Pharmacokinetics, Safety, Efficacy and Immunogenicity of Adalimumab Biosimilar ABP-501in Rheumatoid Arthritis and Plaque Psoriasis

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Declaration

It is hereby declare that

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3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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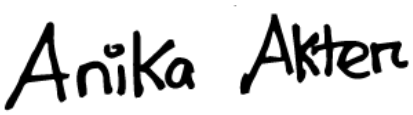

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Approval

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Ethics Statement

The study does not involve any kind of animal and human trial.

Abstract

ABP-501 is a biosimilar of Adalimumab (Humira) and a tumor necrosis factor-alpha inhibitor that is responsible for inflammatory effects on the body. ABP-501 is equally effective against moderate to severe rheumatoid arthritis (RA) and plaque psoriasis (PsO). In this review, the pharmacokinetics, safety, efficacy, and immunogenicity data of ABP-501 were demonstrated. ABP-501 has been already approved by USFDA and EMA as a treatment option for RA and PsO. The phase-3 study pre-clinical and clinical data affirm ABP-501 was safe and effective against mild to moderate RA and PsO. ABP 501 is also reported for high similarity in structure, function, and pharmacodynamics (PD). This study also focuses on different regulatory issues with biologics and biosimilar such as their development, approval process, criteria that need to be met prior to approval.

Keywords: TNF-alpha, rheumatoid arthritis, biologics, biosimilars, adalimumab, ABP-501, pharmacokinetics, safety, efficacy, immunogenicity, plaque psoriasis, inflammation.

Dedication

Dedicated to my parents.

Acknowledgement

First and foremost, I would like to express my deepest gratitude towards Almighty Allah for giving me the blessing, the strength, the patience, and the chance to complete my project work properly.

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List of Acronyms

PK	Pharmacokinetics
PD	Pharmacodynamics
FDA	Food and Drug Administration
EMA	European Medicines Agency
mAB	Monoclonal Antibody
ANDA	abbreviated New Drug Application
RBP	Reference Biotherapeutic Product
BMR	Batch Manufacturing Record
WHO	World Health Organization
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ESA	Erythrocyte Sedimenting Agent
Sc	Sub-Cutaneous
SAE	Severe Adverse Events
OLE	Open-Lebel Extension
AE	Adverse Events
PASI	Psoriasis Area and Severity Index
IPC	In-Process Control
DMF	Drug Master File
CCP	Critical Control Points
Qbd	Quality by Design
TEAE	Treatment-Emergent Adverse Events
CI	Confidence Interval
CQAs	Critical Quality Attributes
ADA	Anti-Drug Antibodies
GMRs	Geometric Mean Ratios
IND	Investigational New Drug
QbD	Quality by Design
ACR	American College of Rheumatology
CAT	Cambridge Antibody Technology
TNF	Tumor Necrosis Factor
EU	European Union

G-CSF	Granulocyte- Colony Stimulating Factor
CMC	Chemistry, Manufacturing, and Controls
USP	United State Pharmacopeia
BP	British Pharmacopeia
IGBA	International Generic and Biosimilar Medicine Association
UC	Ulcerative Colitis
NHL	Non-Hodgkin’s Lymphoma
RA	Rheumatoid Arthritis
PsO	Plaque Psoriasis

Glossary

TNF-α inhibitor:	Tumor necrosis factor (TNF) α inhibitors are a special class of drugs (antibodies) that are intended for inhibiting inflammation and treating different inflammatory diseases like rheumatoid arthritis, Crohn's disease, Inflammatory bowel disease, and plaque psoriasis
ACR:	American College of Rheumatology (ACR) is a treatment response that is measured as a percentage to demonstrate the effectiveness of the drugs. ACR 20 defines 20% of patients have an improvement in swollen joint or tender in different clinical studies
PASI Score:	Psoriasis Area and Severity Index (PASI) score defines the grade and severity of psoriasis as well as the response of the patients towards the treatment.
Geometric Mean Ratio:	The geometric mean ratio is used to explain the mean ratio of maximum concentrations and area under the curve.
Loading dose:	Loading dose can be described as a primary higher dose that has been given to a patient to get spontaneous therapeutic concentration until a lower maintenance dose.

Chapter 1

1.1 Introduction

Biosimilars can be referred to as an alternative version of a biologic that is officially regulated and approved. Biosimilars are not as same as generic drugs due to the complexity in the structure and expenses in the manufacturing process (*Biosimilar and Interchangeable Products | FDA*, n.d.-a). The term "biosimilar" is mostly used in Europe whereas in the USA it is mostly referred to as "follow in biologics" (JJ et al., 2020).

Adalimumab is a biological medicine in the class of medication called Tumor Necrosis Factor (TNF) inhibitors. It acts on the immune system by blocking the action of TNF that is responsible for causing inflammation. Adalimumab is known as biologics as it is derived from mammalian cell expression systems through recombinant DNA technology (JS et al., 2019). Adalimumab has1330 amino acids in its structure and the molecular weight is almost 148 kilodaltons. Adalimumab drug development started in 1993 by BASF Pharma with the help of Cambridge Antibody Technology (CAT) which is a biotechnology company focused on antibody technology. The pharma basically wanted to produce a TNF neutralizing human antibody using advanced technology (Coghlan et al., 2021a). Additionally, within 3 years the pharma isolated "adalimumab" as a lead compound and the further journey of adalimumab started. The drug candidate had to go through pre-clinical and clinical studies, regulatory approvals, manufacturing, testing, and marketing (O'Callaghan et al., 2019). Therefore, Adalimumab became the first human monoclonal antibody approved by USFDA in 2008 and it got approval from EMA in 2007. In 2012, it was the world's best-selling drug with a total sale of $12.89 billion. This outstanding commercial success of adalimumab made it a target for biosimilar manufacturers (Bellinvia et al., 2021.). In contrast, biologics are recognized as one of the expensive drugs in the world. A single shot of biologics can cost USD 10,000 and above. Though for developed countries insurance policies bear the cost of the drug (Crespi-Lofton & Skelton, 2017). For developing and undeveloped countries, the patient needs to pay the price of the drug from their pocket and the effective drugs are really expensive. For this reason, the US passed a "fast-track" law for the rapid approval of biosimilars (*U.S. Biosimilars Market Size, Growth | Forecast Report, 2028*, n.d.). Therefore, the development of biosimilars can save a lot of money for patients & time for manufacturers, as biosimilars cost at least one-third less

than the originator drug. For example, Infectra (Infliximab-dyyb); Remicade. a biosimilar of Infliximab cost 19% less than the original drug (de Mora, 2019).

Table 01: Price comparison of a few biosimilars with their reference product (de Mora, 2019)

INN	Name	Strength	Price	Cost of Difference (%)
Filgrasim	Neupogen (Reference Biologic)	300 mg	$324.30	16.21%
	Zarxio (Corresponding Biosimilar)	300 mg	$275.66	
Filgrastim	Neupogen (Reference Biologic)	480 mg	$516.45	16.22%
	Zarxio (Corresponding Biosimilar)	480 mg	$438.98	
Infliximab	Remicade (Reference Biologic)	100 mg	$940/vial	44%
	Inflectra (Corresponding Biosimilar)	100 mg	$525/vial	
Infliximab	Remicade (Reference Biologic)	100 mg	$1167.82/vial	35%
	Renflexis (Corresponding Biosimilar)	100 mg	$753.39/vial	

INN= International Non-proprietary Names

The establishment of the latest biosimilars has brought numerous treatment options for some non-curable diseases such as psoriasis and chronic rheumatic diseases (Zhou et al., 2021). The patent of adalimumab (Humira) expired in the US in December 2016 and Europe in October 2018. After that, different manufacturers started seeking regulatory approval and entered the market with new biosimilars of adalimumab. In the year between 2016 to 2020, FDA (Food and Drug Administration) and EMA (European Medicines Agency) have approved 8 biosimilars as shown in Table 02.

Table 02: Biosimilars of Adalimumab approved by USFDA and EMA

Reference Product	Biosimilar	Manufacturer	Phase of Development
Adalimumab	ABP 501 (L. J et al., 2016)	Amgen (USA)	Approved in EU (2017), USA (2016)
	BI 695501 (V et al., 2020)	Boehringer Ingelheim (Germany)	Approved in EU (2017, withdrawn in 2019), USA (2017)
	SB5 (G et al., 2019)	Biogen/Samsung Bioepis (South Korea)/Merck (USA)	Approved in EU (2017), USA (2019)
	GP2017 (X et al., 2020)	Sandoz (Switzerland)	Approved in EU (2018), USA (2018)
	MSB11022 (Zhou et al., 2021)	Fresenius Kabi (Germany)	Approved in EU (2019)

	FKB327 (V et al., 2020)	Fujifilm Kyowa Kirin Biologics (Japan)/Mylan (USA)	Approved in EU (2018), USA (2020)
	PF-06410293 (Zhou et al., 2021)	Pfizer (USA)	Approved in EU (2020), USA (2019)
	CT-P17 (Cingolani et al., 2021)	Celltrion (South Korea)	Approved in EU (2020)
	LBAL (V et al., 2020)	LG Life Sciences (South Korea)/Mochida Pharmaceutical (Japan)	Phase III clinical trial (completed)
	ONS-3010 (Vulto & Jaquez, n.d.)	Outlook Therapeutics (former Oncobiologics) (USA)	Phase III clinical trial (completed)
	MYL-1401A (Zhou et al., 2021)	Mylan (USA)	Phase III clinical trial (completed)
	M923 (JJ et al., 2020)	Momenta Pharmaceuticals (USA)	Phase III clinical trial (completed)
	BCD-057(Vulto & Jaquez, n.d.)	Biocad (Russia)	Phase III clinical trial (completed)
	AVT02 (Markus et al., 2019a)	Alvotech Swiss AG (Switzerland)	Phase III clinical trial (completed)
	DMB-3113 (Wolff-Holz et al., 2019)	Meiji Seika Pharma (Japan)	Phase I clinical trial
	TUR01 (Lu et al., 2021a)	Turgut İlaçları A.Ş. (Turkey)	Phase I clinical trial
	BMO-2 (Kaur et al., 2021)	Mylan (USA)	Phase I clinical trial

Different researchers reviewed the recent studies going on adalimumab and demonstrated three complete trials of adalimumab biosimilars BCD-057 and ABP-501 and three ongoing trials of adalimumab biosimilars M923, SB5, and GP2017 that target TNF- α (Markus et al., 2019b). Therefore, physicians are not switching to biosimilars since the pharmacokinetics, pharmacodynamics, safety, efficacy, and immunogenicity for different biosimilars are not completely similar to their biologics. Hence, the practice of switching is still missing.

