▪ MALDI-TOF-MS ▪ CZE-LIF

	Monosaccharide/ Sialic acid content	▪ RP-FLD ▪ HPAEC-PAD ▪ NP-WAX-FLD
Product-related variant/ Purity	Aggregates/ fragments (sub-visible and visible particles)	▪ SEC-UV ▪ SDS-PAGE ▪ SEC-RI/MALS ▪ CE-SDS-UV/LIF ▪ DLS/AF4 ▪ MFI/LO ▪ SE/SV-AUC ▪ DOSY-NMR
	Charge variant	▪ CEX-UV ▪ cIEF-UV ▪ icIEF-UV ▪ CZE-UV ▪ CZE-ESI-MS ▪ 2D-LC-ESI-QTOF-MS ▪ SCX-LC-Native-orbitrap-MS
	Related protein	▪ RP-UV/QTOF-MS ▪ HIC-UV ▪ RP/HIC/Boronate affinity chromatography-FLD
Process-related variants	Host Cell Protein	▪ ELISA ▪ 2D PAGE/ DIGE ▪ RP-ESI-QTOF-MS ▪ CZE-MS ▪ 2D LC/CE-MS
	Host Cell DNA	▪ qPCR/Picogreen ▪ Threshold assay

Further difficulties that Biosimilar developers have to overcome are Stringent Regulatory Scrutiny, Manufacturing Challenges, and Market Access and Competition (39, 41, and 45). Regulatory agencies impose stringent demands on biosimilar developers to provide comprehensive data supporting biosimilarity, meticulous documentation and adherence to stringent regulatory standards which adds layers of complexity and time to the regulatory approval process (39). As manufacturing of Biosimilars involve intricate biotechnological processes such as recombinant DNA technology, fermentation, and purification achieving consistency in manufacturing is challenging, leading to variations in the final product that can impact quality and efficacy (41). Gaining market access for Biosimilars, especially in regions dominated by established Biologics,

requires overcoming resistance from healthcare providers, payers, and patients. Competitive pricing becomes a critical factor in navigating this complex landscape and securing acceptance (45). Table 3 summarizes the Biosimilar products approved by the US FDA and products which are there at various stages of development in different companies.

Table 3: Biosimilar products approved by the US FDA and products those are in pipeline at various stages of development in different companies (4, 24).

Molecule	Reference Products (Manufacturer)	Approved Biosimilar Products (Manufacturer)	Products in Pipeline (Manufacturer, development stage)
Filgrastim	NEUPOGEN (Amgen)	ZARXIO (Sandoz)	GRASTOFIL (Accord-Apotex, Pending)
		NIVESTYM (Pfizer)	TX01 (Tanvex, Pending)
		RELEUKO (Amneal)	LUPIFIL (Lupin, Ph 1)
Epoetin	EPOGEN (Amgen) / PROCRIT (J&J)	RETACRIT (Pfizer-Vifor)	APO-EPO (Apotex, Ph 3)
Pegfilgrastim	NEULASTA (Amgen)	FULPHILA (Mylan)	LAPELGA (Accord-Apotex, Pending)
		UDENYCA (Coherus)	LUPIFIL-P (Lupin, Pending)
		ZIEXTENZO (Sandoz)	TX04 (Tanvex, Ph 1)
		NYVEPRIA (Pfizer)	-
		STIMUFEND (Fresenius)	
		FYLNETRA (Amneal)	
Insulin Glargine	LANTUS (Sanofi)	SEMGLEE (Viatris-Mylan)	-
		REZVOGLAR (Eli Lilly)	
Ranibizumab	LUCENTIS (Genentech)	BYOOVIZ (Biogen)	XLUCANE (Stada, Ph 3)
		CIMERLI (Coherus)	LUBT010 (Lupin, Ph 3)
Aflibercept	EYLEA (Regeneron)		M710/MYL-1701P (Mylan-Momenta, Pending)
			ABP 938 (Amgen, Ph 3)
			FYB203 (Coherus, Ph 3)
			SB15 (Biogen-Samsung, Ph 3)
			ALT-L9 (Alteogen, Pre-clin)
			SCD411 (Sam Chun Dang, Ph 3)
			AVT06 (Alvotech, Ph 3)
			CT-P42 (Celltrion, Ph 3)
			SOK583A1 (Sandoz-Hexal, Ph 3)

Infliximab	REMICADE (J&J)	INFLECTRA (Pfizer)	NI-071 (Nichi-Iko, Ph 3)
		RENFLEXIS (Organon)	
		AVSOLA (Amgen)	
Etanercept	ENBREL (Amgen)	ERELZI (Sandoz)	YLB113 (Lupin, Ph 3)
		ETICOVO (Samsung)	
Adalimumab	HUMIRA (AbbVie)	AMJEVITA (Amgen)	AVT02 (Alvotech-Teva, Pending)
		CYLTEZO (BI)	
		HULIO (Viatris)	
		HYRIMOZ (Sandoz)	
		ABRILADA (Pfizer)	
		YUSIMRY (Coherus)	
		HADLIMA (Organon)	
		IDACIO (Fresenius)	
		YUFLYMA (Celltrion)	
Natalizumab	TYSABRI (Biogen)	TYRUKO (Sandoz)	-
Tocilizumab	ACTEMRA IV/SC (Genentech)	TOFIDENCE (Biogen)	Tyenne(Fresenius, Pending)
			CT-P47 (Celltrion, Ph 3)
			DRL_TC (Dr. Reddy's, Ph 3)
Ustekinumab	STELARA IV/SC (J&J)	WEZLANA (Amgen)	-
Certolizumab	CIMZIA (UCB)	-	Xcimzane (Xbrane-Biogen, Pre-clin)
Golimumab	SIMPONI (J&J)	-	BAT2506 (Bio-Thera, Ph 3)
			AVT05 (Alvotech, Ph 3)
Eculizumab	SOLIRIS (Alexion)	-	SB12 (Samsung Bioepis,Ph 3)
			ABP 959 (Amgen, Pending)
Omalizumab	XOLAIR (Alexion)	-	CT-P39 (Celltrion, Ph 3)
			BP11 (Aurobindo, Ph 3)
			TEV-45779 (Teva, Ph 3)
Rituximab	RITUXAN (Genentech)	TRUXIMA (Teva)	DRL RI (Dr. Reddy's, Ph 3)
		RUXIENCE (Pfizer)	SAIT101 (AZ-Archigen, Ph 3)
		RIABNI (Amgen)	MABIONCD20 (Mabion, Ph 3)
Bevacizumab	AVASTIN (Genentech)	MVASI (Amgen)	SB8 (Organon-Samsung, Pending)
		ZIRABEV (Pfizer)	FKB238 (AZ-Centus, Pending)
		ALYMSYS (Amneal)	TX16 (Tanvex, Ph 1)
		VEGZELMA (Celltrion)	ABEVMY (Mylan-Biocon, Pending)
		AVZIVI (Sandoz)	
Trastuzumab	HERCEPTIN (Genentech)	KANJINTI (Amgen)	TX05 (Tanvex, Pending)
		OGIVRI (Mylan)	EG12014 (Sandoz, Pending)
		TRAZIMERA (Pfizer)	HD201 (Prestige Bio, Ph 3)
		HERZUMA (Teva)	Zercepac (Accord, Pending)
		ONTRUZANT (Organon)	

