Concepts and Challenges of Biosimilars to Mitigate the Oncology Drug Expenses

By

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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
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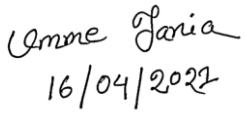

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Approval

The thesis titled "Concepts and Challenges of Biosimilars to Mitigate the Oncology Drug Expenses" submitted by Umme Tania (16346032) of Summer, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 16th April, 2021.

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Ethics Statement

The study does not involve any kind of animal or human trials.

Abstract

Biosimilars is way more likely to genuine generic drugs of the innovator. Time to time expiry of generic drugs helps manufacturer to think about biosimilars which has wide cost effectiveness as well as expanded patient accessibility to medicines especially for malignancy patients. This article gives a refreshed audit of the biosimilar pharmaceutical products affirmed for disease treatment in the US and EU through strict pre-clinical, clinical as well as pharmacovigilance touchstones. Diverse oncological biosimilar drugs that are right now being utilized like epoetins (alpha and zeta), filgrastim, as well as mAb (rituximab, trastuzumab and bevacizumab) are being exhibited in this article.

Keywords: Biosimilars; Interchangeability; Cancer therapy; Monoclonal antibodies; Biologic medicines; Comparability exercise.

Dedication

I want to dedicate this thesis paper to my family and my honorable supervisor, Dr. Md. Aminul Haque (Assistant Professor, Department of Pharmacy Brac University).

Acknowledgement

"The woods are lovely, dark and deep

But I have promises to keep

And miles to go before I sleep."

These are few lines of Robert Frost; these few lines keep motivates me to work harder and to keep me in track to pass all the hurdles. Along these, the final output of this paper would not have been possible without sincere aid and nonstop guidance from few people. I would like to show my gratitude to all of them.

At first, I would like to express my gratitude to almighty Allah for keeping me and my dearest ones in a very good health during this pandemic situation and for giving me immense strength to complete this paper and to dream big through all the hardships and challenges. With His countless blessings and protections, I am the person who I am today.

I am wholeheartedly indebted to my supervisor Dr. Md. Aminul Haque (Assistant Professor, Department of Pharmacy Brac University) for his continuous support, supervision, feedbacks, suggestions and who ultimately has been my strong pillar to complete this thesis paper successfully, otherwise this would not have been possible for a newbie.

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Then, I would like to thank my mother and moreover, my family for their constant guidance, support and inspirations. Without whom, I could never come this far.

I would like to emphasize at the end that the limitations of this thesis are entirely mine.

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List of Acronyms

AIDS	Human Immunodeficiency Infection
ADAs	Antidrug Antibodies
BPCIA	Biologic Price Competition and Innovation Act
BIO	Biotechnology and Innovation Organization
CAGR	Compounded Annual Growth Rate
EPO	Erythropoietin
EMA	European Medicine Agency
EU	European Union
EC	European Commission
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
FD&C	Federal Food, Drug and Cosmetic Act
FSH	Follicle-Stimulating Hormone
G-CSF	Granulocyte Colony Stimulating Factor
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HCPCS	Healthcare Common Procedure Coding System
HCP	Healthcare Professionals
HGH	Human Growth Hormone

mAb	Monoclonal Antibody
MOA	Mechanism of Action
NASs	New Active Substances
NDAs	New Drug Applications
OS	Overall Survival
ORR	Overall Response Rate
PRCA	Pure Red Cell Aplasia
PFS	Progression-free Survival
PHSA	Public Health Service Act
PHS	Public Health Service
RCT	Randomized Controlled Trial
RLD	Reference Listed Drug
R & D	Research and Development
rhGH	Recombinant Human Growth Hormone
SEAs	Serious Adverse Events
SDG	Sustainable Development Goals
SCNIR	Severe Chronic Neutropenia International Registry
USFDA	Unite States Food and Drug Administration
UN	United Nations

WBC	White Blood Cell
WHO	World Health Organization

Chapter 1

Introduction

Biologics are one of the quickest developing classes of therapeutics. It plays a significant role in medical care. These are rapidly dominating little particle drugs, speaking to $232 billion in worldwide income (Unni, 2020), which is over 25% by estimation. The quantity of biologic medications endorsed by the FDA keeps on expanding. 48 new novel medications were endorsed by the FDA, 15 of these were biologics, in 2019. Roughly 40% of the biologics affirmed in 2018 were for the therapy of cancer. Biologics seem to be more expensive to create and manufacture, as well as more sophisticated than the drugs made up of small molecules. In 2009, the US regulatory authorization adopted the BPCIA law to explain and speed up the endorsement cycle for biosimilars on the grounds of the advantages acknowledged in Europe (Wish, 2019). Over the following decade (Table 1), patent licenses on certain biologic medications being utilized in malignancy care has been terminated or about to terminate (Choy and Allen Jacobs, 2014). Now many biosimilars are sold in Europe that has a refund of about (20-35) % relative to the price of their reference products. This helps patients to undergo therapies that were not easily accessible. Notwithstanding the way that biosimilar steady consideration specialists have been accessible for use in oncology for a quite a long but, it is just more as of late that biosimilar mAbs for the chemotherapeutic treatment, like rituximab, trastuzumab, and bevacizumab biosimilars, have gotten administrative underwriting. It is being projected whether biosimilars elsewhere in USA would minimize gross expenditure on biologics around US$54 billion between 2017 until 2026 (Gottlieb, 2019).

Biologic	Expiration Date in US	Expiration Date in EU
Adalimumab	2016	2018
Bevacizumab	2019	2022
Cetuximab	2016	2014
Darbepoetin alfa	2024	2016
Etanercept	2028	2015
Filgrastim	2013	2006
Infliximab	2018	2015
Interferon beta-1a	2015	2015
Palivizumab	2015	2015
Pegfilgrastim	2015	2017
Rituximab	2016	2013
Trastuzumab	2019	2014

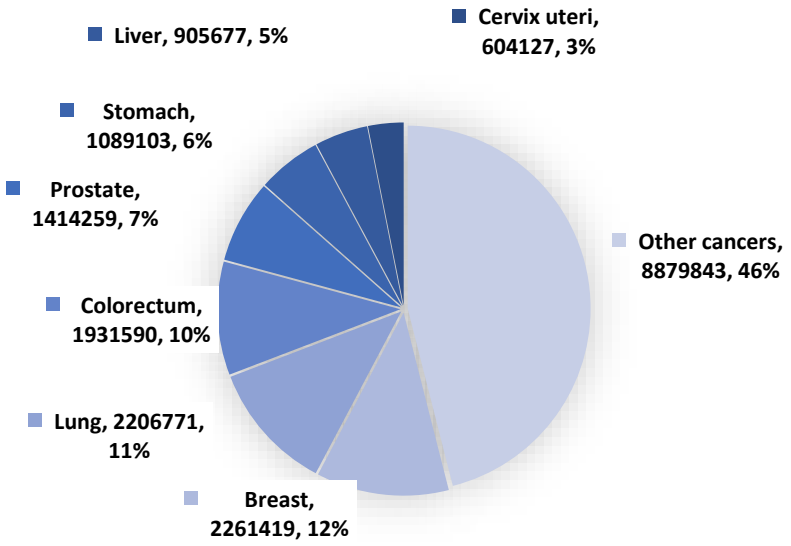
Table 1: Projected expiration dates of patent rights for chosen biologic drugs (Choy and Allen Jacobs, 2014)

On this paper, I would like to incorporate more recent and potential difficulties encountered in cancer treatment regarding biosimilar utilization as well as why to use biosimilar with cheap rate for the malignant growth treatments. Investigating the most recent guidelines on their creation, endorsement, compatibility as well as replacement strategies, we intend to introduce the logical standards underlying biosimilars.

1.1 Global Cancer Burden

In spite of generous therapy progresses, cancer was the subsequent driving reason for death worldwide (after cardiovascular infection) in 2017 (Roth et al. 2018; Xu and Li 2020). About 21 million potential cancer occurrences as well as 13 million mortality predicted yearly by 2030, the magnitude of cancer is growing (Krendyukov, Andriy Schiestl, Martin, 2020). Deaths brought about by malignant growth (17%) far surpassed those brought about by transmittable

illnesses, for instance, AIDS (1.7%), tuberculosis (2.1%), or intestinal sickness (1.1%) (Cortes et al. 2020). Somewhere in the range of 2007-2017 (Cortes et al. 2020), mortality rate of malignant growth expanded by 25.4%. In 2018, what GLOBOCAN assessed is that around 18.1 million individuals have been determined to have malignancy. Around 9.6 million individuals kicked the bucket from disease around the world (Bray et al. 2018). Around 4% of the de novo cancer reports happened in countries with a steep growth index (Bray et al. 2018; Cortes et al. 2020). Around 16% happened in regions with a moderate growth index, the rest of in high or very regions with a strong growth index. Almost half of cancer growth cases plus 60% of disease deaths happened in Asia , yet just 6.5% (Bray et al. 2018; Cortes et al. 2020) of individuals are under record-book.



Total: 19 292 789

Figure 1. Estimated number of new cases in 2020, worldwide, both sexes, all ages ("Cancer Today", 2020)

Aim 3.4 of the SDG of the UN to minimize unforeseen losses from non-communicable infections by 33% before 2030 will not be reached if attention is not given to reduce gaps in exposure to care of diseases including excellent consideration (Cortes et al. 2020). By 2024,

world-wide consumption for biological drugs is projected to reach $394 billion, escalating at a CAGR of 10.3% from 2016 to 2024 (Unni, 2020).