1.2 Rationale of the Study

The study focused on the effectiveness, safety, pharmacokinetics, and immunogenicity of adalimumab biosimilar ABP-501 which is an approved adalimumab reference product. Rheumatoid arthritis is a long-term autoimmune disorder that causes severe damage in joints thus decreasing the quality of life of patients. There were very limited treatment options were

available for the extremely costly disease. Biosimilars of adalimumab have brought revolutionary treatment options and major advancements in the treatment. FDA stated adalimumab as an excellent drug for the treatment of rheumatoid arthritis in terms of safety and efficacy(Z. S et al., 2018). But long-term use of such expensive drugs is considered a principal deficiency for chronic autoimmune disease. Moreover, the patent expiration of biologics leads to the devolvement of different biosimilars. Recently, FDA and EMA approved 7 biosimilars of adalimumab (Humira) that have demonstrated similarities in terms of pharmacokinetics, safety, efficacy, and immunogenicity. There are subtle dissimilarities between biologics and biosimilars in the structure of the inactive part. As some of the biosimilars got regulatory approval recently, the available information is insufficient to compare different factors with the reference product. Thus, the review focuses to summarize the pharmacokinetics, safety, efficacy, and immunogenicity of ABP-501 with its biologic by reviewing the data from clinical trials.

1.3 Aims of the Study

The review aims to comprehend parameters such as pharmacokinetics, safety, efficacy, and immunogenicity of adalimumab biosimilar ABP-501 and signify ABP 501 is equally safe and effective to its reference product.

1.4 Objective of the Study

The objective of the review is:

1. To gather information about different biosimilars of adalimumab approved by regulatory bodies.

2. To understand the pharmacokinetics, safety, efficacy, and immunogenicity of ABP-501 in different diseases like RA and, PsO.

Chapter 2

Methodology

The literature review was conducted through three-step procedures. They are:

1. An assemblage of probably related articles using different sources,

2. Selection of possibly related articles and,

3. Investigation of selected studies.

First of all, from the PubMed database, related articles of adalimumab biosimilars were reviewed and summarized. These articles mainly focused on PK studies of different biosimilars in different clinical stages, investigation of safety and efficacy of biosimilars with the reference product, adalimumab biosimilars for the treatment in rheumatoid arthritis and psoriasis. Some articles were taken from ScienceDirect based on updated information about the comparison of the different variables of biosimilars. Also, the data was collected from different regulatory agencies' websites, post-marketing surveillance studies, and also searched “ClinicalTrials.gov” to analyze the unpublished data of clinical trials of adalimumab biosimilars. The inspection was performed using several keywords such as adalimumab, biosimilar, comparison, safety, immunogenicity, efficacy, Rheumatoid arthritis, ABP 501, MSB11022, BI695501, GP2017, SB5, etc. After that, the references were inspected through the Mendeley library and inserted into the review paper. Finally, a bibliography of all the references that have been cited was organized.

Chapter 3

3.1 What are Biologics

According to the US FDA, biologics can be defined as an extensive array of products including blood and blood components, somatic cells, vaccines, allergens, tissue, and recombinant proteins, and gene therapies (*What Are "Biologics" Questions and Answers | FDA*, n.d.). Biologics are isolated from the different natural origins such as sugars, nucleic acids, proteins, or multiplex combinations of these substances (Frazier-Mironer et al., 2014).

With the help of biotechnology, biological drugs are obtained from different microorganisms, animals, and humans. Protein-containing biologics control the actions of different cellular processes and proteins. In the same way, biologics contain genes that are responsible for controlling the production of viral proteins, hormones, and cells that construct components that further switch on or repress ingredients of the immune system(*What Are Biologics? Definitions and Potential Benefits | Bioanalysis Zone*, n.d.). As biologics alter the process of functioning of natural biologic cellular and intracellular actions, biologic drugs are often called "biologic response modifiers" (*Biologics: Definition, Side Effects, Uses & Drug List*, n.d.-a). There are numerous types of biologics. They are:

i. **T- cell inhibitor:** This inhibitor suppresses the communication among T cells (white blood cells) (AG & OA, 2017).

ii. **B-cell inhibitor:** B cells are a type of white blood cell that transport protein which further can trigger an immune response. B-cell inhibitors influence B cells (Pelechas et al., 2018a).

iii. **Tumor necrosis factor (TNF) inhibitor:** This inhibitor prevent a chemical responsible for driving inflammation in the body (*Biologics for Rheumatoid Arthritis (RA): What To Expect*, n.d.).

iv. **Interleukin-1 (IL-1) blocker:** The blocker inhibits the chemical that is responsible for causing inflammation.

v. **Interleukin-6 (IL-6) or interleukin-17 blocker:** The blocker hinders inflammation-causing chemicals from coupling to the cells (Fda, 2016).

3.2 What are Biosimilars

Biosimilar (FDA approved) can be referred to as a biological product that has been compared with a biologic (FDA-approved) which is also acknowledged as a "reference product" (Fda, 2016). European Medicines Agency (EMA) states a biosimilar as a biological agent that is almost identical to previously approved biologic in the European Union (EU) (*Biosimilars_ A Multidisciplinary Perspective | Elsevier Enhanced Reader*, n.d.). The United States (US) Food and Drug Administration (FDA) states biosimilars as a drug that has "no clinically meaningful differences" from an originator drug (*Biosimilar and Interchangeable Products | FDA*, n.d.-a). The phrase articulates the biosimilar drug should be almost equivalent to the reference product in terms of safety, purity, efficacy, and immunogenicity (Zhou et al., 2021). All the regulatory authorities such as USFDA, WHO, and EMA addresses identical definitions for biosimilars that are the biological drug that has a high similarity with licensed originator's drug (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.).For example, Amjevita (adalimumab-atto) is the first approved biosimilar for the blockbuster Humira (adalimumab) for the treatment of psoriasis and rheumatoid arthritis (*What Are Biosimilars? Top Facts You May Not Know*, n.d.). Other examples of these groups are infliximab (Remicade®), rituximab (MabThera®), adalimumab (Humira®), etanercept (Enbrel®), and many more.

Biosimilars and reference products are bulky in size and complex molecules which are manufactured from living organisms very cautiously in order to maintain consistent quality. A biosimilar is much the same as the reference product. For approval from regulatory authorities, the structures and functions of the biosimilars need to be matched with the reference product (Sauerborn et al., 2010). Other key factors that are kept in mind during the approval of biosimilars are bioactivity, purity, and molecular structure (Kaur et al., 2017a). While comparing biosimilar with the reference product, the data must state that the biosimilar is highly similar to the reference product. However, it is important to mention that there might be a slight difference from the inventor in some factors such as pharmacokinetic (clinical performance and biological properties), pharmacodynamics, safety, immunogenicity, and efficacy. For this reason, prior to approval, different regulators ask a comparative study on these factors to the respective originator with the reference product (European Medicines Agency, 2018). While manufacturing the biosimilars every step starting from selecting amino acids, establishing biosimilarity, demonstrating equivalent safety and efficacy is maintained

cautiously and mimicking the steps of originator followed by the production of biologics to exhibit the similarities (Vulto & Jaquez, n.d.). All the biosimilars are prescription drugs.

3.3 History of Biosimilars

The history of biosimilars is not very long. Based on the totality of the evidence, biosimilars and reference medicines are very much alike on the criteria of different functional and structural parameters such as pharmacokinetics, immunogenicity, safety, and pharmacodynamics. Sandoz discovered the first biosimilar product called Omnitrope® (somatropin) which is a human growth hormone. (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.). It was the first product that got approval from the EU in the year 2006. For getting approval from regulatory authority Sandoz sent the preclinical, clinical, and analytical data to the EMA claiming that somatropin or Omnitrope® has higher similarity with reference biologic Genotropin® manufactured by Pfizer. Later on, FDA approved somatropin as a new drug based on the data of the reference product rather than a biosimilar as the approval concept of biosimilar was quite new at that time(GR & U, 2015). Sequentially, only lower molecular weight containing biologics had biosimilars until 2013 (Kesik-Brodacka, 2018). However, in 2013, EMA first approved two biosimilar versions of Infliximab which is a monoclonal antibody (mAb) in nature. Recently, in January 2021, there were a total of 29 biosimilars products got approved in the US, and 58 products were approved in the EU (*Comparing U.S. and E.U. Biosimilar Regulations | RegDesk | Professional*, n.d.). Therefore, there were no significant differences were found between the approved biosimilars and biologics in the past 10 years. But an issue has been raised that whether a patient can switch to a newly discovered biosimilar of the biologics as the patient is already been exposed to the reference product. Finally, FDA and EMA do not distinguish between biosimilars and reference drugs and advise the prescriber to prescribe these drugs according to the necessity of the patient (O'Callaghan et al., 2019).

3.4 Market Share of Biologics and Biosimilars

Though biosimilar is still a new concept to the era of medicine, the market share of biologics and biosimilars is gradually increasing day by day. Therefore, biosimilars require to show highly similar data with their biologics in terms of pharmacokinetics, safety, efficacy, and

immunogenicity. Filgrastim, a drug intended for treating low neutrophil count was the first biosimilar authorized by USFDA in the year 2015 (Misra, 2012). After that, USFDA started to approve more and more biosimilars with the passage of time. For instance, in the year 2016, 3 biosimilars were approved by USFDA. Similarly, in the year 2017; 5 biosimilars, in the year 2018; 7 biosimilars, in the year 2019; 10 biosimilars were approved by USFDA (*What Are Biologics? Definitions and Potential Benefits | Bioanalysis Zone*, n.d.). There is different market segmentation of biosimilars depending on the nature of the diseases such as autoimmune diseases, cancers, blood disorders, ophthalmic diseases, female infertility, hypoglycemia, postmenopausal osteoporosis, myocardial infarction, chronic kidney diseases, etc. Among them, the market share of autoimmune diseases is 59.5 % which is the highest in the world (Kesik-Brodacka, 2018). In the same way, different hospitals and retailers are promoting these biosimilars, so the accessibility of these drugs is also improving (Zhou et al., 2021). The total market value of biosimilars in 2020 is USD 13.2 billion and is expected to be reached 83 billion USD in 2028 (*U.S. Biosimilars Market to Display a CAGR of 27.0% till 2028*, n.d.). In 2010, the market sales value of the top 12 biologics reached $100 billion worldwide. In contrast, in 2015, the annual sales of biologics become $20 billion. Therefore, the global market for biosimilars was 1.776 billion dollars in the year 2010 and increased almost 915 million dollars in the year 2011.

Table 03: Global market for biosimilars (ER et al., 2019)

Region/Year	2010	2011	2016
USA	$507.00	$1,097.00	$1,343.00
Europe	$946.00	$377.00	$625.00
APAC (Asia Pacific Region)	$605.00	$683.00	$1,113.00
Rest of the world	$308.00	$335.00	$522.00
Global	$1,766.00	$2,491.00	$3,603.00

However, the impact of COVID-19 had a very serious effect on the global biosimilars market. Therefore, the market projected 121.2% of lower growth in 2020 compared to 2017. It is expected that the market will grow at least 27.00% in 2028 once the pandemic is over. Moreover, the demand for biosimilars is increasing day by day due to the availability of the drugs and cost-effectiveness in comparison to their biologics (*US Biosimilars Market Size to Reach $22,996 Million By*, n.d.).