- ✓ Pending is defined as any stage of development between BLA/aBLA submission and full FDA approval (BLA) or Abbreviated Biologics License Application (aBLA) and full FDA approval.
- ✓ Ph 1: Phase I studies, Ph 2: Phase 2 studies, Ph 3: Phase 3 studies

B. THE PROS AND CONS OF BIOSIMILARS VS GENERICS:

The pharmaceutical industry is witnessing a transformative shift with the advent of Biosimilars and Generics, offering cost-effective alternatives to complex Biologics and traditional Small-molecule drugs, respectively. While both Biosimilars and Generics aim to enhance accessibility to essential medications, they operate in distinct realms, each presenting a unique set of advantages and challenges (9).

One of the primary advantages of Biosimilars is that they offer affordable treatment options and they have potential to significantly reduce healthcare costs. The democratization by providing the access to advanced therapies fosters innovation and competition between Biosimilars and Reference Biological Products, and between Biosimilars. This Increased competition often leads to reduced prices for both Biosimilars and Reference Biological Products. Biosimilars diversify treatment options, providing physicians and patients with a broader range of choices (33, 47). On the other side Biosimilars product development process requires significant financial investments due to the complexities involved in replicating the structure and function of biologics. Achieving similarity without complete identity to the Reference product poses scientific challenges, and the regulatory pathway demands comprehensive data to establish bio-similarity**.** Due to their complexity of structures they could be Immunogenic, which also needs to be confirmed through additional studies. This yield in high development costs which may impact the extent of cost savings that can be passed on to consumers. Additionally, per US FDA additionally studies are required to be done for to classify the Biosimilar as interchangeable, if not done then it is required that the prescription to be written

specifically for Biosimilar to be used than of its Reference Product brand name (40, 44). Finally, gaining acceptance for Biosimilars in the market often faces resistance from healthcare providers, payers, and patients, due to their unawareness, who may be skeptical about the interchangeability and safety of Biosimilars compared to Reference product (25, 32 and 47).

Generics have their own advantages and challenges as compared against Biosimilars. Generics have long been recognized for their role in making medications more affordable. By offering lower-cost alternatives to brand-name drugs, generics enhance accessibility to essential treatments for a broader population (36, 40). Generic drugs typically follow a more streamlined regulatory approval process compared to Biosimilars. This efficiency facilitates faster market entry, enabling patients to access cost-effective alternatives sooner. Generics benefit from an established track record of safety and efficacy, as they are exact copies of their brand-name counterparts (25, 35). This familiarity instills confidence in both healthcare providers and patients, contributing to their widespread use. The development of Generics is generally less resource-intensive than Biosimilars because of the straightforward chemical synthesis process and the absence of extensive clinical trials. Generics have virtually no immunogenic potential and due to their exact sameness with reference products they are interchangeable with Reference products (35, 38). Though not very critical Generics do have challenges like the approval pathways are limited to small-molecule drugs, excluding complex biologics from their scope. This limitation restricts their ability to address the growing demand for more affordable alternatives to Biologics. While generics provide cost-effective alternatives, they do not drive therapeutic innovation. Unlike Biosimilars, which introduce competition in the Biologics space, Generics primarily replicate existing chemical entities without contributing to therapeutic advancements (38). The widespread reliance on a limited number of manufacturers for generic drugs poses the risk of supply chain issues. Disruptions in manufacturing or distribution can lead to shortages and impact patient access to essential medications. Finally, some patients may be sensitive to variations in

formulations between brand-name drugs and their Generic counterparts (35). Table 4 summarizes the Pros and Cons of Biosimilars and Generics as discussed above.

Table 4: Pros and Cons of the Biosimilars and Generics

Pros	Cons
Biosimilars	
Cost Savings: By providing alternatives to expensive Biologics, Biosimilars contribute to more affordable treatment options for patients, healthcare systems, and payers.	Complex Development Process: Developing Biosimilars involves intricate scientific processes and rigorous regulatory scrutiny.
Therapeutic Advancements: This democratization of access fosters innovation.	High Development Costs: Resource-intensive requiring high development costs and long-time for approval.
Fosters healthy competition: Yielding more cost-efficient and competitive pharmaceutical landscape.	Market Access Hurdles: Resistance from stakeholders due to their concerns about the efficacy and the safety of Biosimilars.
Diverse Treatment Options: Advantage of tailoring treatments to individual patient needs and preferences	Immunogenicity: Immunogenic studies are required requiring additional costs and time.
	Interchangeability: Additionally studies are required to classify as interchangeable.
Generics	
Cost-Effectiveness: Offers low-cost alternatives to brand-name drugs and enhance accessibility to essential treatments for a broader population.	Approval pathways are limited to Small Molecules: This restricts their ability to address the growing demand for more affordable alternatives to Biologics.
Regulatory Efficiency: Follow streamlined regulatory approval process facilitates faster market entry.	Lack of Therapeutic Innovation: They do not drive therapeutic innovation because they primarily replicate existing chemical entities.
Established Track Record of Safety and Efficacy: This familiarity instills confidence in both healthcare providers and patients, contributing to their widespread use.	Potential for Supply Chain Issues: Limited number of manufacturers for generic drugs can lead to shortages and impact patient access to essential medications.