Chapter 2

Approaches to Decreasing Cancer Medicine Costs

2.1 Definitions

Biologics are medicines that have used procedures as with coordinated gene expression recombinant DNA technology using the active drug substance generated or retrieved from a multicellular being which is indeed responsible for the synthesis of mAb (Simoens, Verbeken, and Huys 2012). Biosimilars are endorsed in four significant remedial regions, including EPO for anemic patients undergoing renal dialysis, G-CSF for decreased post-chemotherapy WBC counts, HGH, FSH for propagate, as well as rheumatology mAb. The below table 2 represents the difference between non-biologic, biologic and biosimilar drugs.

Characteristic	Nonbiologic Generic	Biologic	Biosimilar
Size	Small	Large	
Molecular weight	<1000 Da	200-1000 times the size of a small molecule	4000 to >14000 Da
Structure	Simple to relatively simple	Complex	Biosimilars potentially have structural variations but are designed to be highly similar to their biologic reference product

Manufacturing	Predictable and bioequivalent to the brand name	Piece of DNA added to a cell; a protein is generated and becomes the biologic	Stepwise process to make a similar compound
Complexity	Easy to characterize	Difficult to characterize	Difficult to characterize
Stability	Stable	Sensitive to handling and storage	Sensitive to handling and storage
Immunogenicity	Low potential	High potential	Goal is to demonstrate that immunogenicity of the biosimilar is not increased relative to the reference product; this process is assessed by evaluating the upper limit of immunogenicity incidence based on experience with the reference product
Approval requirements	Small clinical trials in healthy volunteers	Standard FDA guidelines	Large clinical trials; development of a biosimilar must include >=1 clinical study, including assessment of immunogenicity and

			PK or PD; licensure pathway for a biosimilar is an abbreviated pathway
Class example	Loop diuretics, nonsteroidal anti-inflammatory agents	Therapeutic proteins and monoclonal antibodies	Therapeutic proteins and monoclonal antibodies

Table 2. Differences Between Biosimilars and Biologic Agents, Brand-Name Drugs, and Their Generic Equivalents (Nabhan et al. 2018)

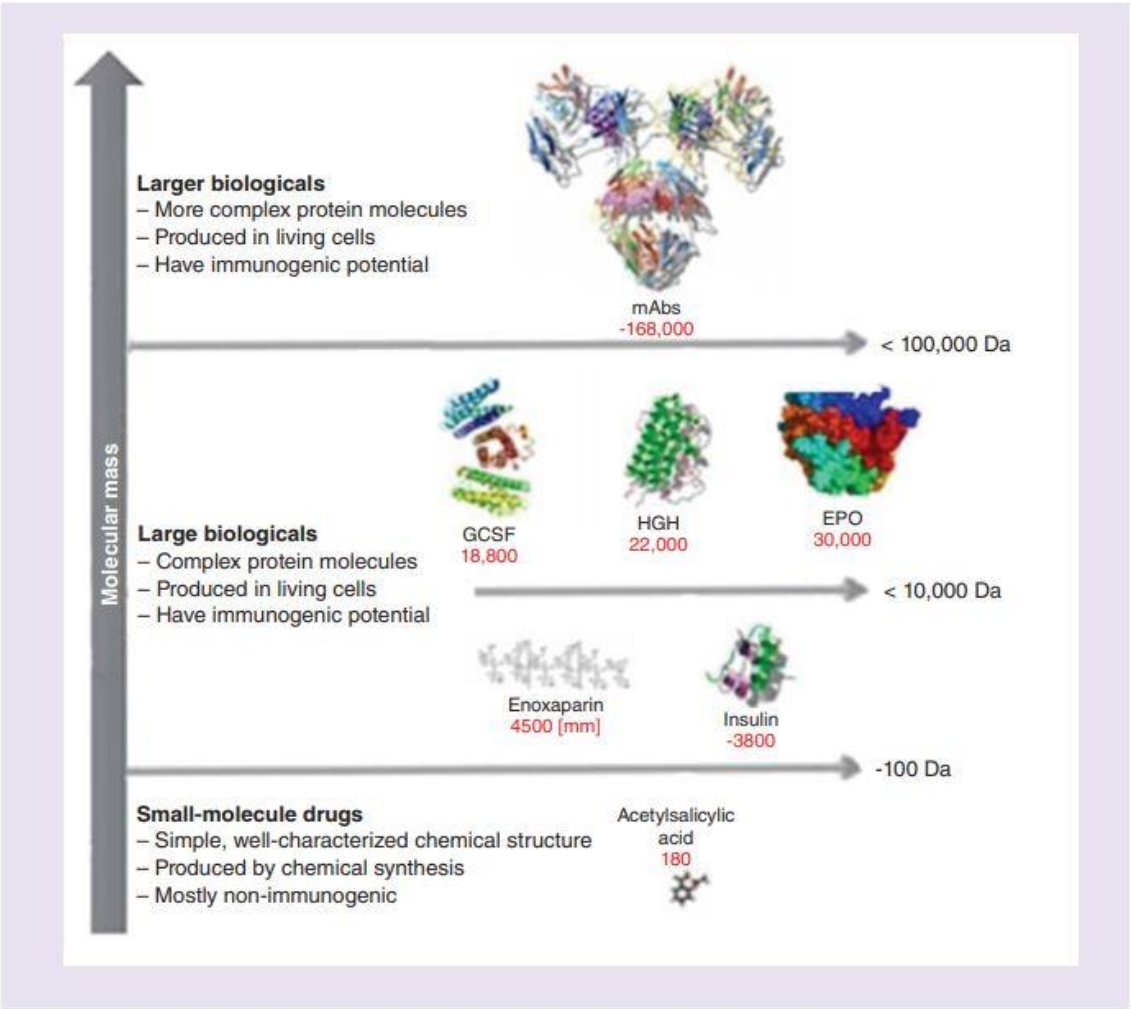


Figure 2. Molecular weight comparisons: small-molecule drugs versus larger biologicals (Thill et al. 2019)

A biosimilar is a therapeutic product with comparable security, effectiveness, consistency and efficiency to a biological product already approved (Kleppin, 2020). All are produced by, or derived from, a biological origin such as yeast or perhaps a bacterium. Subsequently, absence of critical contrasts must be clinically demonstrated by proper improvement of every biosimilar. Biosimilar is characterized by the BPCI in the US as 'a highly similar biologics to the reference standard, despite trivial contrasts in therapeutically dormant components;' or even 'with hardly any clinically significant contrasts between both the biologic as well as the reference product mostly in safety, purity and potency of its drug.' For its accreditation, the growth of a biosimilar medicine requires a connection to the trailblazer item (Advancement

and Pharmacology, 2018). The below table 3 shows different definitions and names of biosimilar according to different regulatory agencies.

Agency	Naming	Definition
FDA (Food and Drug Administration), USA	Follow-on Biologic or Biosimilar	"A biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which 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" (FDA, 2017).
EMA (European Medicines Agency)	Biosimilar	"A biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established" (AL-Sabbagh et al. 2016; EMA, 2015).
WHO (World Health Organization)	Similar Biotherapeutic Product	"A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product" (World Health Organization 2009).
PMDA (Pharmaceutical and Medical Devices Agency), Japan	Follow-on Biologic or Biosimilar	"A biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived product (hereinafter "reference product") of an innovator" (Ascef, Lopes, and De Soárez 2020).

Health Canada	Subsequent Entry Biologic	"A biologic product that is similar to and would enter the market subsequent to an approved innovator biologic product" (Health Canada, 2019).
ANVISA (Agencia Nacional de Vigilancia Sanitaria), Brazil	Biologic Product	"A biologic medicine with known biologic activity that contains no new molecules, already licensed in Brazil and that has gone through all the production steps (including formulation, vialing, freeze drying, labeling, packaging, storage, quality control and biologic product lot release)" (The Center for Biologic Policy Evaluation, n.d.).

Table 3. Names and Definitions of Biologic Copies According to Different Regulatory Agencies (Tsuruta, Lopes dos Santos, and Moro 2015)

2.2 History of Biosimilars

A rhGH called Omnitrope was the very first biosimilar medicine. Primarily approved in the EU in 1988, Pfizer's Genotropin was the standard restorative substance proposed for Omnitrope (Farhat et al. 2018). Sandoz International demanded market authorization in Europe in 2001. Commercial validation of Omnitrope was strongly advised in June of 2003 by the Science Committee and the Committee for Medicinal Products of the EMA for human use. At a certain point, the EC rejected it. It did not authorize the Authority to advertise it. Then, it started to argue that Sandoz should have chosen the "indispensable resemblance" passageway. In a collaborative effort with the European Tribunal of First Place formal interventions have taken place to abandon the Commission's option. On March 31, 2004, a systematic as well as official framework for biosimilars was introduced across the EU *(The European Medicines Agency and The European Commission, 2019)*. In July 2004, Sandoz went after for the subsequent chance to seek after the market approval for the Omnitrope (Macdonald et al. 2015). In January 2006,

EMA gave a better favorable impression, bringing Omnitrope's endorsement on 12 April 2006. Not long after Omnitrope, Valtropin, another biosimilar, an element from Bio partner as well as rhGH, was endorsed. In a way like the protocol for many other biologics, every other biosimilars are dependent upon a similar exact scientific evaluation of EMA. The two authorized meds, Omnitrope and Valtropin, the torchbearers mostly in biosimilar growing marketplace which has been prepared for countless biosimilar organizations. EMA delivered rules and an enrollment procedure, explicit for biosimilars endorsement, somewhere in the range of 2005 as well as 2006. By 2016, the EMA had enacted 23 biosimilars across diverse medicinal fields, along with somatropin in 2006, accompanied by so many erythropoietin equivalents including, most of the time, FSH antineoplastic representatives but also biosimilars. Sandoz's Somatropin BS human growth hormone (Appendix A7) drug was the first accredited biosimilar in Japan in June 2009 (Gascon et al. 2019). In U.S. On 6 March 2015, five years after the Affordable Healthcare Act was made into law in 2010, Zarxio was approved by the FDA to have been the first biosimilar product for purchase (Development and Pharmacology, 2018). President Obama enacted into law the Biosimilar Act in March 2010 as part of a massive health care reform (Brougher, 2014). As of December 2019, a sum of 26 biosimilars have been affirmed by the FDA. By the end of 2020, 9 patents for the main 20 biologic medications are set to lapse. Somewhere in the range of 2013 as well as 2024, 8 biologic medications utilized in oncology will have patents terminating. With these forthcoming patent lapses, there has been an expansion in the quantity of biosimilars read for the therapy of disease, with in excess of 250 progressing clinical preliminaries (Unni, 2020). Table 4. illustrates an overview of the market of biosimilars (Amgen market report, 2020).