3.5 Different Biologics & Biosimilars are Available till 2021 February

Biosimilars can be approved centrally by EMA. It works as a backbone for the establishment of biosimilars. In 2005-2006 EMA approved different guidelines for the approval of biosimilars and many developed countries like Korea, Japan, Singapore, Canada and, Australia adopted the guidelines (O'Callaghan et al., 2019). In 2006, Omnitrope was the first biosimilar that got marketing approval from EMA. From 2006-2021, EMA approved a total of 77 biosimilars of different classes, they are 1. TNF inhibitor, 2. Insulin, 3. GCS factors, 4. Human growth hormone, 5. FSH, 6. Monoclonal antibodies, 7. Parathyroid hormone, and, 8. Erythropoiesis stimulating agent (Wolff-Holz et al., 2019). The list of biosimilars approved till February 202 are given below in Figure 01:

Biosimilar Proprietary Name	Drug Product	Owner	Status	Authorization
Abasaglar (previously Abasria)	Insulin Glargine	Eli Lilly Regional Operations GmbH	Authorized	9/9/2014
Abseamed	Epoetin Alfa	Medice Arzneimittel Pütter GmbH & Co. Kg	Authorized	8/28/2007
Accofil	Filgrastim	Accord Healthcare Ltd	Authorized	9/18/2014
Alpheon	Recombinant Human Interferon Alfa-2a	Biopartners GmbH	Refused	-
Amgevita	Adalimumab	Amgen Europe	Authorized	3/22/2017
Amsparity	adalimumab	Pfizer	Authorized	2/13/2020
Aybintio	bevacizumab	Samsung Bioepis Uk Limited (Sbuk)	Authorized	8/19/2020
Bemfola	Follitropin Alfa	Gedeon Richter Plc.	Authorized	3/27/2014
Benepali	Etanercept	Samsung Bioepis Uk Limited (Sbuk)	Authorized	1/14/2016
Binocrit	Epoetin Alfa	Sandoz GmbH	Authorized	8/28/2007
Biograstim	Filgrastim	Abz-Pharma GmbH	Withdrawn	9/15/2008
Blitzima	Rituximab	Celltrion	Authorized	7/13/2017
Cegfila (previously Pegfilgrastim Mundipharma)	pegfilgrastim	Mundipharma Biologics	Authorized	12/19/2019
Cyltezo	Adalimumab	Boehringer Ingelheim International GmbH	Authorized	11/10/2017
Epoetin Alfa Hexal	Epoetin Alfa	Hexal Ag	Authorized	8/28/2007
Equidacent	bevacizumab	Centus Biotherapeutics	Authorized	9/24/2020

Erelzi	Etanercept	Sandoz GmbH	Authorized	6/23/2017
Filgrastim Hexal	Filgrastim	Hexal Ag	Authorized	6/2/2009
Filgrastim ratiopharm	Filgrastim	Ratiopharm GmbH	Withdrawn	9/15/2008
Flixabi	Infliximab	Samsung Bioepis Uk Limited (SBUK)	Authorized	5/26/2016
Fulphila	pegfilgrastim	Mylan	Authorized	11/20/2018
Grastofil	Filgrastim	Apotex Europe BV	Authorized	10/18/2013
Grasustek	pegfilgrastim	Juta Pharma (USV)	Authorized	6/20/2019
Halimatoz	Adalimumab	Sandoz GmbH	Authorized	7/26/2018
Hefiya	Adalimumab	Sandoz GmbH	Authorized	7/26/2018
Herzuma	Trastuzumab	Celltrion Healthcare Hungary Kft.	Authorized	2/9/2018
Hyrimoz	Adalimumab	Sandoz GmbH	Authorized	7/26/2018
Hulio	adalimumab	Mylan/Fujifilm Kyowa Kirin Biologics	Authorized	10/16/2018
Idacio	adalimumab	Fresenius Kabi	Authorized	4/24/2019
Imraldi	Adalimumab	Samsung Bioepis UK Limited (SBUK)	Authorized	8/24/2017
Inflectra	Infliximab	Hospira Uk Limited	Authorized	9/10/2013
Inhixa	Enoxaparin Sodium	Techdow Europe Ab	Authorized	9/15/2016
Insulin aspart Sanofi	insulin aspart	Sanofi-Aventis	Authorized	6/25/2020
Insulin lispro Sanofi	insulin lispro	Sanofi-Aventis	Authorized	7/18/2017
Kanjinti	Trastuzumab	Amgen/Allergan	Authorized	5/16/2018
Kixelle	insulin aspart	Mylan	Authorized	CHMP positive opinion 10 Dec 2020
Livogiva	teriparatide	Theramex Ireland	Authorized	8/27/2020
Lusduna	Insulin Glargine	Merck Sharp & Dohme Limited	Authorized	4/1/2017
Movymia	Teriparatide	Stada Arzneimittel Ag	Authorized	1/11/2017
Mvasi	Bevacizumab	Amgen Europe B.V.	Authorized	1/15/2018
Nepexto	etanercept	Mylan	Authorized	5/25/2020
Nivestim	Filgrastim	Hospira Uk Ltd	Authorized	6/8/2010
Ogivri	trastuzumab	Biocon/Mylan	Authorized	12/12/2018
Omnitrope	Somatropin	Sandoz GmbH	Authorized	4/12/2006
Onbevzi	bevacizumab	Samsung Bioepis	Authorized	CHMP positive opinion 21 Nov 2020
Ontruzant	Trastuzumab	Samsung Bioepis Co., Ltd.	Authorized	11/17/2017
Ovaleap	Follitropin Alfa	Teva Pharma B.V.	Authorized	9/27/2013
Pelgraz	pegfilgrastim	Accord Healthcare	Authorized	10/20/2018
Pelmeg	pegfilgrastim	Cinfa Biotech/ Mundipharma	Authorized	11/20/2018
Qutavina	teriparatide	EuroGenerics Holdings	Authorized	8/27/2020
Ratiograstim	Filgrastim	Ratiopharm GmbH	Authorized	9/15/2008
Remsima	Infliximab	Celltrion Healthcare Hungary Kft.	Authorized	9/10/2013
Retacrit	Epoetin Zeta	Hospira Uk Limited	Authorized	12/18/2007
Ritemvia	Rituximab	Celltrion	Authorized	7/13/2017
Rituzena (previously Tuxella)	Rituximab	Celltrion	Authorized	7/13/2017
Rixathon	Rituximab	Sandoz GmbH	Authorized	6/15/2017
Riximyo	Rituximab	Sandoz GmbH	Authorized	6/15/2017
Ruxience	rituximab	Pfizer	Authorized	4/1/2020
Semglee	Insulin glargine	Mylan S.A.S.	Authorized	3/27/2018
Silapo	Epoetin Zeta	Stada Arzneimittel Ag	Authorized	12/18/2007
Solumary	Insulin Human	Marvel Lifesciences Ltd	Refused	-
Solymbic	Adalimumab	Amgen Europe	Authorized	3/22/2017
Yuflyma	adalimumab	Celltrion Healthcare	Authorized	CHMP positive opinion 10 Dec 2020
Terrosa	Teriparatide	Gedeon Richter Plc.	Authorized	1/4/2017

Figure 01: Different biosimilars approved by USFDA and EMA till February 2021 (Cohen et al., 2017; C. J et al., 2021; M et al., 2020)

3.6 Future Biosimilars

There are multiple widely prescribed biologics whose patent will expire soon by making way for biosimilars to enter the drug market. Table 04 consists of some biosimilars expected to lose patent protection if the clinical trials are successfully completed. These products may enter the market as biosimilars near future (AS et al., 2021).

Table 04: Biosimilars under investigation of regulatory bodies

Reference Product (Brand, Manufacturer)	Estimated Patent Expiration	Indication	Biosimilar	Manufacturer	Published Data
Adalimumab (Humira, AbbVie) (Coghlan et al., 2021b)	2022	RA, psoriatic arthritis, AS, UC, Crohn's Disease, psoriasis, HS, JIA	GP2017 PF-06410293 BCD-057	Sandoz Pfizer Biocad	Phase III clinical trial under-way, Phase I clinical trial under-way, Phase III clinical trial (2017)
Bevacizwnab (Avastin,Genentech) (I.-W. A & T, 2019)	2019	Colorectal, lung, and renal cancers	BCD-021 PF-06439535 ABP 215	Pfizer Biocad Amgen	Phase I clinical trial completed, Phase III clinical trial completed, Phase III clinical trial under-way
Cetuximab (Erbitux, Eli Lilly) (V et al., 2020)	Expired (2016)	Colorectal, head, and neck cancers	ABP 494	Amgen	Phase III clinical trial under-way
Darbepoetin alfa (Aranesp,Amgen) (Z. S et al., 2018)	2018	Anemia due to CKD or chemotherapy	BCD-066	Biocad	Phase III clinical trial under-way (2017)
Enoxaparin (Lovenox, Sanofi-Aventis)	Expired (2010)	DVT, VTE	BCD-080	Biocad	Phase III clinical trial

(Kaur et al., 2017a)					under-way (2016)
Epoetin alfa (Epogen,Amgen)(AB & A, 2016)	Expired (2015)	Anemia due to CKD or chemotherapy	HX575	Sandoz	Phase III clinical trial completed
Glatiramer acetate (Copaxone,leva)	Expired (2014)	Multiple sclerosis	BDC-063	Biocad	Phase III clinical trial under-way (2016)
Infliximab (Remicade, Janssen Biotech) (V et al., 2020)	September 2018	Autoimmune diseases including RA, psoriasis, UC, Crohn's disease	GP 1111 PF-06438179 ABP 710 BCD-055	Sandoz Pfizer Biocad Amgen	Phase III clinical trial under-way, Phase III clinical trial under-way, Phase III clinical trial, (2017) No data Available
Pegfilgrastim (Neulasta,Amgen) (W.-H. E et al., 2019)	Expired (Ocotber 2015)	Chemotherapy-induced neutropenia	LA-2006	Sandoz	File Accepted by FDA at the end of 2015
Rituximab (Rituxan,Genentech) (I.-W. A & T, 2019)	September 2016	Lymphoma	GP2013 BCD-020 PF-05280586 CT-P10 RTXM83 ABP 798	Sandoz Pfizer Biocad Celltrion mAbxience Amgen	Phase II & III clinical trial under-way, Phase I clinical trial under-way Phase III clinical trial under-way, Phase III clinical trial completed, Phase III clinical trial completed,

					No Date available
Trastuzumab (Herceptin,Genentech) (I.-W. A & T, 2019)	June 2019	Breast Cancer	BCD-022 PF-05280014 ABP 980 CT-P6	Amgen Pfizer Biocad Celltrion	Phase III clinical trial under-way, Phase I clinical trial complete, Successful, phase 1 clinical trial, Phase III clinical trial completed

Therefore, different biologics will be facing competition in the market once their patent expiry. According to "Affordable care act" the patent protection last for 12 years and in these years manufacturer can monopolize the sale of biologics from the day of license (Hung et al., 2017).