Reduced Development Costs: Due to the straightforward chemical synthesis process and the absence of extensive clinical trials.	Patient Sensitivity to Formulation Changes: Although generic drugs must meet strict bioequivalence standards, subtle differences can affect patient response in certain cases.
Immunogenicity: Virtually no Immunogenic potential	
Interchangeability: Upon approval by FDA automatically qualify for interchangeability.	

The debate between Biosimilars and Generics encapsulates a nuanced evaluation of their respective pros and cons. Biosimilars, with their potential for cost savings, therapeutic advancements, and increased competition, address the evolving needs of the pharmaceutical landscape (47). Generics, on the other hand, remain stalwarts in providing cost-effective alternatives for small-molecule drugs, albeit with limitations in addressing the complexities of biologics. As the pharmaceutical industry continues to evolve, both Biosimilars and Generics will play pivotal roles in shaping a more accessible, cost-effective, and innovative healthcare landscape. The careful consideration of their advantages and challenges informs strategic decisions by stakeholders, contributing to a more nuanced and patient-centric approach to medication access and affordability (28, 35)

C. REGULATIONS:

Every biological product sanctioned by the US FDA, encompassing all Biosimilars, undergoes a thorough assessment. This ensures that healthcare providers and patients can have assurance in the safety, effectiveness, and quality of these products (23). The complex nature of biologics required a distinct regulatory approach, leading to the formulation of The Biologics Price Competition and Innovation Act (BPCIA). The BPCIA emerged as part of the Affordable Care Act (ACA), signed into law in March 2010. The primary objective was to create a pathway for the approval of Biosimilars, promoting competition and affordability in the biologics market (2). This process, distinct

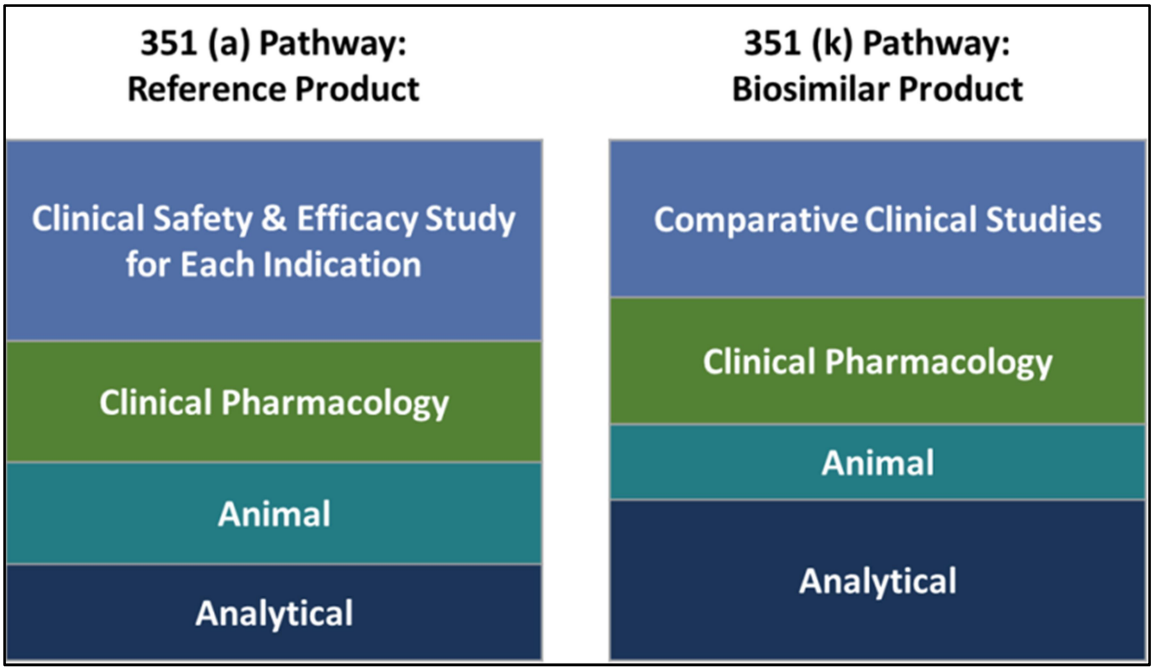
from small-molecule generics, involves comprehensive analyses to determine biosimilarity to reference products (36). Before the BPCIA, generic drugs dominated the pharmaceutical landscape, offering cost-effective alternatives to small-molecule innovator drugs (48). The Biologics Price Competition and Innovation Act (BPCIA) have a significant history shaped by the need for a regulatory framework that accommodates the unique challenges posed by Biosimilars**.** In 2012, the FDA issued draft guidance on the BPCIA, outlining the procedures for submitting Biologics License Applications (BLAs) for Biosimilars. This marked a crucial step in operationalizing the abbreviated approval pathway**.** In March 2015, the FDA granted approval to the first biosimilar under the BPCIA. Zarxio (filgrastim-sndz) was approved as a biosimilar to Neupogen, a granulocyte colony-stimulating factor (20). In 2017, the FDA issued guidance on the interchangeability of Biosimilars, defining the standards and requirements for a Biosimilar to be deemed interchangeable with its Reference product (50). In 2015-2018 the "patent dance" provisions of the BPCIA, outlining the process for resolving patent disputes between Biosimilar developers and innovator biologic manufacturers, faced legal challenges. The Supreme Court ruled on aspects of this process in cases like Sandoz v. Amgen (49). In 2020s witnessed an expansion of the Biosimilars market, with increased approvals and a growing number of Biosimilar applications under review by the FDA. Efforts were made to enhance competition and reduce healthcare costs through broader Biosimilar adoption (28). In 2021-2022 the US FDA continued to refine its guidance documents and regulatory approach to Biosimilars, aiming to provide clarity for developers and ensure a robust framework for the approval of safe and effective Biosimilars (2). Biosimilars are eligible for authorization only once the patent protection period of bio-originators expires. In the US, this patent protection for biologic references lasts for a mandated 12-year period, as outlined in the 2009 Biologics Price Competition and Innovation Act (BPCIA) (31). The above explained history of the BPCIA reflects the evolving landscape of biopharmaceuticals and the ongoing efforts to strike a balance between encouraging innovation, protecting intellectual property, and expanding access

to more affordable biologic therapies. As the Biosimilars market continues to mature, the BPCIA remains a critical piece of legislation shaping the regulatory framework for these complex therapeutic products.