Category	Reference Product	Number of Approved Biosimilars	Number of Launched Biosimilars	Earliest Biosimilar Launch Date	Biosimilar Share by Volume
	Herceptin® (trastuzumab)	5	5	July 18, 2019	40%
Oncology Therapeutics	Avastin® (Bevacizumab)	2	2	July 18, 2019	40%
	Rituxan® (Rituximab)	3	2	November 11, 2019	20%
	Neulasta® (Pegfilgrastim)	4	3	July 26, 2018	28%
Supportive Care	Neupogen® (Filgrastim)	2	2	September 2015	52%
	Epogen/ Procrit® (Epoetin alfa)	1	1	November 12, 2018	25%
	Remicade® (Infliximab)	4	3	November 2016	20%
Inflammation	Humira® (Adalimumab)	6	0	Not yet launched	0%
	Enbrel® (Etanercept)	2	0	Not yet launched	0%

Table 4. U.S. Biosimilar Market Share (Philip Chen, Kayleigh McGlynn, and Jenny Shmuel, 2021)

Chapter 3

Biosimilar Medicines

3.1 Brief on Biosimilars

The principle of bio similarity, which is the capacity of the biosimilar medicinal product to demonstrate resemblance regarding consistency, protection as well as efficacy to the original biological medicinal substances (Agbogbo et al. 2019). Biosimilars are deliberated to be delivered in an equal dose on the similar pathway as the guide biologicals as well as to treat comparable abnormalities (Santos, 2018). It ensures that the sign of treating diseases of the standard products can be applicable to biosimilars also (Santos, 2018). Given their manufacturing process, which makes use of living systems, the variability in biosimilars is still present and therefore, the exact versions of the standard biologicals are also no more the same (Santos, 2018). Such discrepancies entail subtle changes, named micro-heterogeneity. It can lead to therapeutic pastime modifications as well as immunogenicity (Appendix A3) growth. The creation of a biosimilar begins with the assessment and characterization of its desired quality attributes. In 3 phases (Santos, 2018), the comparability study with standard biologicals is subsequently performed: I) Appraisal of physical, biochemical features; (ii) non-clinical tests; as well as (iii) clinical tests. In phase I, the most prevalent physical, biochemical tests that must be done to ensure that the originator's biological as well as biosimilar molecules are as close as possible which are summarized in Table 5 (Santos, 2018). Phase (ii) as well as (iii) evaluate if the tiny variations between both the biosimilar as well as its biological comparison impact the protection as well as effectiveness of the established therapeutic agent by evaluating the benefits, threats as well as immunogenicity (Santos, 2018).

Physicochemical assays	Biological assays
• Examination of the amino corrosive arrangements of the essential design (peptide planning) • Evaluation of post-translational changes (comparative study of N-linked oligosaccharide detaining as well as glycan sequences of the glycosylation designs) • Heterogeneity Assessment (discovery of isoforms) • Assessment of immaculateness and presence of leftover cycle debasements (correlation of the degrees of monomers and high-atomic mass species)	• Assessment of cytotoxic effects of within vitro cell • Compatible biochemical function visualization (receptor-binding experiments in animal models)

Table 5. The most common physicochemical and biological assays performed to assure similarity between originator biological and biosimilar molecules (Santos 2018)

Biosimilars must meet certain production criteria in the identical way as other medicines, with producers periodically inspected by regulatory bodies before release to the market. The production process of biosimilar medicines is summarized in figure 3 (Santos 2018).

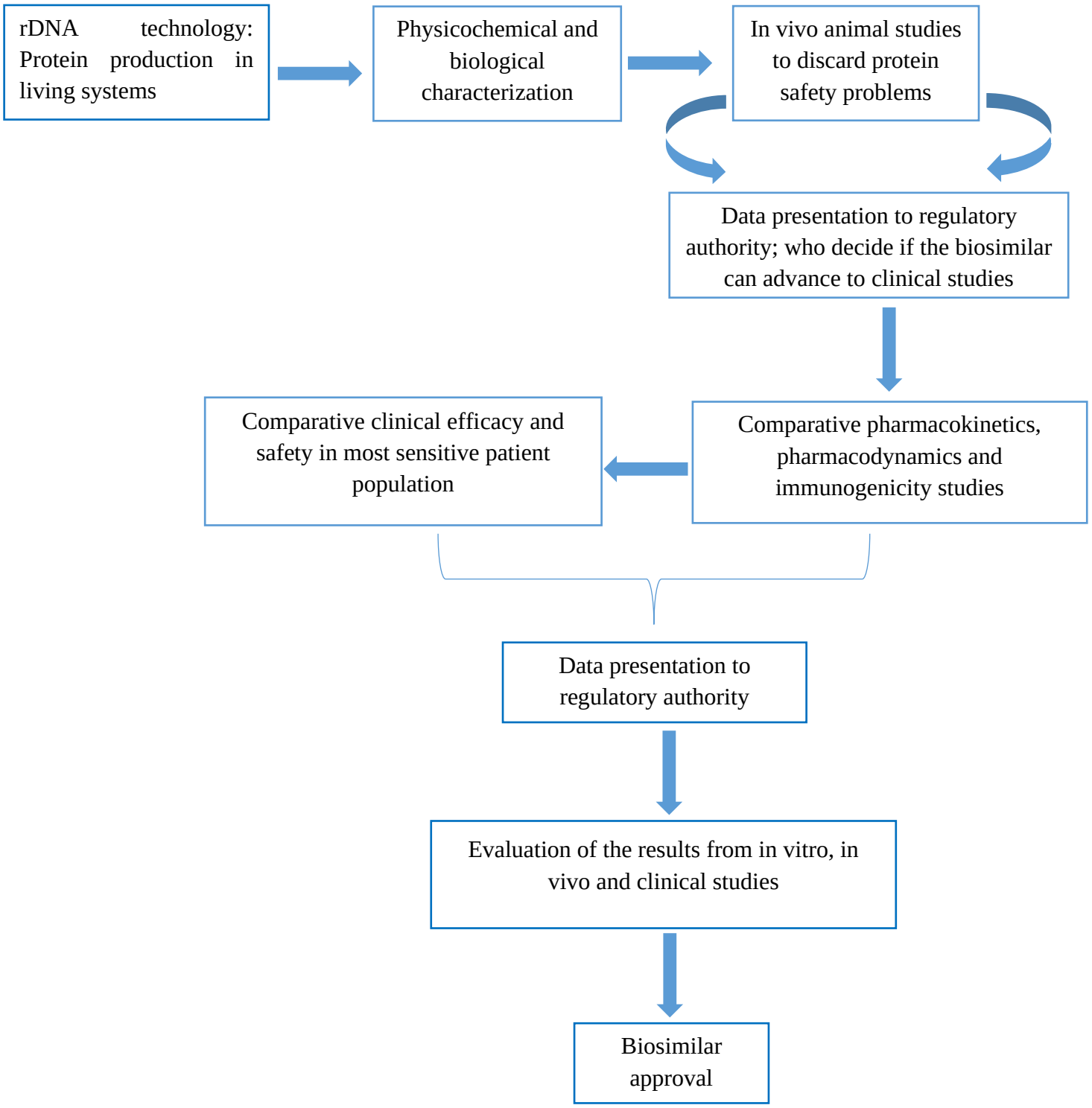


Figure 3. The production process of biosimilar medicines (Santos 2018)

Eight classes of existing biosimilar pharmaceutical products are divided: epoetins, insulins (Appendix A6), interferons (Appendix A19), follitropin, mAb, growth hormones, filgrastim also low molecular weight heparins (Santos 2018). Here, we report on biosimilars that are being used to fight cancer (Santos, 2018). The below table 6 describes the EU-licensed biosimilars utilized as anticancer drugs (Santos, 2018).

Active substance					
Epoetin		**Filgrastim**	**Monoclonal antibody**		
Alpha	**Zeta**	Hexal®	**Rituximab**	**Trastuzumab**	**Bevacizumab**
Abseamed®	Silapo®	Nivestim®	Ritemvia®	Kanjinti®	Mvasi®
Binocrit®	Retacrit®	Ratiograstim®	Rituzema®	Ontruzant®	
Hexal®		Tevagrastim®	Rixathon®	Trazimera®	
		Zarzio®	Riximyo®	Herzuma®	
		Udenyca®	Truxima®		
			Blitzima®		

Table 6. Biosimilar drugs accredited mostly in EU as anticancer drugs (Santos, 2018)

Chapter 4

Primary Concerns of Biosimilar Considerations

4.1 Naming and Labeling

Proper naming is significant in light of the fact that biosimilars as well as reference biologics don't have indistinguishable synthetic qualities. It was decided that each biosimilar specialist should get an interesting identity to distinguish from many other biosimilars as well as the innovator drug (Wish, 2019), irrespective of whether the FDA allocated the biosimilar to the standard item as "exchangeable" (Wish, 2019). This is critical to limit accidental replacement and for pharmacovigilance, which means if an antagonistic response ought to happen it will be simpler to follow it back to a particular specialist (Misra, 2012; Wish, 2019). In a guidance document, the USFDA has recently detailed their latest research on the non-proprietary naming practice (Chang 2019). For both as of late approved originator organic things, related natural things, and biosimilar things, a particular postfix made out of four lowercase letters ought to be gotten together with a hyphen to the middle name to shape a fitting name (Unni, 2020).