3.7 Preparations Available for Biologics

There are limited preparations available for biologics. Oral routes are not appropriate for the administration of biosimilars as they are protein molecules, rapidly digested and inactivated. Therefore, intravenous routes such as injection or infusion are suggested. Also, biological drugs can be manufactured as a powder for infusion, solution, or injection (JJ et al., 2020).

3.8 Target Diseases of Different Biosimilars

Biosimilars are considered as most advanced treatment options for several chronic diseases. For example, rheumatoid arthritis (RA), Cron's disease, Ulcerative colitis (UC), and other autoimmune diseases can be improved using different biosimilars and biologics (Dixit et al., 2010). Different biosimilars that can treat rare diseases such as:

3.8.1 Zarixo: Biosimilar of Neupogen

FDA gave license to the first biosimilar of Neupogen in March 2015 in the US under the brand name Zarixo (Filgrastim-sndz). Filgrastim is a recombinant GCS factor used to induce the production of granulocytes (white blood cells) after the (Granulocyte Colony-Stimulating factor) cancer therapy (W.-H. E et al., 2019). Filgrastim is similar to the reference drug Neupogen and no significant differences can be observed in terms of safety, efficacy, potency, and purity. FDA declared Zarixo as "Robust" upon the investigation of PK and PD studies of biosimilarity compared with Neupogen.

In July 2018, another biosimilar of Neupogen named Filgrastim-aafi got approved by FDA (*What Are Biosimilars? Top Facts You May Not Know*, n.d.).

3.8.2 Inflectra: Biosimilar of Remicade

FDA approved its second biosimilar infliximab-dyyb under the brand name Inflectra. It is a TNF-α inhibitor and a biosimilar of Remicade that had been approved as a biologic in 1998. Inflectra has several clinical indications such as Spine arthritis, Rheumatoid arthritis, Plaque psoriasis, Cron's disease, ulcerative colitis, etc. Renflexis is the second biosimilar of Remicade approved by the FDA in April 2017 (E. A et al., 2018). After that, 2 more biosimilars of Remicade got approved recently named Ixifi and Avsola.

3.8.3 Erelzi and Eticovo: Biosimilars of Enbrel

Erelzi was approved by USFDA in 2016 and it was the biosimilars of Etanercept-szzs. Erelzi is a TNF-α inhibitor and the first approved biosimilar for Etanercept. The clinical indication of Erelzi is ankylosing spondylitis, rheumatoid arthritis, plaque psoriasis, polyarticular juvenile idiopathic arthritis, and psoriatic arthritis. Eticovo was the second biosimilars of Enbrel approved by the FDA in 2019 (*Biosimilar and Interchangeable Products | FDA*, n.d.-b). These biosimilars are marketed as subcutaneous injections and precautions are mentioned in the labels

of the products. Precaution includes drugs that are highly immunosuppressive and increase the risk of infection and malignancies. At least 5% of patients commonly suffer from the side effects like infections and reactions at the site of injection (E. A et al., 2018).

3.8.4 Amjevita, Cyltezo, Hyrimoz: Biosimilars of Humira

Adalimumab's biosimilar Amjevita was the first biosimilar approved by FDA in September 2016. It has several indications. Amjevita is effective against treating different inflammatory diseases including ulcerative colitis, rheumatoid arthritis, Cron's disease, and plaque psoriasis (Markus et al., 2019a). Although, FDA did not approve Amjevita as a substitution for Humira. Therefore, doctors need to be extra cautious during prescribing these medications. Amjevita is dispensed via a prefilled syringe or auto-injector (Chung et al., 2012). The second biosimilar of Humira got licensed in August 2017 under the name of "Cyltezo". It is also used for the same indication as Amjevita, such as ulcerative colitis, rheumatoid arthritis, Cron's disease, and plaque psoriasis. FDA suggested this similar should not be interchanged with Humira at the primary level of the treatment. Cyltezo is dispensed via a pre-fill syringe and auto-injector. The drug can be used alone or in conjugation with methotrexate or other anti-rheumatoid agents. Additionally, the third biosimilar of Humira was approved by FDA in October 2018 (Coghlan et al., 2021b). The latest biosimilars of Humira are Haldima (Adalimumab-bwwd), Abrilada (Adalimumab-atzb) and, Huilo (Adalimumab-fkjp)(Lu et al., 2021b).

3.8.5 Mvasi: Biosimilars of Bevacizumab

USFDA first approved the only biosimilar for cancer Bevacizumab-awwb under the brand name Mvasi. Mvasi is the biosimilar of Avastin (brand name) that got licensed in September 2017. Next, Zirabev (Bevacizumab-bvzr) was approved by FDA as a second biosimilar of Avastin (I.-W. A & T, 2019). Both of the biosimilars are intended to treat various cancers such as cervical cancers, metastatic colorectal cancers, brain cancers, non-squamous non-small cell lung cancer (NSCLC), and metastatic renal cell carcinoma. Scientists portray there are no significant dissimilarities between Mvasi and Avastin (ER et al., 2019). Moreover, primary cancers and fallopian tube cancers cannot be treated with Mvasi and Zirabev and the instructions are provided on top of the label of the drugs. Although FDA declares these biosimilars cannot be interchanged with bevacizumab (I.-W. A & T, 2019).

3.8.6 Ogirvi, Herzuma, Ontruzant, Trazimera, Kanjinti: Biosimilars of Trastuzumab (Herceptin)

FDA approved a total of 5 biosimilars for the biologic Trastuzumab (I.-W. A & T, 2019). These biosimilars are shown in the table below:

Brand Name	Generic Name	Reference Product	Manufacturing Company	Year of Approval by FDA
Ogivri	Trastuzumab-dkst	Herceptin (Trastuzumab)	Mylor GmBH	2007 (December)
Herzuma	Trastuzumab-pkrb	Herceptin (Trastuzumab)	Celltrion and Teva	2018 (December)
Ortruzant	Trastuzumab-dttb	Herceptin (Trastuzumab)	Sum Sung Bioepis	2019 (January)
Trazimera	Trastuzumab-qyyp	Herceptin (Trastuzumab)	Pfizer	2019 (March)
Kanjinti	Trastuzumab-anns	Herceptin (Trastuzumab)	Amgen	2019 (June)

Figure 02: Licensed biosimilars of Trastuzumab (Uifălean et al., 2018)

Herceptin biosimilars are intended for treating different cancers. All of the approved biosimilars of Herceptin are intended for the same use except Herzuma. This is exclusively for the treatment of HER2+ breast cancer and stomach cancer of malignancy stage (Uifălean et al., 2018). However, FDA approved the biosimilar Herzuma only for treating breast cancer.

USFDA first give a license to Ogivri (Trastuzumab-dkst) for the treatment of breast cancer and stomach cancer. The further biosimilars of Herceptin were approved by the FDA intended for treating every type of cancer.

Active Substance	Reference Trade Name/Manufacturer	Biosimilar Trade Name/Manufacturer	Authorization Date
		EMA	
epoetin alpha	Eprex/Erypo/Janssen-Cilag	Abseamed/Medice Arzneimittel Pütter GmbH & Co. KG	Aug-07
	Pharma GmbH	Binocrit/Sandoz GmbH	Aug-07
		Epoetin Alfa Hexal/Hexal AG	Aug-07
epoetin zeta	Eprex/Erypo/Janssen-Cilag	Retacrit/Hospira UK Limited	Dec-07
	Pharma GmbH	Silapo/Stada Arzneimittel AG	Dec-07
filgrastim	Neupogen/Amgen Europe B.V.	Tavagrastim/Teva GmbH	Sep-08
		Ratiograstim/Ratiopharm GmbH	Sep-08
		Zarzio/Sandoz GmbH	Feb-09
		Filgrastim Hexal/Hexal AG	Feb-09
		Nivestim/Hospira UK Ltd.	Jun-10
		Grastofil/Apotex Europe BV	Oct-13
		Accofil/Accord Healthcare Ltd.	Sep-14
bevacizumab	Avastin/Roche Registration GmbH	Mvasi/Amgen Europe B.V	Jan-18
trastuzumab	Herceptin/Roche Registration GmbH	Ontruzant/Samsung Bioepis UK Limited (SBUK)	Nov-17
		Herzuma/Celltrion Healthcare Hungary Kft.	Feb-18
		Kanjinti/Amgen Europe B. V	May-18
		Trazimera/Pfizer Europe MA EEIG	Jul-18
		FDA	
epoetin alpha-epbx	Epogen/Procrit/Amgen Inc	Retacrit/Hospira INC	May-18
Filgrastim-sndz	Neupogen/Amgen Inc.	Zarxio/Sandoz GmbH	Mar-15
		Nivestym (filgrastim-aafi)/Pfizer	Jul-18
Pegfilgrastim-jmdb	Neulasta/Amgen Inc	Fulphila/Mylan GmbH	Jun-18
Trastuzumab-dkst	Herceptin/Genentech Inc	Ogivri/Mylan GmbH	Dec-17

Figure 03: Biosimilars approved by EMA and USFDA exclusively to treat breast cancer (Uifălean et al., 2018)

Moreover, Herceptin biosimilars can be interchanged with reference Herceptin although the biosimilars are HER-2 receptor antagonists like Herceptin (Hercogová et al., 2020). It requires the permission of the doctor if any patient wants to switch from Herceptin-to-Herceptin biosimilars. Finally, from the pharmacy patients cannot switch the product without the prescription.

3.8.7 Reneflexis and Ixifi: Second and Third Biosimilars of Remicade

The second biosimilar of Infliximab got approved by FDA in April 2017. Reneflexis is also a tumor necrosis inhibitor like its parent drug. Infliximab-ada is sold as a biosimilar of Remicade under the brand name Reneflexis. The clinical indications for Reneflexis are ulcerative colitis, rheumatoid arthritis, Cron's disease, psoriatic arthritis, plaque arthritis, and ankylosing

spondylitis (Frazier-Mironer et al., 2014). FDA found only minor differences in the inactive part of the structure of Reneflexis but the safety, efficacy data is similar to Remicade.