Approval Pathways for Reference Products and Biosimilar Products:

The US FDA grants approval to Reference Products and Biosimilars via distinct statutory approval routes. Reference products undergo approval through a "standalone" application utilizing the Public Health Service Act (PHSA) Biologic License Application (BLA) section 351(a) pathway. In contrast, Biosimilars and interchangeable Biosimilars receive approval through the Biologics Price Competition Act (BPCIA) abbreviated section 351(k) pathway, which relies on a comparison between the proposed Biosimilar and the Reference product (35). In 351(k) applications, evidence must be presented to demonstrate the biosimilarity of the product to the reference product (11).

Figure 3: Set of data required comparison of 351 (a) Pathway Vs 351 (k) Pathway (adapted from 11)



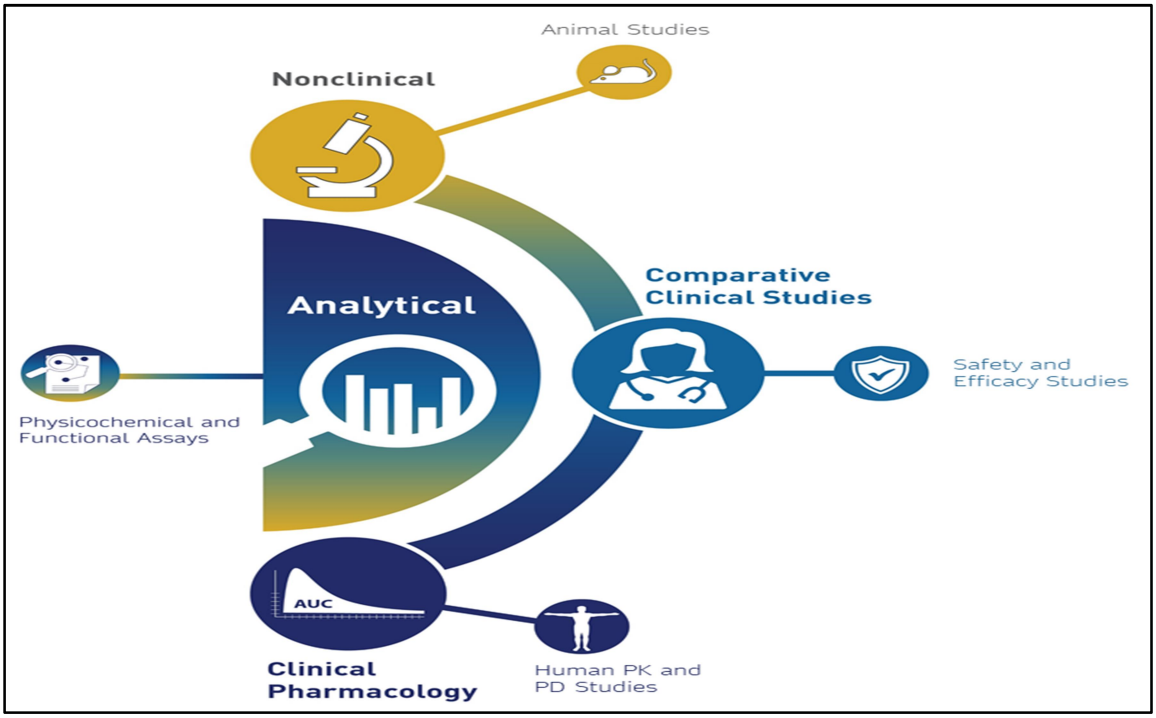
Prerequisites' for the approval of Biosimilar product per US FDA are follows (6):

- ✓ 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.

- ✓ Proposes condition(s) of use in labelling that 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 biologic continues to be safe, pure, and potent.

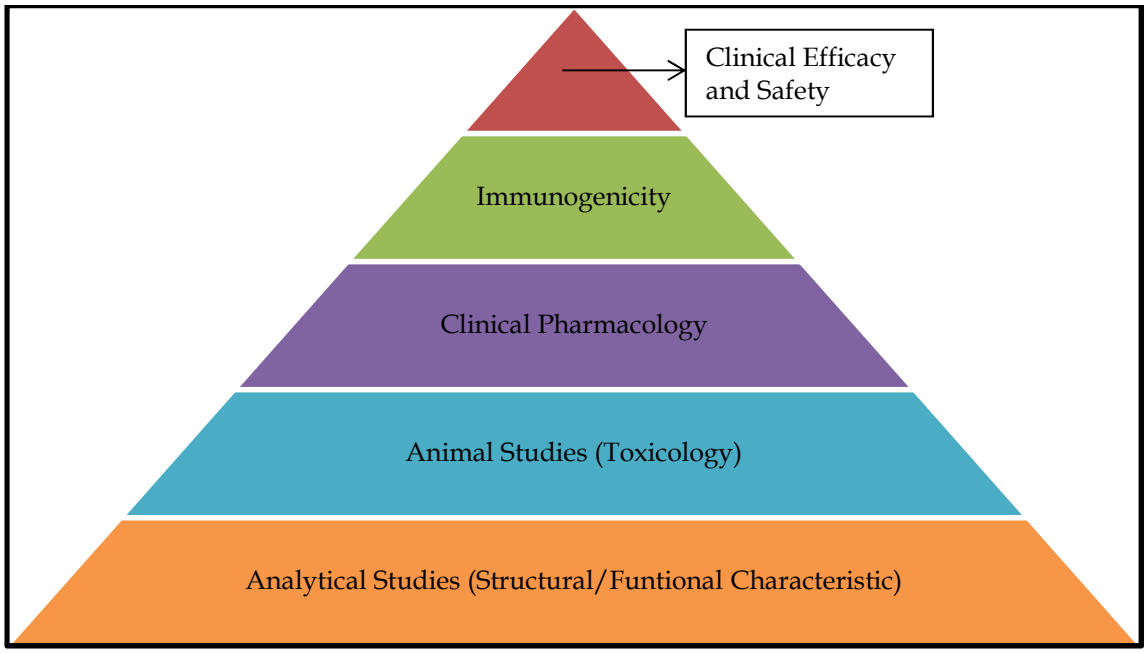
Proposed Biosimilar product is required to demonstrate that it is highly similar to Reference Product and there are no clinically meaningful differences between them. The foundation of Biosimilar approval process is the comparative Analytical studies (Physiochemical assays and Functional assays) of Biosimilar and Reference product, which demonstrates high similarity. Whereas, Animal studies, Comparative Clinical Pharmacology studies and Comparative Clinical studies are performed to demonstrate no clinically meaningful differences between the Biosimilar and Reference Product, (Figure 4) (6).