4.2 Trend-setter Patents, Prolongation of Exclusivity Rights, and Patent Disputes

The earliest market passage date for a biosimilar become the latest termination date for applicable licenses as well as information including market selectiveness rights, but broad licenses are the main impeding segment of the business sector (Rader, 2013). Patent (Appendix A12) protection is a lawful limitation on new biosimilar market passage, but patent guarantee, also market selectivity are tools for the recovery of R&D costs for trend-setter biologicals. Picking or adjusting distinctive manufacturing process may prompt contrasts in the final result, which at that point should be appeared as not affecting adequacy as well as security in patients.

The first approved biosimilar mAb, infliximab biosimilar, was unable to specifically enter the majority of the European market due to the 6-month outgrowth of market uniqueness given in return for the filing of an extra pediatric indication of the innovative medicinal product Remicade R (GaBI, 2013; Moorkens et al. 2016). Most naturally gathered medications, regardless, have been supported under the PHSA (Under the new biosimilar law, starting on 23, march 2020, NDAs). The Medication Value Rivalry as well as Patent Term Reclamation Demonstration of 1984, consistently known as the Hatch-Waxman Act, set up a patent suit scheme for drugs supported under the FDCA (S. Chow, 2013). The Hatch-Waxman Act cut down the over-the-top administrative support costs that creators of conventional medications defied, and for producers of marked prescriptions Hatch-Waxman expanded patent terms and clarified patent rights (Winegarden, 2018).

4.3 Interchangeability

With respect to the exhibition of compatibility, the degree of concerns communicated by the trailblazers was without a doubt higher. Innovative organizations assume that standard item should obviously be distinguished mostly from biosimilar, so medical care providers including patients could be fully informed of the cancer therapy they utilize (Sarzi-puttini et al. 2019). The FDA recommends that the exchange of research should evaluate treatment improvements that result in at least two rotating submissions to the proposed exchangeable as well as the reference object. Thimmaraju et al. have prescribed that biosimilar associations may need to advance endeavors on get-together persuading verification to show comparability, for instance, results from pharmacovigilance analyzes, to support market invasion (Chang, 2019).

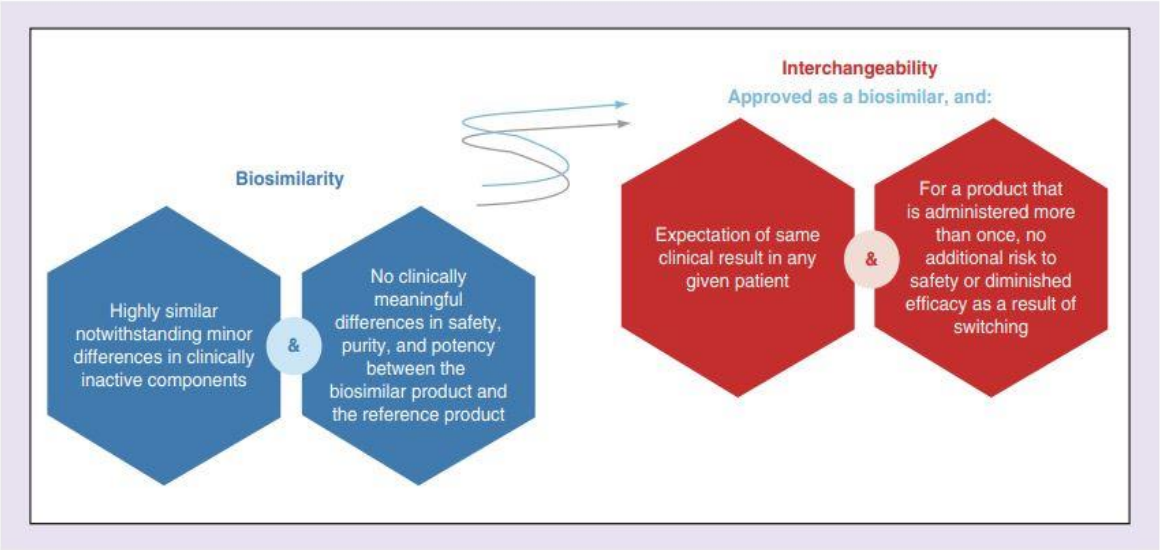


Figure 4. US FDA standards for an interchangeability designation (Thill et al. 2019)

4.4 Automatic Substitution

Interchangeability (Appendix A13) itself is switch directed by a doctor focusing on the knowledge of the particular product as well as the patient (Choy and Allen Jacobs, 2014). On the contrary, automatic replacement (Gravel, Naik, and Le Cotonnec; 2020) is a process where replacement occurs at the dispensary level without any of the involvement or even knowledge of the prescribing doctor (Moorkens et al. 2016). As biosimilars really aren't indistinguishable from their comparable biologics as well as some laws have requirements, that swapped medications have to have the same potent bioactive components (Uifălean et al. 2018). Almost all of the constitutional provisions have similar features (Wish, 2019): (1) the biosimilar ought to be appointed "viable" by the FDA (Wish, 2019), (2) the prescriber can hinder the substitution by communicating "apportion as composed," (Wish, 2019) (3) the prescriber ought to be recounted any substitution made by the medication store (Wish, 2019), also (4) When a biosimilar is filled in for a standard biologic the drug store should hold a put-down account (Wish, 2019).

4.5 Immunogenicity

Since they are intricate particles combined in living frameworks, mAbs as well as their biosimilar partners become conceivably immunogenic (Choy and Allen Jacobs, 2014). Amongst all biotechnological products, immunogenicity is a significant security concern and is caused by a number of risk variables, including biological properties, persistent qualities, concomitant therapy and prior openness to comparative biologic specialists (fig. 5) (Choy and Allen Jacobs, 2014; Schellekens, 2002). Because of immunogenic reactions, bioavailability (Appendix A10) features as well as quality of the products could be degraded, which may even lead to death to a persona (Choy and Allen Jacobs, 2014).

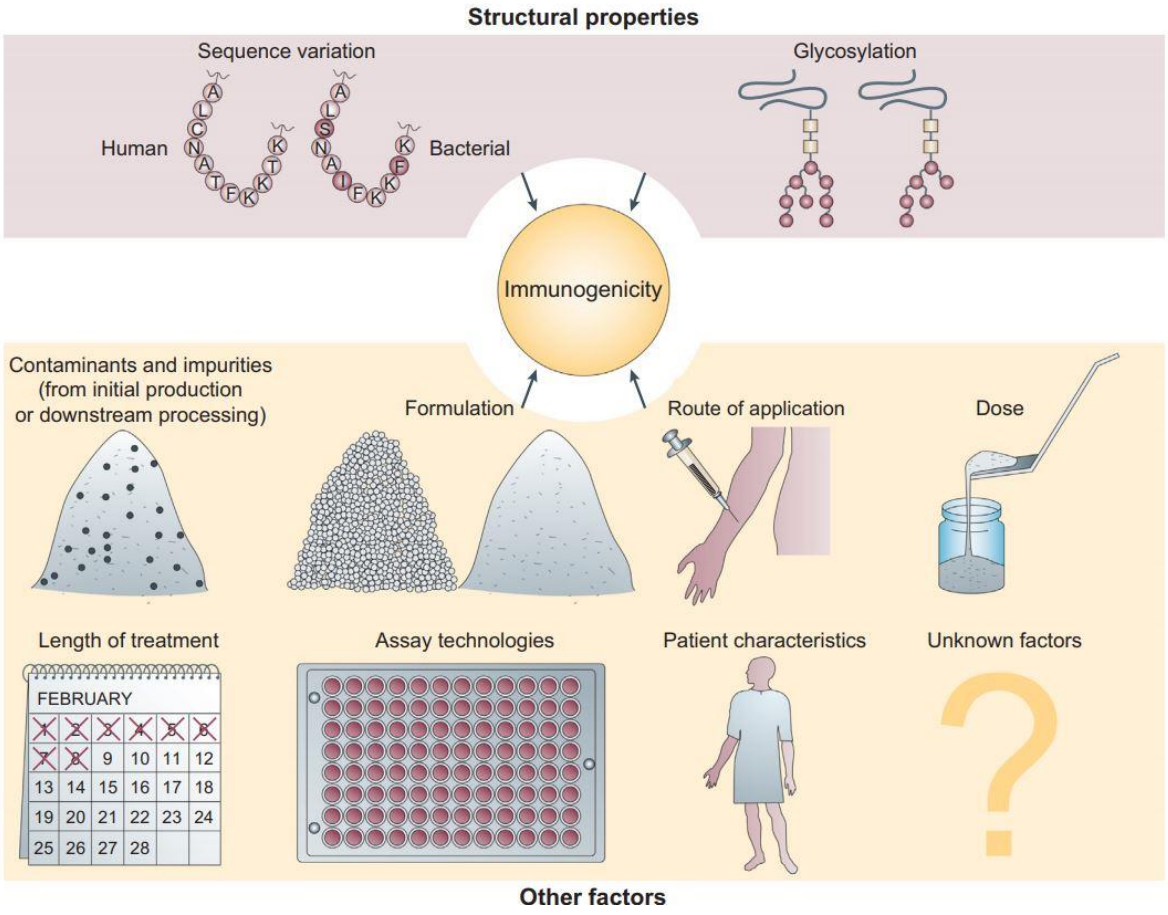


Figure 5. Components that impact immunogenicity of biopharmaceutical (Choy and Allen Jacobs, 2014)

The consequences of developing immunogenicity in patients could lead to certain mild responses to meaningful SAEs in body (World Health Organization 2009), such as: (1)

increments or diminishes drug removal from the body (Choy and Allen Jacobs, 2014); (2) Counteracts the pharmacological activity (Appendix A15) of an active substance (Choy and Allen Jacobs, 2014); (3) The pharmacological activity as well as its endogenous cross-reactive counterpart are nullified (Choy and Allen Jacobs, 2014); Either (4) Induces an immunological response either hyperactivity response (Appendix A16) (Choy and Allen Jacobs, 2014; Cai et al. 2012).