The third biosimilar of Infliximab got approved by FDA in December 2017. Ixifi is a human-murine monoclonal antibody that deactivates the tumor necrosis factor. For 8 clinical indications, FDA approved Infliximab-qbtx under the brand name Ixifi including RA, UC and, Crohn's disease (Velayudhan et al., 2016). In phase 3 clinical trials the dose of Ixifi versus Remicade was administered intravenously in the volunteers with mild to severe RA to observe the safety, efficacy and, immunogenicity. The study demonstrates the biosimilars were able to get ACR 20 (American College of Rheumatology) when given in conjugation with methotrexate at week 40. The study was supported by FDA and got approved. But, Ixifi cannot be interchanged with Remicade without any prescription (O. J et al., 2019).

3.8.8 Retacrit: Biosimilar of Epogen and Procrit

The first biosimilar of Epogen got approved by FDA in May 2018. Epoetin- α-epox was the biosimilar of Epoetin α and Procrit (AB & A, 2016). It is sold in the market under the brand name Retacrit. The biosimilar got license exclusively to treat anemia caused by chemotherapy, anti-HIV drugs and, chronic kidney disease. Also, for patients who have gone through non-vascular, noncardiac, and elective surgery; Retacrit can be prescribed to them by chacking other clinical reports. Retacrit is an ESA (Erythropoiesis Stimulating Agent) and very similar to its biologic Epogen snd Procrit (Markus et al., 2019b). FDA did not find any significant clinical dissimilarities among the biosimilars and biologics in terms of purity, potency, safety, and efficacy.

3.8.9 Fulphila: Biosimilar of Neulasta

FDA approved 4 biosimilars for the biologic Neulasta (Pegfilgrastim) as shown in the table:

Table 05: Approved biosimilars of Neulasta by FDA (ER et al., 2019)

Brand Name	Generic Name	Biologic	Manufacturing Company	Year of Approval by FDA
Fulphila	(Pegfilgrastin-jmbd)	(Neulasta) Pegfilgrastin	Bicon	2018 (June)
Udenya	(Pegfilgrastin-cbqv)	(Neulasta) Pegfilgrastin	Caherus Bioscience	2018 (November)

Ziextenzo	(Pegfilgrastin-bmez)	(Neulasta) Pegfilgrastin	Sandoz	2019 (November)
Nyvepria	(Pegfilgrastin-apgf)	(Neulasta) Pegfilgrastin	Pfizer	2020 (June)

All of the biosimilars of Neulasta are PEGylated growth colony-stimulating factors. It means they reduce different infections and signs of infections caused by chemotherapy (*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product | FDA*, n.d.). During chemotherapy, the immune system becomes suppressed and the chance of occurring infection is high as the immune of WBC becomes less due to the cytotoxic nature of the chemotherapeutic agents. Therefore, these biosimilars reduce the risk of infection caused by cancer treatments.

3.8.10 Tuxima: Biosimilar of Rituxan

For specific diseases like NHL (Non-Hodgkin's Lymphoma) and, T cell lymphoma; FDA approved Rituximab-abbs under the brand name of Truxima as a biosimilar in November 2018 (O'Callaghan et al., 2019). This is the first biosimilar of Rituxan approved by any regulatory authority. It is also considered as the first biosimilar that got licensed for NHL. It is widely used in conjugation with chemotherapeutic agents to treat different grades of cancers (Jacobs et al., 2016). The second biosimilars of Rituxan got approved in July 2019 named Ruxience (Rituximab-pvvr). This biosimilar also had the same type of clinical indication as Truxima.

3.9 Drug-Drug Interactions for Biologics

Biologics can interfere and alter the mechanism of action of several drugs causing drug-drug interaction. For example, Adalimumab (Humira) affects the immune system, thus it can interfere with the efficacy of vaccines (Rahalkar et al., 2021). In addition, prescribers do not suggest life attenuated vaccines while taking biological drugs. Prescribers advised them beforehand to take all immunization prior to biological drugs. As biosimilars and biologics suppress the immune system, they can cause severe infection if taken with other immune-suppressant drugs.

3.10 Adverse Effects Associated with Biologics and Biosimilars

Biologics and biosimilar drugs can cause adverse effects on the body. The severity of adverse effects depends on the method of administration and the type of drug (R et al., 2019). Common adverse effects that can be visible after the introduction of the drugs are:

i. A large number of biologics and biosimilars can cause hypersensitivity reactions

ii. Biologics that are intended for treating RA and Psoriasis can suppress the immune system and increase the chance of having infections.

iii. As most of the biologics and biosimilars are administered via intravenous routes, injection site reactions are most likely to occur (GR & U, 2015).

iv. As some of the drugs are given by injection, they can induce infusion reactions

Moreover, drug-specific side effects are weakness, Chills, diarrhea, rash, vomiting, itching, and, constipation (*Biologics: Definition, Side Effects, Uses & Drug List*, n.d.-b). These drug reactions vary from drug to drug and all biosimilars do not necessarily show each of these side effects. Serious and rare side effects of biosimilars include hepatitis, cancer, hypothyroidism, stomatitis, infection, antibody generation, thyroid, anaphylaxis, blood clots, etc (M et al., 2020).

Chapter 4

4.1 Different Regulatory Aspects of Biosimilars

Because of the extremely high price of the biologics that makes it inaccessible to most of the patients, the concepts of the biosimilars had evolved. In addition, the initiation of biosimilars enables a variety of treatment options, cost-effectiveness, and better accessibility (O'Callaghan et al., 2019). When the regulatory exclusivity of the biologics is expired, different manufacturers can pursue FDA and other regulatory authorities to seek permission to make another highly similar version of the biologic. For the authorization process by EMA, biosimilars need to be exactly similar in quality and other requirements in terms of safety, efficacy, and immunogenicity. In 2004, the first biosimilar approval application had come to the EU parliament, where 14 biosimilars got approved by EMEA by the year 2011. Table 06 explains the evolution of different guidelines in the past decades. In between these years, different countries like Argentina, South Africa, Venezuela, Egypt, etc modified their guidelines from the EU submitted the draft version. On the contrary, countries like Japan, Korea, Canada, Australia, etc. completely adopted the guidelines of the EU and implement them in the following years.

Table 06: The summary of guidelines (Rahalkar et al., 2021)

				Taiwan						
				Malaysia	WHO	Saudi Arabia				
				Turkey	Japan	Brazil	Singapore	Mexico		
	EU			Australia	Korea	Canada	Peru	India		Iran
2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
				Argentina		S. Africa	Chile	Venezuela	Peru	Jordan
								Egypt	Colombia	
								USA		
								Italy		
								PRC		

	Final Guideline Implementation
	Draft version/Concept Paper

For example, EMA sets different criteria for approving biosimilars of different products such as somatropin, epoetins and, granulocyte colony-stimulating factor (G-CSF). After that,

Australia acquires EMA guidelines completely, whereas Singapore and Japan modified their guidelines and adopted different guidelines in 2009 by following Canadian guidelines (ER et al., 2019). WHO advised the guideline of EMA to other countries to follow. Similarly, FDA provides 2 different guidelines for the approval of biosimilars, they are the biosimilar approach and the stand-alone approach. Though these regulations are still under maintenance and vary on different biosimilars. FDA approved Omnitrope produced by Sandoz and the manufacturing pathways cannot be copied for the production of other biosimilars (Jha et al., 2013).

4.1.1 WHO Guidelines

In 2009, WHO set several guidelines for RBF (Reference Biotherapeutic Product) based on safety, quality, and efficacy. Therefore, the data on these parameters must be country-specific. In terms of quality, every type of difference should be noted and compared with the reference product (*New WHO Advice on Biosimilar Medicines Aims to Increase Access to Quality Treatment*, n.d.). As clinical data is very limited compared to biologics, pharmacovigilance data at the post marketed phase must be recorded and portrayed along with the clinical data. However, the comparison of the biosimilar with the particular biologics needs to be investigated in terms of bioavailability, absorption, and elimination. Safety and immunogenicity data also need to demonstrate and investigate prior to approval.

4.1.2 EMA Guidelines

EMA has first adopted the concept of biosimilar in 2006 and set a legal and regulatory pathway for the approval of biosimilars which is completely different from the manufacturer's one(CHMP, 2014). EMA was the first among the regulatory agencies to develop quality, non-clinical and clinical guidelines for biosimilars that enclose the manufacturing process, quality, safety, consistency, and efficacy contemplations. After that, EMA set product-specific guidelines for the biosimilars in a detailed manner (O. J et al., 2019). Later on, developed countries like Korea, Japan, Singapore, and South Africa adopted EMA guidelines.

4.1.3 USFDA Regulations

Different analytical studies need to demonstrate for biosimilars which will prove the product is highly similar to the manufacturer's one and there can be slight differences in the inactive components in the structure of the biosimilars (*Biosimilar and Interchangeable Products | FDA*, n.d.-b). Toxicity studies on animal and clinical studies including pharmacokinetics, pharmacodynamics, and immunogenicity studies are performed so that the data can portray the biosimilar is safe, effective, and potent. In the same way, PK and PD studies are also performed in humans in order to show there were no clinical differences between the biologics and biosimilar. PK and PD data is considered the most sensitive study to ensure safety and efficacy. A demonstration of biosimilarity in humans also provides additional data for safety and efficacy. Generally, for approved biosimilars, clinical data is expected and pharmacodynamics data are desirable (Rahalkar et al., 2021). Till now FDA approved more than 10 TNF α biologics for the treatment of psoriasis and chronic rheumatoid arthritis.

4.1.4 The Purple Book

The purple book is an electronic database that contains a list of authorized biological products and biosimilars approved by the FDA. It is considered to be a resource for healthcare professionals for interchanging a reference biologic with the biosimilars. However, as biosimilar are prescription drugs; they cannot be interchanged automatically by the pharmacist (Fda & Cder, n.d.). Only healthcare professionals can substitute a biologic with a biosimilar depending on the nature of the disease. The purple book consists of every single biologic with its corresponding biosimilars and provides information about the conditions when these drugs can be interchangeable (Daller, 2016). For the interchangeability with the originator's drug, biosimilars should not have any clinically meaningful differences in terms of structure, safety, efficacy, and immunogenicity. Although, the routes of administration, delivery instruments, validation and formulation, and indications of biosimilars may be varied from the original drug.

4.2 Chemistry, Manufacturing, and Controls (CMC) of Biologics

To get approval from regulatory agencies like FDA, CMC is a fundamental part of pharmaceutical products like biologics. This process continues all over the product lifecycle, starting from the lead selection stage to post-marketing surveillance and so on (Y et al., 2018).

Basically, CMC ensures biologics are safe effective, and potent for the patients. CMC requires BMR (Batch Manufacturing Record) of biologics during production. This record mainly provides two pivotal pieces of information about biologics, they are:

4.2.1 In-Process Controls

In-process control requires a description of the methods used during the manufacturing process such as harvesting, fermentation, and downstream processing In addition, data of CCP (Critical Control Points) are provided so that the criteria for acceptance or rejection can be understood. Suitable analytical methods were followed for the downstream processing. If there are any changes required for commercial production in the cell line during the fermentation process, revalidation of a cell line is required and further data is anticipated (B. A, 2006).