Figure 4: Analytical, Clinical Pharmacology studies and Clinical studies for Biosimilars (adapted from 6).



US FDA approval of the Biosimilar product is based on the Totality-of-the evidence approach and outlined the stepwise approach for obtaining Totality-of-the-evidence (Figure 5) (20). Assessment of residual uncertainty at each of the step of data generation is required (50).

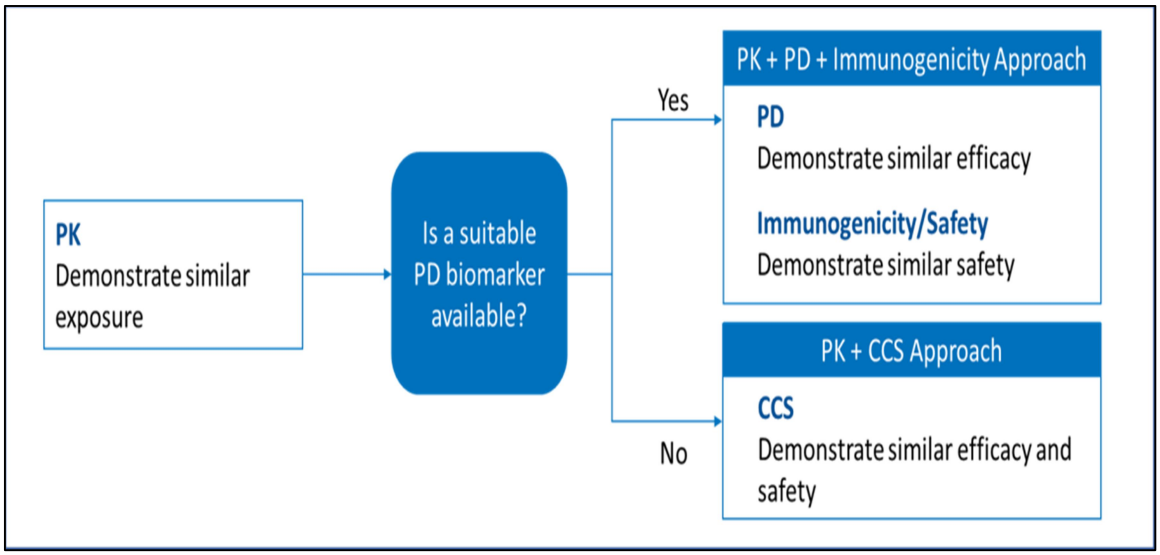
Figure 5: Stepwise approach for obtaining totality-of-the-evidence (adapted from 20).



Stepwise approach consists of Analytical (critical quality attributes at various stages of manufacturing process), Pharmacokinetic (PK) and Pharmacodynmic (PD), and Clinical Similarity (the assessment of immunogenicity, safety/tolerability, efficacy). Further its recommended 3-tier approach for Analytical similarity assessment. Step 1 identify critical quality attributes (CQAs) that are relevant to clinical outcomes, Step 2 classification of CQAs into three tiers according to their criticality or risk ranking relevant to clinical outcomes, Step 3 similarity assessment at each tier. Tier 1 CQAs are most relevant to clinical outcomes (equivalence test), Tier 2 CQAs are mild to moderate relevant to clinical outcomes (quality range approach), Tier 3 CQAs are least relevant to clinical outcomes (raw data and graphical comparison) (20).

Typically, pivotal elements in substantiating biosimilarity involve human pharmacokinetic (PK) and pharmacodynamic (PD) studies comparing the proposed product to the reference product. The clinical study's nature and scope are contingent upon the residual uncertainty about biosimilarity after structural and functional characterization. For example if the Biosimilar product has a PD biomarker available then the Comparative Clinical Studies (CCS) may not be required by US FDA (Figure 6) (13).

Figure 6: Relationship between the PD Biomarker availability and CCS requirement (adapted from 13).

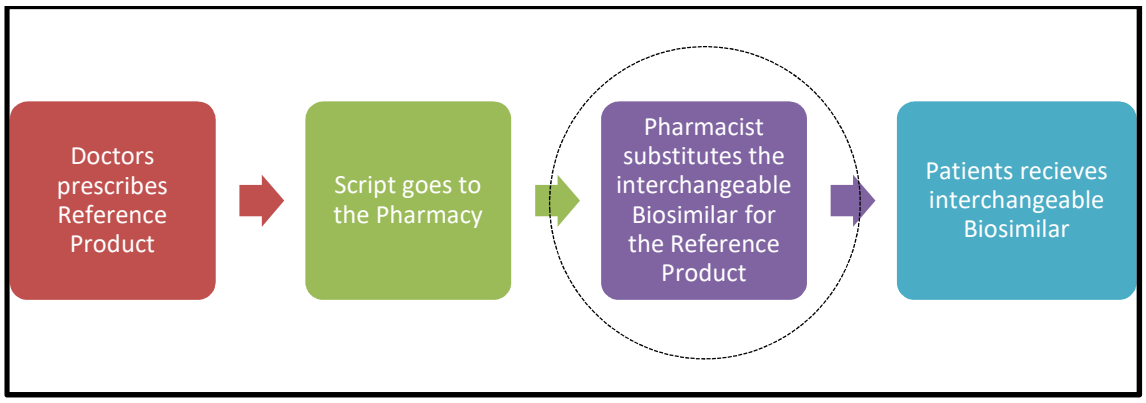


Interchangeability:

An interchangeable Biosimilar has the potential to be substituted at the pharmacy for the reference product, similar to the routine substitution of generic drugs for brand-name drugs, without requiring the involvement of the prescribing healthcare provider. Companies must submit an application containing sufficient information to support the determination of interchangeability for their product to be approved as an interchangeable Biosimilar (Figure 7) (22). It's crucial to emphasize that interchangeability represents a higher standard than biosimilarity. Consequently, not all Biosimilar products demonstrating biosimilarity can be automatically interchanged or switched with their Reference products. The intricate structural complexity of

biologics may yield distinct clinical outcomes, impacting patient safety (10). The US FDA advises researchers to conduct switching trials, involving at least two switch periods, by alternating exposures to potential interchangeable and bio-originator products. This is done to identify any potential risks to patient safety or drug efficacy compared to regular administration of the bio-originator alone. While numerous scientific studies have demonstrated that switching a reference product to its Biosimilar generally poses no undesirable safety issues, especially in treating inflammatory diseases, thorough evaluations of adverse events and immunogenicity remain essential. In essence, interchangeability is deemed feasible, secure, efficient, and cost-effective for the continuity of national healthcare systems, provided there is a comprehensive assessment of the substitution's adverse events and immunogenicity (29, 36).