4.6 Exclusiveness of the Standard Drug

At the period while the 2009 BPCI Act (Appendix A18) had yet to be enacted, passed, the data exclusivity and business exclusivity periods were actively discussed (Chang, 2019) to guarantee a harmony among advancement as well as value rivalry, an optimum period for exclusivity is critical (Chang, 2019). It was determined that the equivalent of the initial investment lifespan for the standard item will be between 12.9 years as well as 16.2 years (Chang, 2019), in view of which a fourteen years selectivity for guide products was proposed by the BIO leader (Chang, 2019). Later, the enactment permitted an eliteness period of twelve years (Chang, 2019). The significant content of the regulation states that perhaps the USFDA cannot apply for a biosimilar or interchangeable product license valid until twelve years afterwards date upon which standard substance had first been registered in compliance with the PHS Act (Mohiuddin, 2019). The 12-year duration is significantly more than that for the latest reference product of a synthetic element (RLD) (Chang, 2019).

Chapter 5

Development as well as Endorsement of the Biosimilar Products

5.1 Indication extrapolation

After the FDA has affirmed a biosimilar, it is possible to extrapolate the indications for the biosimilar from the reference drug. Extrapolation (Appendix A4) permits endorsement of a biosimilar for different signs for which the reference biologic is affirmed, regardless of whether the biosimilar was not concentrated explicitly on those signs or indications (Appendix A5) (Hara, Tajima, and Tanabe 2019). Extrapolation depends on the entirety of the current information and proof remembered for the accommodation for the biosimilar, just as the past security as well as viability information of the bio-originator, and considers different logical variables of the sign (Deep, 2019). Figure 6 shows Comparison of Approval Pathways for reference product vs biosimilar differences between the normal 351(a) administrative pathways

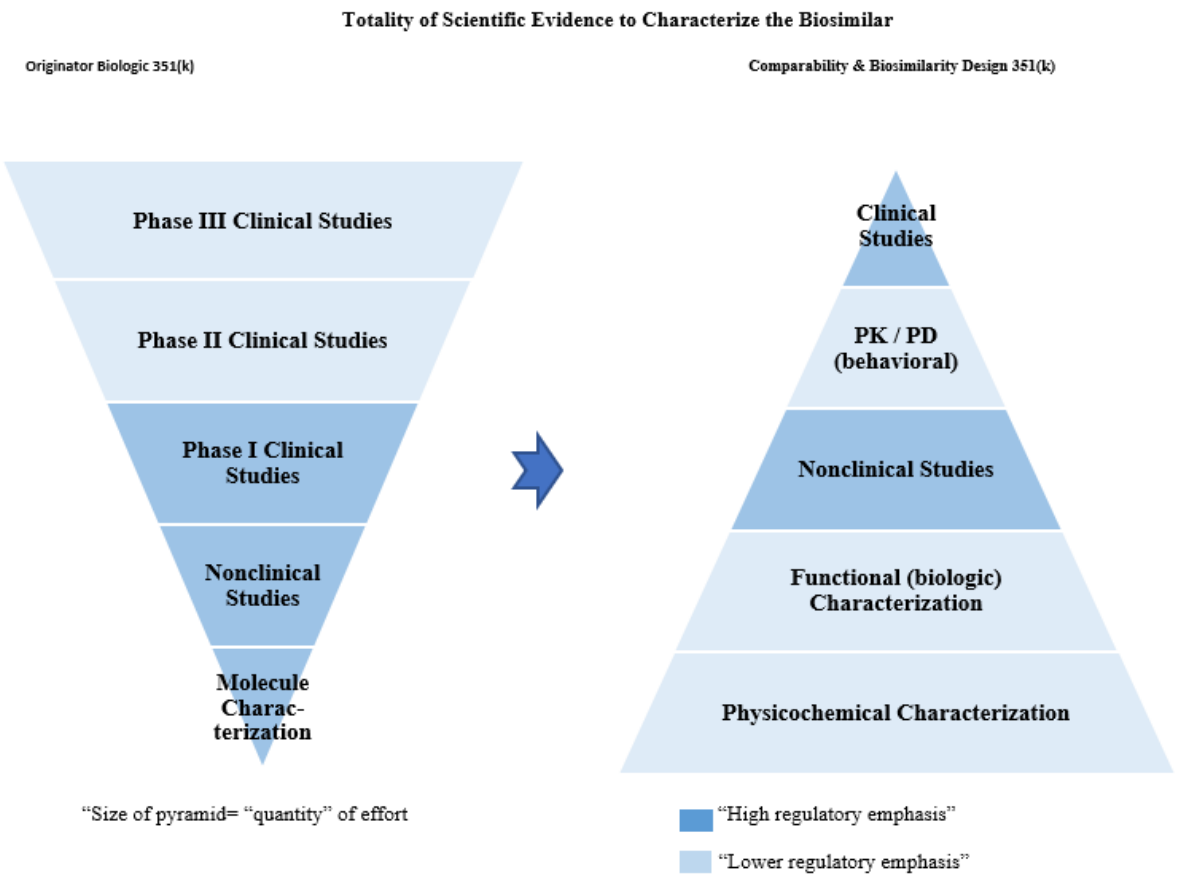


Figure 6. Comparison of Approval Pathways for Reference Product Vs Biosimilar Drugs (Niazi, 2018)

for the assessment of the protection and efficacy of a new biologic product and the biosimilar endorsement pathways of 351(k) (Sisman et al. 2021). To appropriately draw in, clinicians might need to realize that the Pharmacokinetic (Appendix A1) investigation shows identicalness, as it can vary by clinical setting particularly in malignant versus non-malignant conditions (Al-Jahdali et. al., 2020). Since a biological maker performs randomized clinical preliminaries for each ideal sign, the FDA could consider the extrapolation of security and adequacy data from one biosimilar sign to the next (Nabhan et al. 2018).

5.2 “Totality of the Evidence”

The FDA's methodology for assessing bio similarity is portrayed as a "totality of evidence," in light of the fact that different investigations to decide closeness between a biosimilar and its reference drug (Nava-parada, Shelbaya, and Nabhan 2020). From the amount of information obtained from analytical, preclinical, and clinical examinations, this can be characterized. Worldwide, including by the FDA, EMA, and WHO, the entirety of the proof requirement is acknowledged. As per the FDA: "There is nobody size fits all way to deal with biosimilar item manufacturing, to utilize an "entirety of the proof" way to deal with showing bio similarity to the reference item is the objective of a biosimilar production program, not to freely build up security and adequacy of the proposed biosimilar" (Unni, 2020).

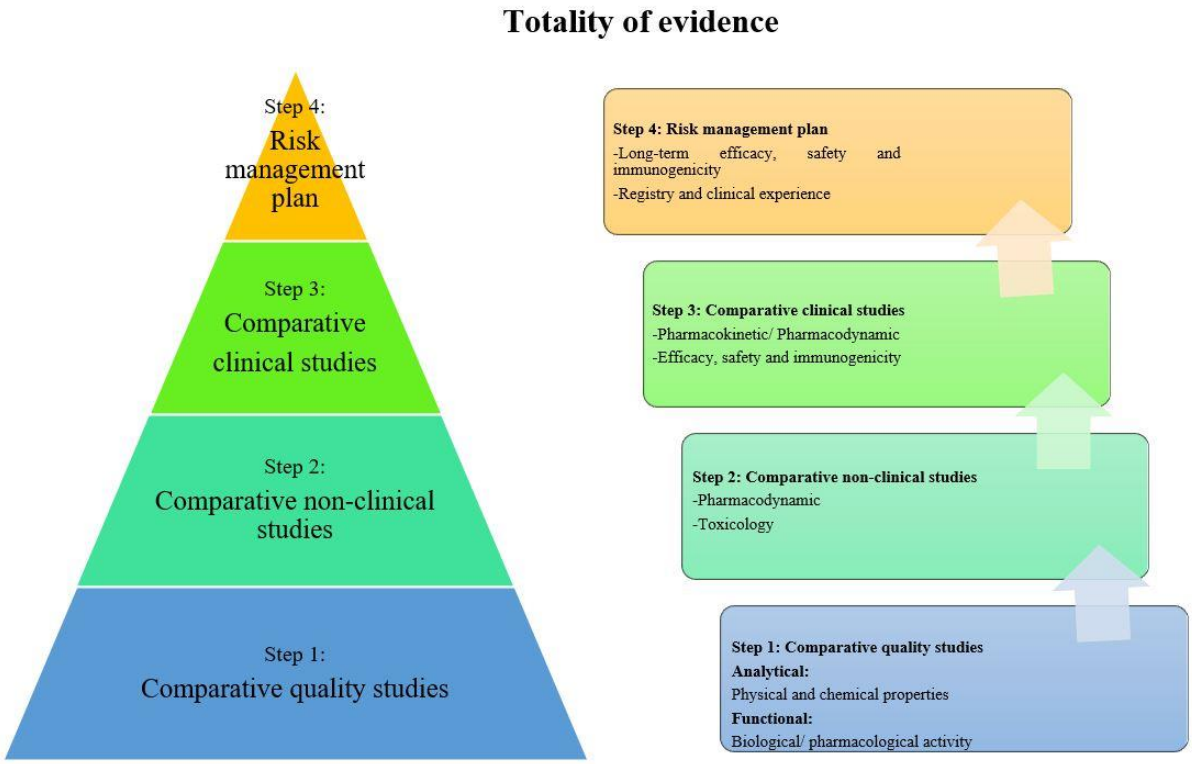


Figure 7. Data necessities for endorsement of a biosimilar (Rezk and Pieper, 2017)

5.3 Biosimilar Comparability Exercise

In attempt to show cumulative bio similarity, the EU- endorsement of a biosimilar helps to ensure broad correlation tests between the biosimilar submitted and the reference medication. These "likeness examines" speak to the foundation of a biosimilar improvement. It includes straight on examination tests intended to research whether there are clinically significant contrasts between the biosimilar as well as the reference medication regarding adequacy, wellbeing, and intensity (FDA, 2017). Comparability quality tests, comparative non-clinical studies and comparative clinical studies are structured in a three-step way through the whole process (Figure 8).