4.2.2 Process Validation

During the harvesting and cell line growth process, the documentation and validation of these processes are mandatory and the data needs to be submitted (Chung et al., 2012). Also, documentation and validation are required for the purification process and this information is included with manufacturing data. If the manufacturer of the biologic wants to follow any specific guidelines for new applications such as USP (United States Pharmacopeia), BP (British Pharmacopeia), or WHO during the process, they need to submit the proof against their claim along with an analysis certificate (JJ et al., 2020). If the manufacturers followed any in-house standard, the details of the standard such as the source of raw materials, specification, characterization, testing protocols and, results are submitted.

These data serve as the proof of the products for ensuring quality, identity, stability, purity, strength, and potency of the biologics. In the meantime, information about the consistency of every lot during the manufacturing process is also noted to provide in the application (B. K & R, 2012). The manufacturer needs to provide the data about primary and secondary packaging such as container closure system, compatibility of the closing system with the active drug, impurity data, etc. Furthermore, data related to the profile tests of the supply chain, toxicity, and compatibility of the biologic with other substances are documented and presented along with the application (B. S et al., 2017). All of the aforementioned data are included in the DMF (Drug Master File). After the manufacturing of the biologic, crucial information like

description about IPCs (In-Process Control) of product sterilization, aseptic and packaging procedure is described in a flow diagram indicating each CCP step (AL-Sabbagh et al., 2016).

4.3 Regulations for Biosimilar Development

Biosimilar development is the process to demonstrate biosimilarity between the manufacture's drug and the proposed biosimilar. Biosimilars are extensively similar to their biologic but it has some structural differences in the active part from the original molecule. However, for developing a biosimilar manufacturers needs to submit an application to a regulatory authority containing PK and PD profile, characterization, comparative clinical test results to avoid any uncertainty (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.). If the manufacturer wants to claim the biosimilar is very similar to its biologic, they must show the animal toxicity study data, data that proves the similarity between biologics and biosimilars, and at least one more study data that indicates the safety, efficacy, and purity of the product as shown in Figure 01:

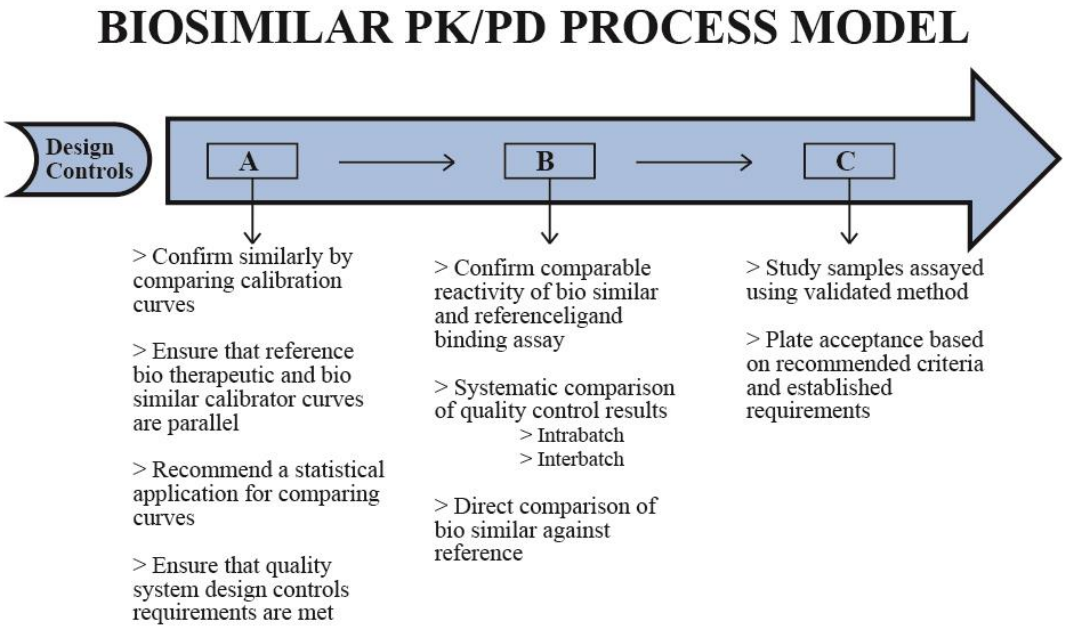

Figure 04: Biosimilar PK/PD process model (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.)

The manufacturer must test the biosimilars for proving at least one of the clinical uses characterized in the labeling of the approved product. The manufacturer is required to provide data of PDs and PKs study in health personnel and clinical tests that analyze and compare numerous safety, efficacy, and immunogenicity with the licensed products described in Figure 02 as below (Calvo & Zuñiga, 2012):

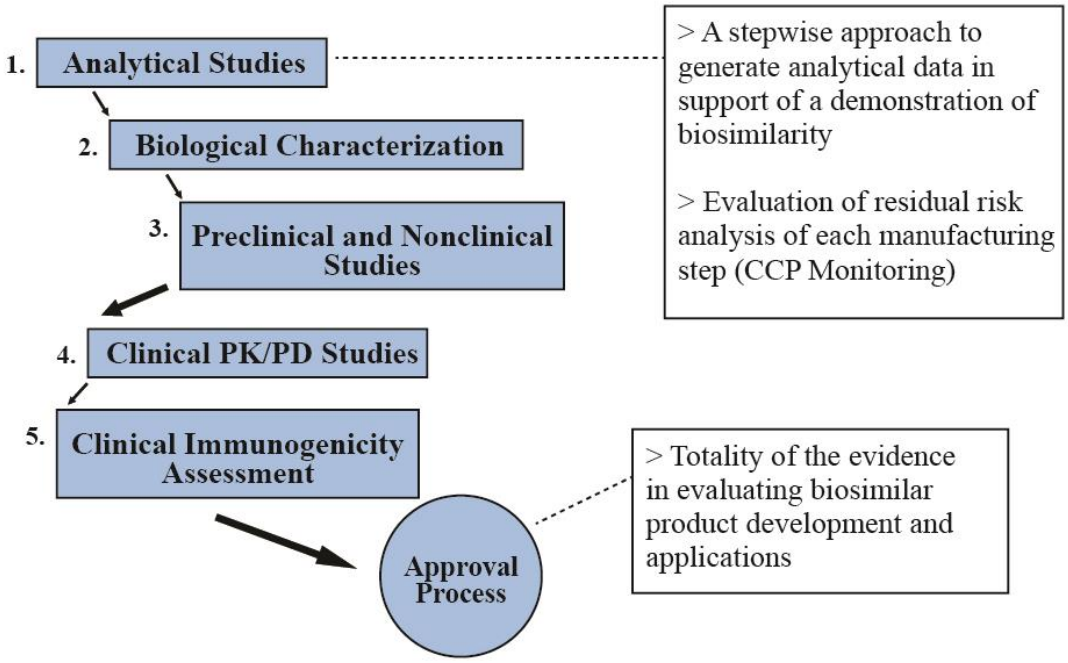

Figure 05: Stepwise evidence of Biosimilar Development (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.)

Moreover, based on the totality of evidence (Figure 03) biosimilars are assessed in terms of characterization, analytical comparison, PKs and PDS study, preclinical and clinical study data (de Mora, 2019). Further, DMF was submitted to FDA by the sponsor via an application as shown in Table 07:

Table 07: Essential requirements for approval of biosimilars (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.)

	Regulatory Requirements	**Applicant's Biosimilar Data Requirements**
Regulatory Demonstration of Similarity	> Analytical Studies > Nonclinical Studies > Clinical Studies	> Physicochemical & functional analytical data demonstrating that biosimilar product is highly similar to US-licensed product. > Animal studies (comparison and confirmation showing the pharmacologic and toxicological profiles of candidate biosimilar & reference products) > Clinical studies to evaluate PK, PD, and safety studies
Clinical Demonstration of Similarity Based on Reference Biologic Studies	> Mechanism of action (Receptor binding assays) > Route of administration (Dosage form and Strength in comparison to US-licensed reference product)	> Selective binding to the G-CSF receptor and showing similarity across all indications for use described in the labeling > Candidate biosimilar product dosage form and strength as US-licensed reference product

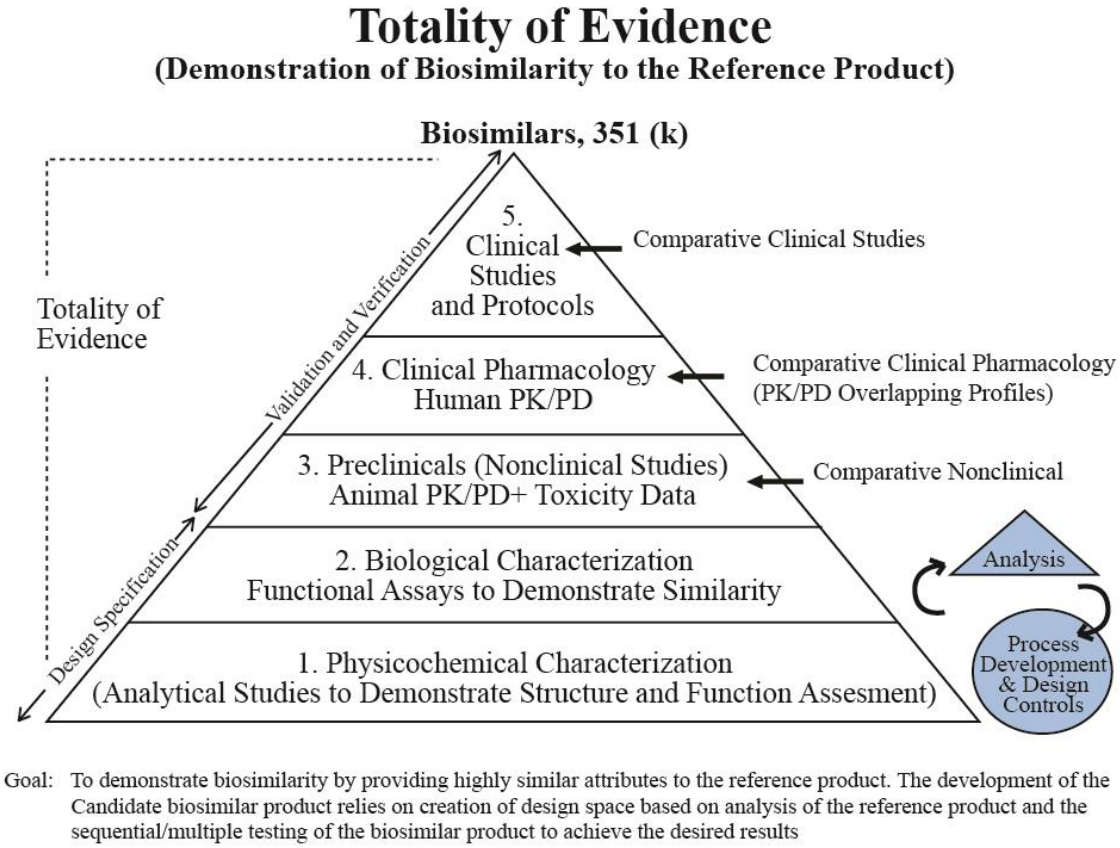

Figure 06: Evidence presenting the similarity between biologic and biosimilar (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.)