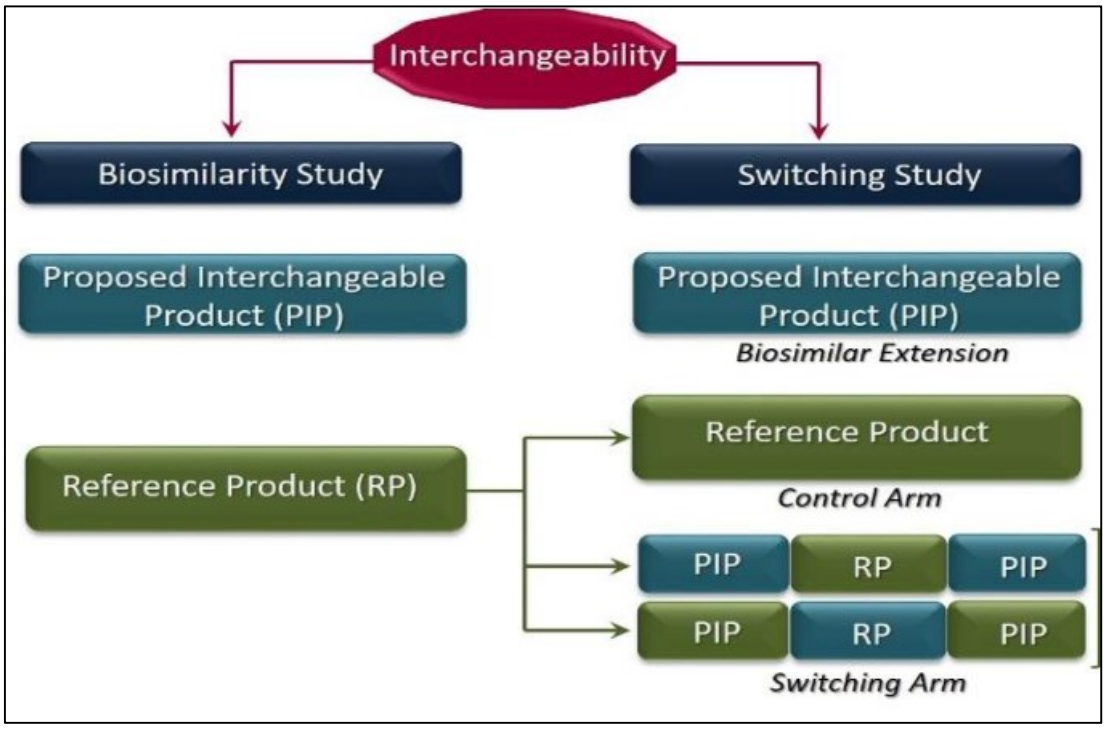
Figure 7: Pharmacy-Level Substitution



A potential study design for demonstrating interchangeability involves focusing on clinical PK as the primary endpoint, which is highly sensitive. Additionally, other crucial clinical endpoints include the evaluation of immunogenicity and safety (29, 50). Various designs, ranging from single switches to multiple switches, have been proposed for alternating or switching studies of Biosimilars. However, the definitive criterion for interchangeability is the state-of-the-art demonstration of biosimilarity coupled with a comprehensive post-marketing surveillance plan to address any concerns related to immunogenicity (50). A legal inconsistency in the BPCIA necessitates a reference product to be

"licensed," a status specific to the United States. This discrepancy becomes apparent in cases where a product is licensed in the US and authorized in the European Union (EU), with essentially the same registration dossier submitted for approval. While the EU does not require a bridging study in such instances, the FDA has recently mandated a PK bridging study. Criticism has been directed at these bridging studies, particularly clinical PK/PD studies, for complicating the global development of Biosimilars. Ideally, bridging studies should be omitted if the reference comparator has been approved in any ICH jurisdiction, and evidence exists in the public domain indicating approval in both jurisdictions based on some of the same Phase III clinical data (7, 44).

Figure 8: Possible Interchangeability Design (Adapted from 50)



Immunogenicity:

Immunogenicity refers to a drug's ability to elicit an immune response, producing antibodies that may lead to allergic reactions, anaphylaxis, or neutralization of both biological products and endogenous proteins. This can result in reduced treatment efficacy for patients using biological products. Several factors influence the immunogenicity of Biosimilars, including their high

molecular weight, complex structure (sequence variation, glycosylation), manufacturing complexities, impurities, formulation, storage, handling, and patient factors (comorbid conditions, previous exposures). Unpredictable immune responses may occur, necessitating clinical trials to assess incidence. Comparative glycoprotein analyses are recommended by US FDA for pre-approval immunogenicity assessment, contrasting the future Biosimilar with the originator to determine variations in anti-drug antibody incidence (34, 36).