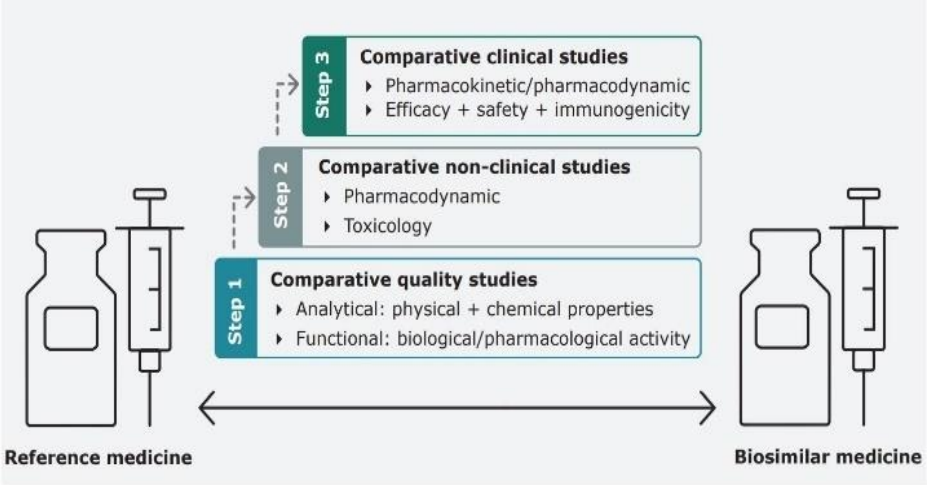


Figure 8. The step-wise process of the comparability exercise required to demonstrate the bio similarity (The European Medicines Agency and The European Commission, 2019)

5.4 Comparative Quality Studies

Asserting the chemical, physical resemblance as well as comparative analysis of biological activity between the biosimilar and the reference medicine is the main focus of the comparative quality investigation (Thill et al. 2019). The strategies utilized in the progression incorporate exact and delicate analytical procedures that are ready to identify small variations between the tried medications (Schneider, 2013). Any distinction found in this progression should be additionally researched as it might influence the end adequacy and security profile.

Characteristic	Attributes	Analytical Tool
Primary structure	Amino acid sequence	RP-HPLC, LC-ESI-MS, LC-ESI-MS Peptide mapping
Higher order structure	Disulfide structure Free thiol analysis Secondary and tertiary structure	LC-ESI-MS peptide mapping Elman assay CD, FTIR, Antibody conformational array, X-ray crystallography
Purity	Thermal stability Monomer content	DSC SEC-HPLC, SEC-MALS, SV-AUC, CE-SDS
Charge heterogeneity/amino acid modification	Charged isoforms	IEF, IEC-HPLC
Glycosylation	Deamidation/oxidation/C-terminal variants N-glycan analysis Glycosylation occurrence Oligosaccharide profile Sialic acid analysis Monosaccharide content (fucose, GlcNAc, galactose, and mannose)	LC-MS peptide mapping LC-MS CE-SDS HPLC HPAEC-PAD HPAEC-PAD
Potency	Antigen and Clq binding FcRn binding Antigen neutralization Apoptosis CDC	ELISA SPR Cell-based neutralization assay Cell-based apoptosis assay Cell-based CDC assay

CD, circular dichroism spectroscopy; CE-SDS, capillary sodium dodecyl sulfate gel electrophoresis; DSC, differential scanning calorimetry; ELISA, enzyme-linked immunosorbent assay; FTIR, Fourier transform infrared spectroscopy; GlcNAc, N-acetylglucosamine; HPAEC-PAD, anion exchange chromatography with the pulsed amperometric detection; IEF, isoelectric focusing; IEC-HPLC, ion exchange chromatography; LC-ESI-MS, liquid chromatography electrospray ionization mass spectrometry; RP-HPLC, reversed-phase high-performance liquid chromatography; SEC-HPLC, size-exclusion chromatography; SEC-MALS, SEC-multi angle light scattering; SPR, surface plasmon resonance; SV-AUC, sedimentation velocity analytical ultracentrifugation.

Table 6. Portrayal of characteristics, attributes and used analytical tools from different analyses (Tsuruta et al. 2015)

5.5 Non-Clinical Empirical Research

The relative non-clinical examinations intend to analyze the pharmacodynamic (Appendix A2) as well as the harmful properties of the two assessed meds (World Health Organization, 2009; *The European Medicines Agency and The European Commission, 2019*). As referenced, the form and the degree of non-clinical in vitro tests rely upon the degree of proof procured in the immediate passed step. Pharmacodynamic in vivo (Appendix A8) analyzes utilizing creature models are required uniquely without reasonable in vitro (Appendix A9) models (Uifălean et al. 2018).

5.6 The final part, Empirical Medical Findings

The Comparative clinical examinations are customed fitted to research the dissimilarities saw in the physicochemical, organic or in vitro properties. It also addresses any vulnerabilities from prior phases. The last intention is to preclude any clinically significant contrasts between the biosimilar and the reference and to affirm bio similarity. Since the effectiveness of the reference medicinal product has just been illustrated in patients, the biosimilar had to showcase equivalent clinical outcomes profiles to those of the reference medicinal product (Branch and Agranat 2014). However, extrapolation should be deductively legitimized and considered inside the setting of the entirety of the scientific, nonclinical, and clinical proof supporting bio similarity (Stebbing et al. 2020).

5.7 “Bio-Better” or “Bio-Superior”

These are biosimilars that have clinically validated MOA or have proof-of- viability that has been developed. It is the biosimilars where superfluous values can be picked up. There are a few beneficial effects from making a profoundly separated bio-superior drug. Dissimilar to with a biosimilar, there is for the most part no compelling reason to trust that licenses will terminate on the grounds that all bio-betters are treated as new molecular entrants from an

administrative viewpoint. Regardless of these advantages, creating bio-betters accompanies difficulties. The regulatory process would be longer and more costly as compared to biosimilars (Sleep D., 2017), as the agent is viewed as an entirely new entry (Burchiel, Aspbury, and Munday 2019).

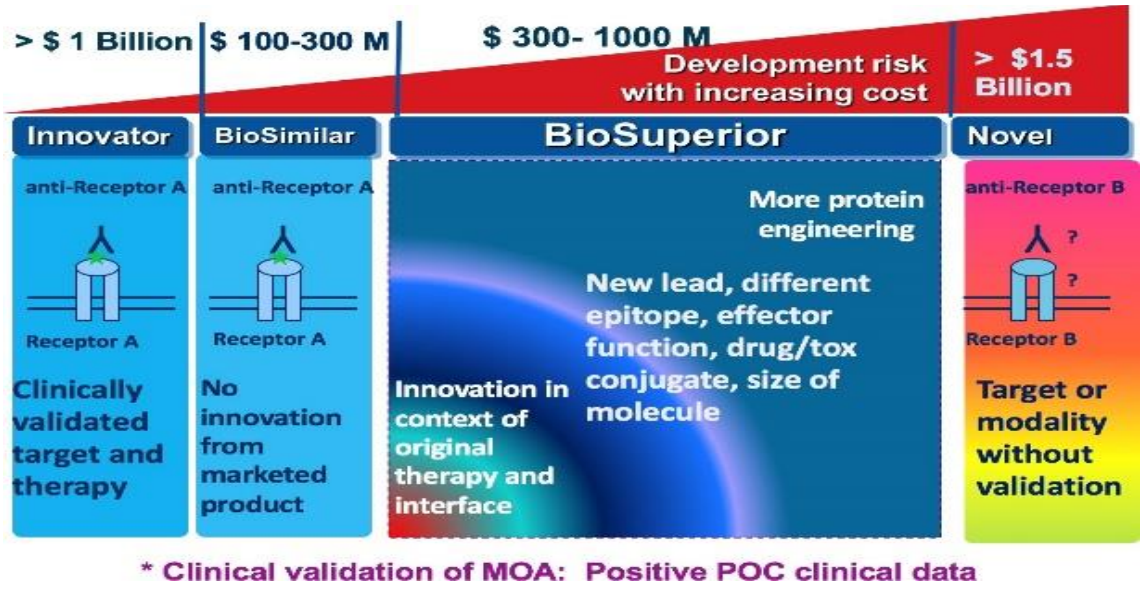


Figure 9. Comparison between reference product, Biosimilar, Bio-Superior/ Bio-Better, Novel drug (Unni, 2020)