4.4 Approval Process for Biosimilar

The biosimilars development process needs five to nine years and the approval process requires safety and efficacy data to demonstrate there are not any significant dissimilarities between biosimilars and the reference product (B. S et al., 2017). According to FDA, for getting approval from regulatory authorities, a Biologics License Application (BLA) form needs to be filled that acts as a request for the introduction of a biologic into the market (Dos Reis et al., 2016). The BLA consists of different data for the evaluation of product effectiveness, safety, efficacy, and potency. (Z. L & B, 2010). The development and approval process of biologics is also similar to the development of small molecules.

In the biosimilar approval process, at first analytical studies like in-vitro studies are performed. In this study, physicochemical properties, purity, stability, structural and functional

assessments were performed. After that, preclinical studies that include in-vitro studies were carried out. The in-vitro study includes the assessment of pharmacokinetics, pharmacodynamics, and toxicology. Next, clinical pharmacology studies are executed in which the pk equivalence was measured (Kaur et al., 2017a). Finally, clinical studies that include safety, efficacy, and immunogenicity comparison were performed. For example: in this review, the result of phase 3 studies was to demonstrate the similarity between ABP-501 and Humira in moderate to severe RA and PsO(Markus et al., 2019a). Though in this process sufficient data are provided as evidence, additional data are required to support the evidence. The supporting data can be achieved from additional manufacturing data, and non-clinical data, in-process controls and put together in an IND (investigational New Application) form("FDA Promotes Efficient Biosimilar Approval," 2018).

On the contrary, in the conventional approval pathway, the process is complete upside down (Figure 04). In the pathway, firstly clinical studies were performed and then preclinical studies, clinical pharmacology, and analytical studies were executed respectively (F, 2015).

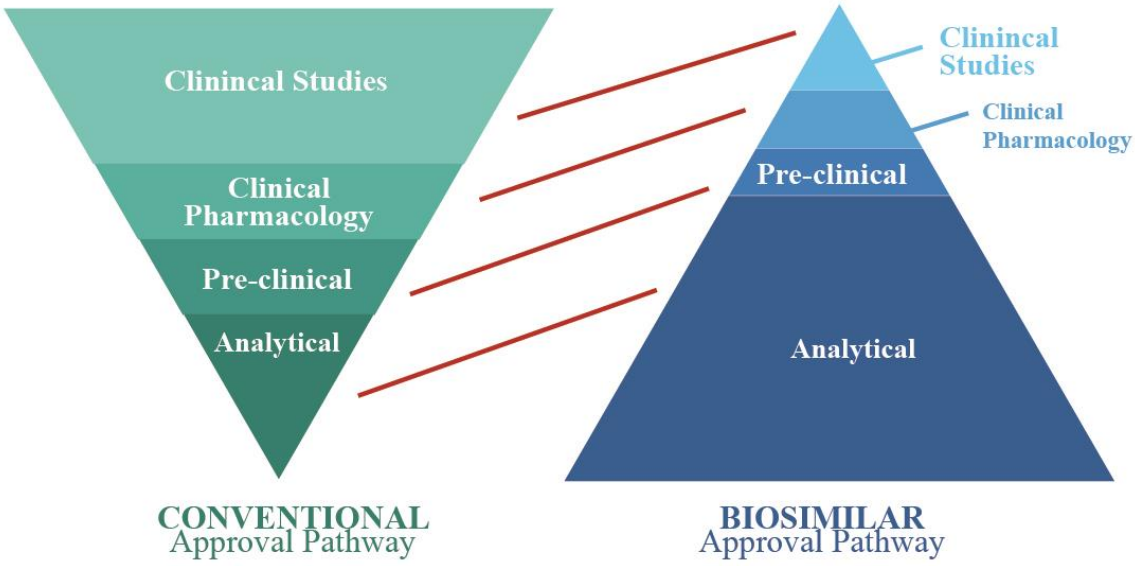

Figure 07: Approval pathway for a biosimilar (Kaur et al., 2017a)

The studies that need to be performed before approval are:

1. Qbd (Quality by Design) approach for biosimilar application and development.
2. Control of study design, verification, and validation of different studies.
3. Statistical concern for exhibiting analytical similarity.

4. Clinical data of the proposed drug includes clinical study design, assessment of immunogenicity, extrapolations, and interchangeability.
5. Labeling guidance of biosimilar proposed by FDA (S.-R. L, 2018).

4.5 Harmonization Process of Biosimilar Development

The harmonization process of biosimilar development leads to a reduction in the workload of regulators through international collaboration and by the reduction in repeated clinical trials to exhibit biosimilarity (International Conference on Harmonisation, 1994). IGBA (International Generic and Biosimilar Medicines Association) states it is very important to harmonize the regulatory issues for biosimilars. IGBA became an assembly member of ICH (International Conference on Harmonization of Technical documents) in 2016 and by 2018 it becomes a Management Committee Member of ICH (Dixit et al., 2010). Furthermore, for getting ICH approval, biosimilars must fulfill FDA's cGMP (current Good Manufacturing Practice)/QbD (Quality by Design) guidelines (International Conference on Harmonisation, 1994) (Markus et al., 2019a). ICH 2009 describe QbD guideline as a systematic approach for the development of biosimilar that asses the quality risk management (Kim et al., 2020). The guidelines ensure the quality of the biosimilars from production to the post-market surveillance stage. ICH Q8 and Q10 inspect risk analysis and monitoring of the finished product(Hung et al., 2017). In 2009, the US adopted the guidelines of Q9& Q10. Therefore, ICH guidelines Q10 enhances the link between drug manufacturing and drug development throughout the product life-cycle (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, n.d.).

Chapter 5

5.1 Pharmacokinetics (PK) of ABP-501 with Adalimumab

ABP-501 was the first biosimilar of adalimumab that is a monoclonal antibody for tumor necrosis factor α inhibitor. The indications are the same as adalimumab. In this review, 2 sources of reference adalimumab were used, United States: Amjevitam (Adalimumab-atto) and European Union: Amgevita (Adalimumab) (Markus et al., 2019a). Phase-1 pharmacokinetic (PK) equivalence studies in healthy subjects and 2 comparative phase-3 studies in the sensitive patient population having RA and PsO were performed(Markus et al., 2019a). The manufacturers claimed ABP-501 is highly similar to adalimumab in terms of pharmacokinetics, structure, and function. After those different analytical assessments were performed and it had been proved that ABP-501 was functionally and, structurally was similar to adalimumab RP. Pre-clinical studies of ABP-501 demonstrated the similarity of the mechanism of action and toxicity (Markus et al., 2019b).

To confirm the similarity between adalimumab RP and ABP-501; a phase 1, single-dose, single-blind parallel-group study was designed. To determine the PK equivalency, healthy volunteers were administered 40 mg of the subcutaneous (SC) dose of ABP-501 (Markus et al., 2019a). Healthy volunteers were chosen in this stage to provide the most homogenous population to identify any significant differences between adalimumab RP and the reference product (Jacobs et al., 2016). The adalimumab reference product was both collected from the US and Europe. The primary endpoint of the study was shown below in a serum concentration vs time graph (Figure 05) from 0 extrapolated to infinity (AUC_{inf}).

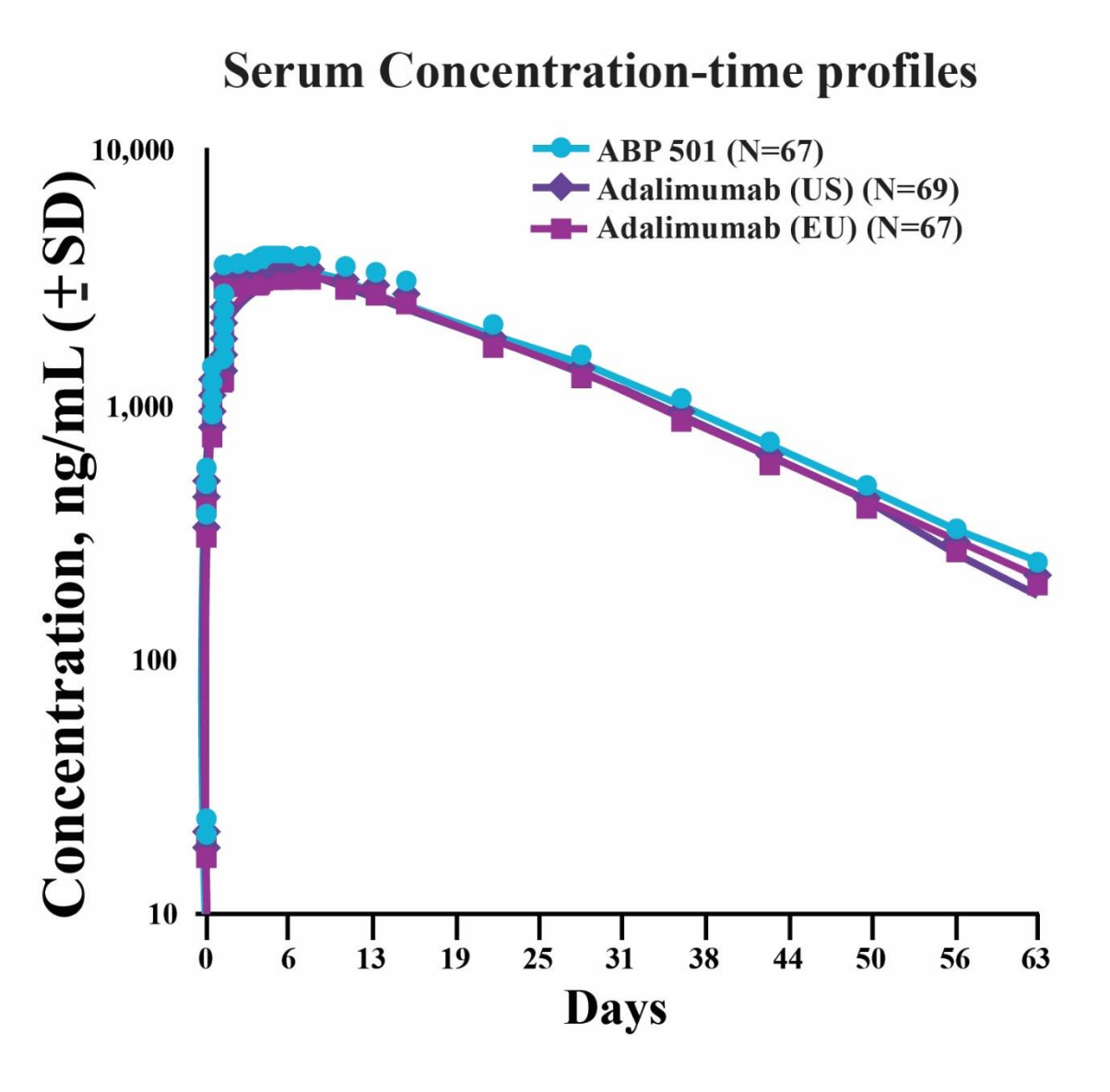

Figure 08: Phase-01 pharmacokinetics study of ABP-501(Markus et al., 2019a)