Extrapolation of Indications:

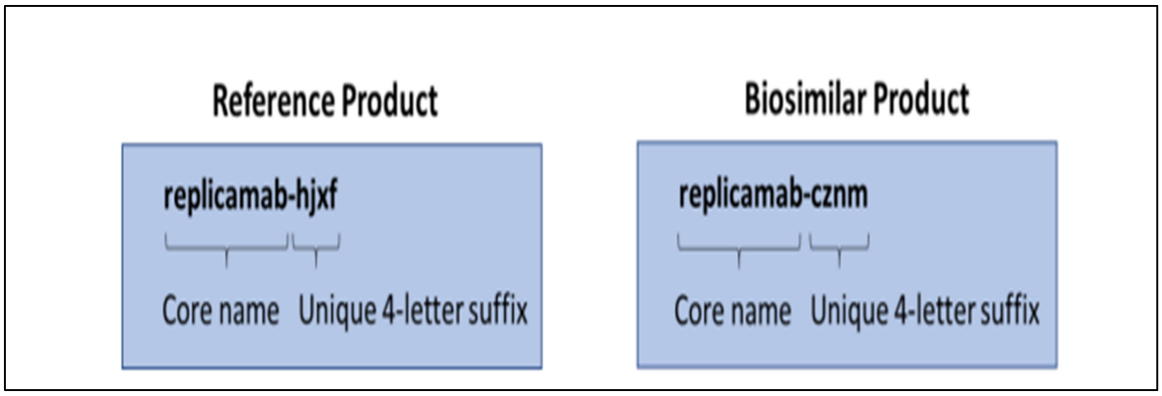
Indication extrapolation in Biosimilar approval involves granting the Biosimilar multiple indications of the licensed reference product based on scientifically justified data from clinical trials in one of the most susceptible populations. A susceptible population is where variations between the Reference product and the Biosimilar are likely to be observed. While some argue against indication extrapolation, stating that clinical evidence is required for all indications, it is permitted when the Biosimilar's efficacy, safety, and immunogenicity profile in various populations are proven safe and effective without significant variations from the reference product data. Indication extrapolation is seen by many researchers as a strategy to reduce development costs by minimizing the need for numerous clinical trials for multiple indications before Biosimilar product approval (36). When it comes to extrapolation, providing ample scientific justification may lead to the approval of a candidate Biosimilar for additional conditions of use beyond those for which the reference product is licensed. US FDA guidance on extrapolation emphasizes the importance of demonstrating the mechanism of action in each condition of use, as well as assessing pharmacokinetics, bio-distribution, and immunogenicity in diverse patient populations to support extending safety data to other indications (50).

Biologics Naming Conventions:

The naming convention combines a nonproprietary core name with a distinctive 4-letter suffix to facilitate product differentiation. While the Biosimilar or

interchangeable Biosimilar shares the same core name as its reference product, it features a distinct 4-letter suffix (Figure 9). The US FDA introduced this naming convention to enhance pharmacovigilance and ensure safe usage of all biologics. This system aids both patients and healthcare providers in identifying the prescribed and dispensed biologic medicine. Health care professionals are advised to incorporate the 4-letter suffix in their ordering, prescribing, dispensing, and recordkeeping practices, including the reporting of adverse events to MedWatch, the US FDA Safety Information and Adverse Event Reporting Program, (Figure 9) (12).

Figure 9: Naming Conventions (adapated from 12)



Key steps taken by the US FDA to encourage innovation and competition in the development of Biosimilars rely on the BIOSIMILARS ACTION PLAN (BAP) 2018 of US FDA. The BAP includes four key elements: improving scientific and regulatory clarity, developing effective communication and education, supporting market competition, and adapting to emerging challenges (5).

- ✓ The US FDA is actively enhancing the Biosimilar and interchangeable product development process by introducing application review templates, providing informational resources, and exploring the use of pharmacodynamic biomarkers. These initiatives aim to increase efficiency, predictability, and overall understanding for sponsors undergoing the US FDA evaluation process.

- ✓ The US FDA is intensifying communication efforts with stakeholders involved in the development, review, and approval of Biosimilar and interchangeable products. Key initiatives include developing guidance for a clearer regulatory pathway, enhancing the Purple Book for improved information accessibility, fostering global partnerships with regulatory authorities, utilizing real-world data for regulatory decisions, and actively engaging the public through hearings to enhance the Biosimilar program.
- ✓ The US FDA is actively involved in educating clinicians, patients, and payers about Biosimilar and interchangeable products through various outreach initiatives. These efforts include providing outreach materials for healthcare professionals and patients to understand key concepts, engaging stakeholders through conferences and webinars, and developing curriculum materials for health care programs to enhance understanding of Biosimilar and interchangeable products.
- ✓ The US FDA is committed to evaluating and addressing potential delays in the approval of Biosimilar or interchangeable competitors. This involves collaboration with partners like the Federal Trade Commission (FTC) and hosting workshops to discourage misleading statements, deter anticompetitive behaviors, and advance competition in the biologic marketplace. The US FDA will release educational resources for consumers, collaborate with legislators to close loopholes, and address anticompetitive strategies by biologic makers. The agency aims to adapt to the evolving Biosimilar marketplace, ensuring regulatory clarity and keeping pace with scientific and technological advancements in biological product development.

D. SOME OF EXAMPLES OF US FDA APPROVED PRODUCTS:

Some specific examples of Biosimilar drugs approved by the US FDA recently are summarized in the table 5 below. The primary objective of doing this summary was to understand what type of studies are submitted by the Biosimilar manufacturers to US FDA to show high similarity and clinically no

meaning difference when compared against the Reference product to establish the totality-of-the-evidence to approve them as Biosimilars (17, 16, 18 and 19). All of them have done the physio-chemical and functional characterization studies for the comparative analytical assessment to show high similarity. Following which it can be seen that none was able to find out the PD biomarker due to which they have to do the CCS. This is seen as the point where efforts can be made by companies to identity the biomarkers which can significantly reduce the timeline and cost of the development of Biosimilars. Finally, there is good evidence from this data that the pathway to review and approve the Biosimilars by US FDA is getting harmonized and streamlined.