Chapter 6

Pharmacovigilance

Viable pharmacovigilance (Appendix A17) of the biosimilar is troublesome (Chen et al. 2019). Wellbeing issues emerge on the grounds that biosimilar products do not precise of the standard drugs (Chen et al. 2019). Numerous antagonistic impacts may show up exclusively after a biosimilar drug is utilized all the more broadly, for a more extended timeframe, in a more noteworthy number of patients. The two makers and prescriber ought to know about the significance of post promoting watchfulness, and cautious on patients taking biosimilar (Kumar and Singh, 2014). For instance, 181 patients with chronic illness created counter acting agent sedated unadulterated red cell aplasia right after openness to long periods of taking of an epoetin composition in which an assembling modification (replacement of polysorbate 80 in replace of egg whites) had made. During the year of 2012, 5 individuals with constant renal illness passed on from hypersensitivity in 2012 following openness to another protein, named peginesatide, which is a sort of novel erythropoiesis invigorating specialist that isn't a biosimilar. Utilization of phenol as a reagent to stabilize the multi-dose vial definitions might have proned to this risk, as before this no single cases have been noticed in omitting of phenol. The WHO's pharmacovigilance information base incorporates in excess of 100 suddenly detailed unfavorable occasion reports for the 3 biosimilar filgrastims which advertised in European nations, however, in Japan, Canada, or U.S not a single report has been found for any individual getting biosimilar drug filgrastim. On the off chance that a replacement from reference drug filgrastim to filgrastim biosimilar happens. The course of pharmacovigilance would include the notification of AEs relevant to the use of biosimilars.

Biosimilar	Comparator Generic (brand)	Additional Pharmacovigilance Activities
Epoetins HX57 (Abseamed, Binocrit, Epoetin-α Hexal)	Epoetin-α (Eprex)	▪ Cohort study to monitor incidence of thromboembolic events ▪ Survey to establish (off-label) subcutaneous use
SB-309 (Retacrit, Silapo)	Epoetin-α (Eprex)	▪ Close monitoring using specific questionnaires to establish PRCA and thromboembolic events ▪ Study to evaluate safety and tolerability of epoetin-zeta administered intravenously for the maintenance treatment of renal anemia (CT-830-04-004) ▪ Post authorization cohort study of epoetin-zeta for the treatment of renal anemia (PMS-830-07-043) ▪ Prospective, open, noncontrolled, multicenter study to evaluate safety and tolerability of epoetin-zeta administered subcutaneously for the treatment of anemia in cancer patients (CT-830-05-0009) ▪ Drug utilization study on use of epoetin-zeta
G-CSFs XM02 (Biograstim, Filgrastim, Ratiopharm, Ratiograstim, Tevagrastim)	Filgrastim (Neupogen)	▪ Signal detection procedure for all incoming adverse drug response reports from whatever sources (including the SCNIR) and indications, and scheduled antibody assessment in case of suspected immunogenicity ▪ Cooperation with SCNIR and analysis of corresponding Biograstim-SCNIR data
EP2006 (Zarzio, Filgrastim Hexal)	Filgrastim (Neupogen)	▪ Pharmacovigilance program for patients with severe chronic neutropenia ▪ A 12-month phase 4 study in patients with severe neutropenia, followed by a 5-year safety follow-up of study patients in cooperation with the SCNIR ▪ 5-year safety follow-up study of healthy stem cell donors in cooperation with apheresis centers
PLD108 (Nivestim)	Filgrastim (Neupogen)	▪ Targeted questionnaire ▪ Follow-up of patients through SCNIR registry ▪ Cooperative program with hematologic transplant centers ▪ Specialized follow-up for long-term data

Table 7. Some Instances of Pharmacovigilance functions for EU-endorsed Biosimilars (Choy and Allen Jacobs, 2014)

This incorporates intentional, unconstrained revealing of AEs as well as prescription mistakes by HCPs to the FDA or maker, even the required announcing by makers the data they have from the FDA mostly to FDA (Choy and Allen Jacobs, 2014; Camacho et al. 2014). These alerts are inserted into a surveillance scheme by the FDA as well as significant security indicators are then detected (Choy and Allen Jacobs, 2014). A pharmacovigilance system includes techniques for timely selection, monitoring, and mapping of AE (Choy and Allen Jacobs, 2014). This will allow newly occurring, deteriorating, or elevated occurrence of known and established safety issues for instance, product recalls or compliance warnings to be identified (Choy and Allen Jacobs, 2014). The implementation of a fair international

nomenclature scheme for biosimilars includes this traceability (Figure 10) (Choy and Allen Jacobs, 2014; Casadevall et al. 2013).

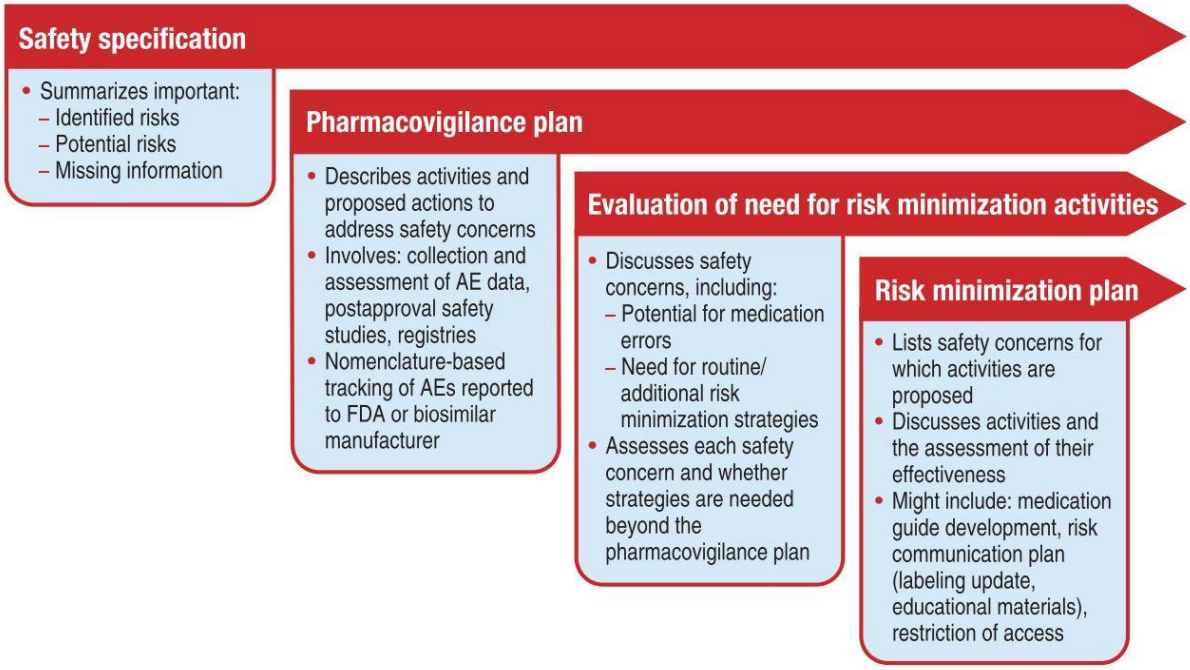


Figure 10. Risk management in terms of risk as well as pharmacovigilance with the biosimilars (Choy and Allen Jacobs, 2014)

Under current FDA pharmacovigilance manages just as where a peril has quite recently been recognized, it is recommended that the producer consider the going with in closing whether to set up a pharmacovigilance plan (Figure 10) (Choy and Allen Jacobs, 2014; Casadevall et al. 2013):

○ “The probability that the AE speaks to a potential danger”

○ "The recurrence with which the occasion happens (e.g., frequency rate, announcing rate, or different estimates accessible)"

○ "The frequency and intensity of the occurrence"

○ "The idea of population(s) in danger"

○ "The scope of sick people under which the item is shown (expansive reach or chose populaces as it were)"

○ "The technique by which the item is administered"

Checklist for HCPs of the information needed for patients to make informed decisions about biosimilar use,

✓ Use of biologic therapies in a specific disease	✓ Insurance coverage/out-of-pocket cost
✓ Definition of a biosimilar	✓ Services available to support the patient
✓ Totality of evidence required of a biosimilar	✓ Clinical trials including standard biosimilar trial design (active innovator comparator; no placebo arm)
✓ Efficacy similar to innovator biologic	
✓ Safety similar to innovator biologic	
✓ Delivery/Administration of agent	✓ Manufacturer identity
✓ Devices use (if applicable)	
✓ Access to treatment	

Table 8. An agenda for HCPs with the data required for patients to settle on educated choices about biosimilar use (Rezk and Pieper, 2017)