Table 5: Summary of Totality-of-the-evidence for few recently approved Biosimilars by US FDA

Biosimilar Product Proprietary Name (Non-proprietary Name) [Approval Date]	**Tofidence (Tocilizumab-bavi) [September 2023]**	**Tyruko (Natalizumab-sztn) [August 2023]**	**Idacio (Adalimumab-aacf) [December 2022]**	**Yuflyma (adalimumab-aaty) [May 2023]**
Reference Product	Actemra (Tocilizumab)	Tysabri (Natalizumab)	Humira (Adalimumab)	Humira (Adalimumab)
Dosage form, administration route, technology of production, amino acids or/and molecular weight of both Reference Product and Biosimilar product	Supplied as injectable; injection; these are produced in mammalian (Chinese hamster ovary) cells. a molecular weight of approximately 148 kDa.	Supplied as injectable; injection; these are produced in a Chinese hamster ovary (CHO) mammalian cell expression system. The molecular weight is 149 kilodaltons	Supplied as injectable; subcutaneous; these are produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and	Supplied as injectable; injection; these are produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and

			removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.	removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.
Comparative Analytical Assessment : Studies Submitted	Physico-chemical & Functional Characteristics like Primary Structure; Post translational modifications ; Higher order Structure; Product-related substances / impurities; Charge profile; Glycosylation ; Biological activity (Fab mediated); Biological activity (Fc mediated); General Properties; Stability Profiles	Physico-chemical & Functional Characteristics like Primary Structure; Post translational modifications; Higher order Structure; Purity and Product-related Variants or impurities; Bio activity; Fc-mediated activity ; General Drug Product Attributes	Physico-chemical & Functional Characteristics like Primary Structure; Amino acid modifications; Product-related Variants and Impurities; Glycosylation; Higher order Structure; Biological activity (Fab mediated); Biological activity (Fc mediated); Drug Product Attributes; Forced degradation studies	Physico-chemical & Functional Characteristics like Primary Structure; Post translational modifications; Higher order Structure; Purity and Product-related Variants or impurities; Fab-mediated Bioactivity; Fc-mediated activity ; Impact of Aglycosylation, Agalactosylation and Amannosylation on Bioactivity; Additional Bioactivity Studies to Support Extrapolation to other Indications Drug Product Attributes

Animal /Non-clinical Studies Submitted	Binding studies with IL-6R a collagen induced arthritis model; Pharmacokinetic (PK) study in male and female monkeys; GLP IV local tolerance study in rabbits	4 week Toxicity Study	-	1-month Toxicity Study
Clinical Studies Submitted	PK Similarity Studies (Comparative PK and Safety study); Comparative Clinical Study (Comparative Efficacy study)	PK Similarity Studies (Comparative PK/PD similarity, Immunogenicity and Safety studies); Comparative Clinical Study (Comparative Efficacy, Immunogenicity and Safety study)	PK Similarity Studies (Comparative PK, Immunogenicity and Safety studies); Comparative Clinical Study (Comparative Efficacy, Safety and Immunogenicity study)	PK Similarity Studies (Comparative PK similarity, Immunogenicity and Safety studies; 120 days Pilot Study to evaluate Safety, PK, Immunogenicity) Comparative Clinical Study (Comparative Efficacy, Immunogenicity and Safety study)
Other Studies	-	Exploratory safety study; Exploratory PK/PD study	-	Studies supporting device development

IV. CONCLUSION:

As the exclusivity period, covering both patent and data, expires for new Biologics, it creates a strategic opportunity for Biosimilar drug companies to introduce competing Biosimilars to the market. While it might seem financially attractive at first, it comes with challenges that create a scenario wherein only the strongest or most well-adapted companies will succeed. Factors such as specialized analytical technologies and tools required for development, complex and sensitive manufacturing processes makes the start difficult. The regulatory demands, including the necessity for clinical and non-clinical studies before approval and to tackle manufacturing variations after approval, restrictions on pharmacy-level substitution, and mandatory switching studies/non-inferiority trials for interchangeable designation, collectively hinder the goal of making Biosimilars more affordable and accessible. Though US FDA is taking steps to reduce some of them by taking lot of different initiatives through BAP, industry experts and regulators need to work more on how to scientifically minimize the clinical/non-clinical testing without compromising on the quality, safety and efficacy of these products. This paper reveals current approaches and key considerations in the field of Biosimilars which are important to be looked upon during development.

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VI. LIST OF ABBREVIATIONS

1D/2D	: One Dimensional/ Two Dimensional
2D-LC	: Two-Dimensional Liquid Chromatography
AF4	: Asymmetrical Field Flow Fractionation
CD	: Circular Dichroism Spectroscopy
CE	: Capillary Electrophoresis
CEX	: Cation Exchange Chromatography
cIEF	: Capillary Isoelectric Focusing
CZE	: Capillary Zone Electrophoresis
DIGE	: Difference Gel Electrophoresis
DLS	: Dynamic Light Scattering
DOSY	: Diffusion Ordered Spectroscopy
DSC	: Differential Scanning Calorimetry
ELISA	: Enzyme-Linked Immunosorbent Assay
ESI	: Electrospray Ionization
FLD	: Fluorescence Detection
FTIR	: Fourier Transform Ion Resonance
HDX-MS	: Ion Mobility-Mass Spectrometry
HIC	: Hydrophobic Interaction Chromatography
HILIC	: Hydrophilic Interaction Chromatography
HPAEC	: High-Performance Anion-Exchange Chromatography
icIEF	: Imaged Capillary Isoelectric Focusing
IM-MS	: Ion Mobility-Mass Spectrometry
IT-FLR	: Intrinsic Fluorescence Spectroscopy
LC	: Liquid Chromatography
LIF	: Laser-Induced Fluorescence Detection
LIF	: Laser-Induced Fluorescence Detection
LO	: Light Obscuration
MALDI	: Matrix Assisted Laser Desorption/ Ionization
MALS	: Multi-Angle Light Scattering

MFI	: Micro-Flow Imaging
MS	: Mass Spectrometry
NanoDSF	: Nano Differential Scanning Fluorimetry
NMR	: Nuclear Magnetic Resonance Spectroscopy
NP	: Normal Phase Chromatography
PAD	: Pulsed Amperometric Detection
PAGE	: Polyacrylamide Gel Electrophoresis
qPCR	: Real-Time/ Quantitative Polymerase Chain Reaction
QTOF	: Quadrupole Time-of-Flight
RI	: Refractive Index
RP	: Reverse Phase Chromatography
SCX	: Strong Cation Exchange Chromatography
SDS	: Sodium Dodecyl Sulfate
SDS-PAGE	: Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis
SE/SV-AUC	: Sedimentation Equilibrium / Sedimentation Velocity Analytical Ultracentrifugation
SEC	: Size Exclusion Chromatography
TCSPC	: Time-Correlated Single-Photon Counting
TOF	: Time-of-Flight
UV	: Ultraviolet
VT-CD	: Variable Temperature-Circular Dichroism
WAX	: Weak Anion Exchange Chromatography
XRC	: X-Ray Crystallography