Chapter 7

Discussion

For the demonstration of bio similarity, detailed systematic research concentrate on multistep methodology are crucial. It is generally perceived by administrative experts for showing of bio similarity. Counterfeiting, has as of late, for instance, been accounted for epoetin. Consequently, scientist recommend that any duplicate rendition of a restorative protein, which has not been created as well as surveyed in accordance with the logical standards of a carefully purely comparative model against a reference item, ought not be named biosimilar (Scientific et al. 2011). Rituximab, trastuzumab as well as bevacizumab bio-like biosimilar drugs were included in the forms of mAb biosimilars that has been found being used in oncology (Yang et al. 2019). Only RCTs documenting the safety profiles of mAb biosimilar drugs compared with mAb standard products have been found. The after-effects of rituximab, trastuzumab as well as bevacizumab biosimilars drugs' targets and functions are distinct (Yang et al. 2019). After the accomplishment of impressive affectability analysis (Yang et al. 2019), the meta-analyses results were robust. The traditional favored endpoints for anti-cancer activity in cancer care include PFS or OS, the PFS or OS will not generally be adequately delicate to build up comparative viability of mAb biosimilars as well as reference items. For this reason, a medical endpoint likewise very initial outcome is being utilized to quantify activity (using of ORR) as per EMA suggestion. The results from the moderate-quality evaluation confirmation (GRADE) show that 3 mAb biosimilar drugs were parallel to reference products as per having equal ORR, PFS as well as OS (Yang et al. 2019). Identicalness or non-mediocrity edges are significant in the trial's design. Three RCTs in the included assessments described the ORR non-mediocrity edge intently at 0.8 to 1.2 (rituximab), 0.81 to 1.24 (trastuzumab), as well as 0.8 to 1.25 (bevacizumab), separately. The consequences of ORR of the meta-examinations were inside

the characterized equality edges. The author's findings (Yang et. al., 2019) demonstrated moderate-quality proof for security results, recommending that the ADE rate was comparative for trastuzumab biosimilars comparative with trastuzumab. The most generally revealed results were the paces of antidrug antibodies (Appendix A14) and neutropenia in the included examinations. In like manner, rituximab biosimilars showed comparable paces of ADE, against drug antibodies, as well as neutropenia, comparative with rituximab reference drug. Similarly, the paces of ADE as well as hostile to sedate antibodies were comparable in ongoing clinical investigations of both biosimilars as well as reference drugs of bevacizumab (Yang et al. 2019). At last, utilization of the GRADE way to deal with survey the nature of proof, which demonstrated comparable adequacy and wellbeing of biosimilars and reference items (Guyatt et al. 2009). Each of these RCTs were clinical pre-marketing research. It generally recruited patients with comorbidity rates lower than those seen in clinical settings. This restricts the generalizability of the outcomes somewhat, specifically with respect to the security results on the grounds that the RCTs were regularly intended for checking adequacy. Both of the regulatory framework emphasizes on the post marketing monitoring which has to be seriously taken to minimize the all sort of adverse reactions between originator and biosimilar products and steps would be required to call out these safety hazards (Kozlowski et al. 2018).

Chapter 8

Challenges and Recommendations

New challengers in the biosimilars market face a couple of troubles and experience various obstacles, for example, manufacturing, market openness, bargains as well as displaying competition. Producers are under pressure to show their possible result resembles the principal drug in preclinical and clinical examinations, despite demonstrating that they can constantly keep up reproducibility at a huge degree inside a comparable site or at different creation areas. The fixed limitations forced on drug stores by administrative specialists are perhaps the greatest hindrance to be tended to in biosimilar showcasing. Despite the commercialization rules, esteeming and reimbursement approaches are a principal thought affecting biosimilar associations' decisions to enter a market or not. Despite the way that biosimilars ought to be a more affordable alternative rather than biologics, biosimilars are essentially anticipated to be (10–20) % more affordable due to the multifaceted design of their unforeseen development and creation (Bennett et al. 2014; Farhat et al. 2018). This has added to the evasion of showcasing of biosimilar organizations in countries with low esteeming systems and vulnerable reimbursement rates to save their projected target bargain costs. A U.S. study has evaluated that the cost of the biosimilars fundamentals would be between 10 to 40 million USD and that the essential interest in amassing measures goes from 250 to 450 million USD (Grabowski, Cockburn, and Long 2006). The evaluation of the expense reasonability of a biosimilar depends upon its relative sufficiency. If a fittingly arranged clinical test shows equivalent sufficiency between the biosimilar and the comparator, by then the most reasonable medication is picked, and this is likely going to be the biosimilar. Another test is that biologics similarly as biosimilars can a portion of the time cause troublesome immunogenic responses due to their protein antigenic (Appendix A11) nature (Giuliani et al. 2019). Prosperity concerns previously

arising with biologicals in oncology as well as hematology may influence specialist trust in biosimilars (Luigi et al. 2019). For instance, constituents' progressions provoking extended immunogenicity in the epoetin RP Eprex® (Janssen-Cilag Restricted, High Wycombe, UK) were connected with a spike in PRCA cases in Europe in 1998–2004 (Camacho et al. 2014). Later investigations of PRCA with biosimilar epoetin's were associated with extended immunogenicity in view of handling and capacity issues.

A couple of Proposals for improving biosimilar take-up

- Doctor level accomplice informational undertakings, incorporating continuing with clinical instructional classes that recollect information for FDA rules for biosimilar support, naming, extrapolation, substitution, trading, costs, prosperity, sufficiency, and pharmacovigilance and information that bases on perceiving conduct monetary issue as a thought that impacts suggesting
- Instructive missions at the patient and guardian stage, including public help
- Declarations financed by the (FDA, producers, web-based media, and oncology/hematology social orders)
- Drug specialist level accomplice informative undertakings, incorporating continuing with drug expert tutoring courses (FDA, makers, clinical social orders, Hematology-Oncology Drug store Affiliation)
- Guarantee that reference creators grant induction to tests to empower progression of new biosimilar things through clinical appraisal (FDA)
- Straightforward estimating that decreases the "rebate trap" has been precluded through transparence of valuing and certifies that refunds focus on patient access as well as cash-based expenses, not rundown value
- Build up techniques to help genuine esteeming zeroing in on 25% as far as possible

- Rearrange cycles of coding and reimbursement and work together with payers to represent the significance of biosimilar, including cutting down costs and improved accessibility to patients (Advancement and Pharmacology, 2019).

Chapter 9

Conclusion

The significant expenses of anticancer mAbs have become a weight on general medical services frameworks in low-pay nations as well as in created nations. Biosimilar improvement doesn't set up wellbeing and adequacy, but instead shows bio similarity to the reference drug (Unni, 2020). Relative examinations exhibiting comparative viability to the reference natural, without immunogenicity and wellbeing concerns, are required at the time of biosimilar growth (Santos, 2018). In equal, the advantages of creating biosimilar drugs that are (25–35) % less expensive permit agricultural nations to get to top notch care (Development and Pharmacology, 2018). Soon, the collected clinical experience will fix any continuing vulnerabilities identified with biosimilars' utilization (Uifălean et al. 2018). In the interim, diligent patient checking under the oversight of the prescriber, dynamic unfavorable occasion announcing, and watchful post-promoting reconnaissance should incorporate the supplanting of the reference medication with a biosimilar (Uifălean et al. 2018). Eventually, the promise of biosimilars is the expansion of quiet exposure by affordable rates (Wish, 2019). Finally, because care is a joint decision between the clinician and the patient, without the informed consent of the patient, no adjustment can be made (Sarzi-puttini et al. 2019).

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Appendix A.

A1: Pharmacokinetics- Pharmacokinetics is the study of what the body does to the drug. pharmacokinetics would outline the timeline of the drug's absorption, bioavailability, distribution, metabolism and how your body excretes it.

A2: Pharmacodynamics- Pharmacodynamics is the study of what the drug does to the body.

A3: Immunogenicity- *Immunogenicity* is the ability of a foreign substance, such as an antigen, to provoke an immune response in the body of a human or other animal.

A4: Extrapolation- Extrapolation based Molecular Systems Biology is the utilization of molecular data from one or many sub-cellular levels to indirectly infer the remaining components of a sub-cellular system via statistical algorithms and priori biological knowledge.

A5: Indication- A circumstance which points to or shows the cause, pathology, treatment or issue of an attack of disease, that which points out, that which serves as a guide or warning.

A6: Insulin- Insulin is a hormone created by your pancreas that controls the amount of glucose in your bloodstream at any given moment.

A7: Growth hormone- Growth hormone (GH) or somatotropin, also known as human growth hormones (hGH or HGH) in its human form, is a peptide hormone that stimulates growth, cell reproduction, and cell regeneration in humans and other animals.

A8: In vivo- In vivo describes a medical experiment or a test that is performed on a living organism, e.g., a human being or a laboratory animal.

A9: In vitro- In vitro is a medical experiment or a study that is performed only in a laboratory dish or a test tube.

A10: Bioavailability- The proportion of a drug or other substance which enters the circulation when introduced into the body and so is able to have an active effect.

A11: Antigens- Substance that is capable of stimulating an immune response, specifically activating lymphocytes, which are the body's infection-fighting white blood cells.

A12: Patent- A patent is a form of intellectual property that gives its owner the legal right to exclude others from making, using, or selling an invention for a limited period of years in exchange for publishing an enabling public disclosure of the invention.

A13: Interchangeability- – In medicine, this refers to drugs that contains the same amount of the same active ingredients, possesses comparable pharmacokinetic properties, have the same clinically significant formulation characteristics, and is to be administered in the same way as the drug prescribed.

A14: Antibodies- Antibody, also called immunoglobulin, a protective protein produced by the immune system in response to the presence of a foreign substance, called an antigen.

A15: Pharmacological Activities- pharmacological activity describes the beneficial or adverse effects of a drug on living matter. When a drug is a complex chemical mixture, this activity is exerted by the substance's active ingredient or pharmacophore but can be modified by the other constituents.

A16: Hyperactivity response- Hyperactivity response or Hypersensitivity is an immunological state in which the immune system "over-reacts" to foreign antigen such that the immune response itself is more harmful than the antigen. All types of hypersensitivity involve: • the adaptive immune response. • i.e., highly specific reactions via T or B cells.

A17: Pharmacovigilance-The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

A18: BPCI Act- The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amends the Public Health Service Act (PHS Act) to create an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference biological product. The BPCI Act is closely related to the Drug Price Competition and Patent Term Restoration Act of 1984**.**

A19: Interferon- Interferon, any of several related proteins that are produced by the body's cells as a defensive response to viruses.