In the study of safety and PK analysis, a total of 203 male and female subjects were involved. The study demonstrated Geometric Mean Ratios (GMRs) for ABP-501 with adalimumab RP (US) were very similar. In the same way, GMRS of ABP-501 with adalimumab RP (EU) was also very homogenous. The 90% of Confidence Interval (CI) GMRs ratio was found both for ABP 501 with adalimumab (US) and ABP-501 with adalimumab (EU) (Kaur et al., 2017b). The PK equivalent criteria range is 0.80-1.25 which means the study was successful. Different Treatment-emergent-adverse-events (TEAEs) were mild to moderate between the volunteer groups. The most common TEAEs were nausea, vomiting, headache, oropharyngeal pain, nasopharyngitis, and sinus conjunction (Zhou et al., 2021). Reduction of Anti-Drug-Antibodies (ADA) was similar to the control group in terms of immunogenicity. Moreover, the

abovementioned PK model was similar for ABP-501 and adalimumab RP, so the overall results.

Pk profile was similar between ABP-501 and adalimumab RP in both healthy and patients having RA and PsO. The phase-3 result demonstrated the clinical similarity between ABP-501 and the reference product in terms of safety, efficacy, and immunogenicity (Liu et al., 2016). Therefore, the phase-3 study containing rheumatoid arthritis patients also demonstrated the similarity between adalimumab RP and ABP-501. In addition, the extension of the study for 72 weeks also continued to show the effects of biosimilar ABP-501 where no new immunogenicity or safety was observed (Markus Helen McBride Monica Ramchandani Vincent Chow Jennifer Liu Dan Mytych Gary Fanjiang & Markus Á J McBride Á M Ramchandani Á V Chow Á J Liu Á D Mytych Á G Fanjiang, 2019).

Chapter 6

6.1 Safety and Efficacy of ABP-501 with Adalimumab

6.1.1 Phase 3 safety and efficacy study in moderate to severe PsO:

A total of 350 patients were randomized for the phase 3 safety and efficacy study. This study was divided into 2 parts. The primary efficacy study was conducted from the day of the study to the 16th week (Z. S et al., 2018). But the overall study was conducted for 52 weeks. This study was a randomized, active-controlled, and double-blind study. Half of the population received adalimumab RP and half of the population received ABP-501 including a 1-week screening period. For the first 16 weeks, volunteers were administered 40 mg of Subcutaneous (SC) dose for 16 weeks (Cingolani et al., 123 C.E.). The patient who improved 50% with PASI 50 (Psoriasis Area and Severity Index) at week 16 were continued to further study for 52 weeks. A total of 152 patients were selected for week 52 studies (AL-Sabbagh et al., 2016). In addition, the patients who were randomized ABP-501 at the first dose were continued with ABP-501. However, the patients who had gotten randomized either ABP-501 or adalimumab RP were switched to ABP-501. Every 2 weeks, all patients received treatment until week 48. Here, a safety follow-up period for 4 weeks was maintained. Therefore at week 50, the final efficacy assessments were performed (Hung et al., 2017). The primary and overall efficacy results are shown in the graph (Figure 06) below:

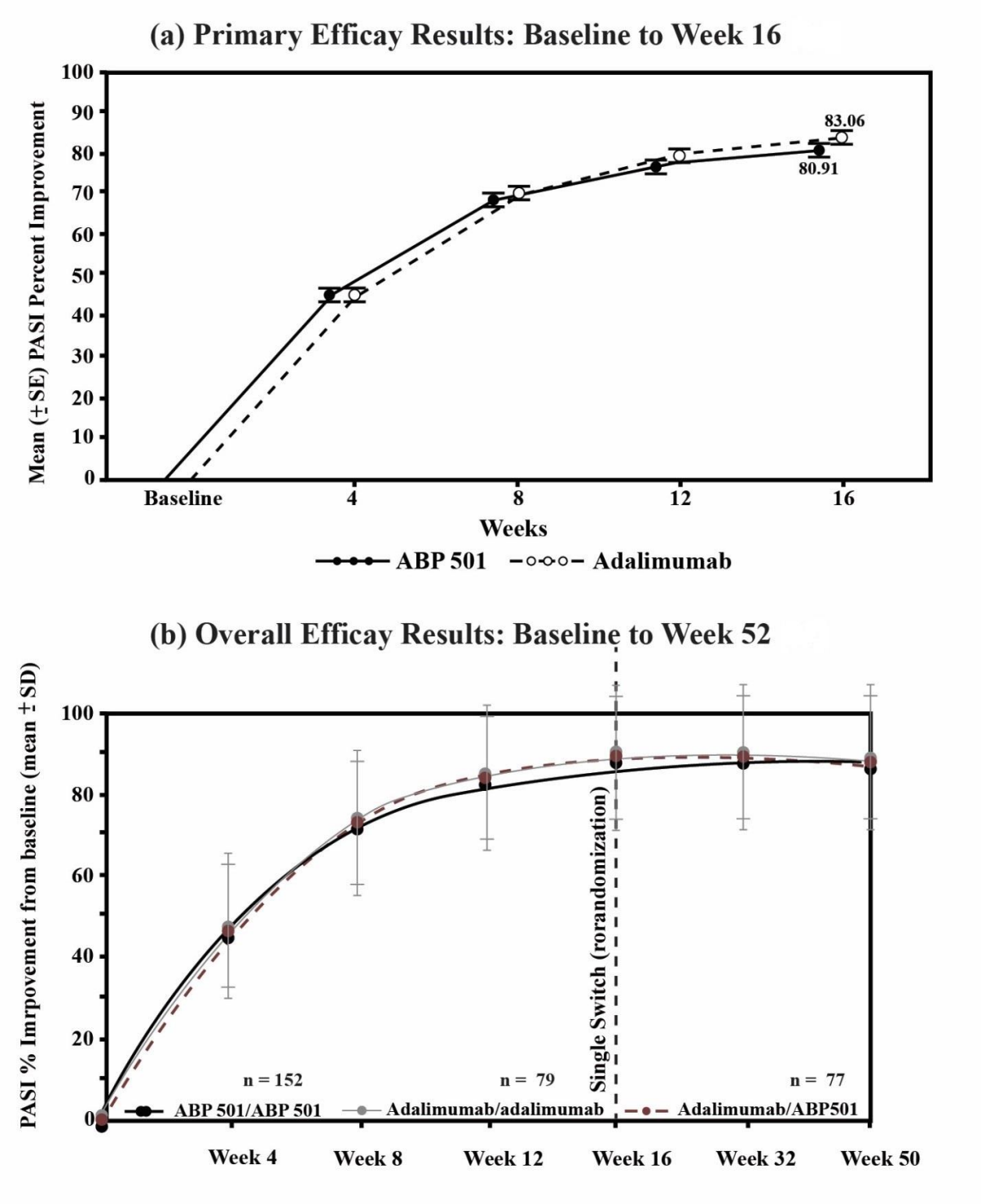

Figure 09: Phase 3 clinical data of the patients having moderate to severe PsO (Markus et al., 2019a).

At week 16, the improved PASI score of ABP-501 was very similar to adalimumab RP with the least mean difference of 2.18 with 94% CI from the baseline (Markus et al., 2019b). During these 16-week treatments, the TEAE incidents were also indistinguishable between ABP-501 and adalimumab RP. Moreover, 67.2% of patients who had taken ABP-501 face TEAEs; on

the contrary, patients taking adalimumab RP faced TEAEs were 63.6%. Therefore, only 5% of patients in any treatment group had upper respiratory tract infection, headache and, nasopharyngitis. Other TEAEs were hypersensitivity, infections, injection site reactions, and serious infection (Cohen et al., 2019).

	Initial week period		Randomized treatment, weeks 16-52		
	ABP 501	Adalimumab	ABP 501/ABP501	Adalimumab/Adalimumab	Adalimumab/ ABP 501
	(n= 174)	(n =173)	(n=152)	(n= 79)	(n=77)
Any TEAE	117 (62.25 %)	110 (63.6%)	108 (71.1%)	52 (65.8%)	54 (70.1%)
SAEs	6 (3.4%)	5 (2.9%)	4 (2.6%)	4 (5.1%)	4 (5.2%)
TEAEs leading to discontinuation	7 (%)	5 (%)	4 (%)	1(%)	2 (%)
Infections	59 (33.9%)	58 (33.5%)	67 (44.1%)	29 (36.7%)	37 (48.1%)
Nasopharyngitis	25 (14.4%)	27(15.6%)	25 (16.4%)	14 (17.7%)	18 (23.4%)
Headaches	13 (7.5%)	18 (10.4%)	5 (3.3%)	8 (10.1%)	2 (2.6%)
Malignancies	1 (0.6%)	1 (0.6%)	1 (0.7%)	0	0
Hypersensitivity	8 (4.6%)	7 (4.0%)	8 (5.3%)	2 (2.5%)	3 (3.9%)
Hematological reactions	0	3 (1.7%)	0	1(1.3%)	1 (1.3%)
Liver enzyme deviations	4 (2.3%)	2 (1.2%)	9 (5.9%)	2 (2.5%)	2 (2.6%)

TEAE = Treatment-Emergent-Adverse-Events
SAE: Serious Adverse Event

Figure 10: Adverse reactions in moderate to severe PsO (Markus et al., 2019a)

Moreover, a sub-analysis of patients with RA also demonstrated the similarity in safety, efficacy, and immunogenicity. At the end of the 16th week, when some patients were switched from adalimumab Rp to ABP-501, the patients demonstrated a similar mean PASI. Therefore,

from week 16 to 52, there were no significant dissimilarities observed between the drugs. Again, after week 16 to the week of the study, almost 1% of patients experienced similar TEAEs. A total of 5% of patients suffered from headaches, diarrhea, back pain, and nasopharyngitis (Su et al., 123 C.E.). Among them, the most common types of adverse reactions were infection and GIT disturbance. Therefore, hypersensitivity was less common in the patients. However, there were no significant clinical differences between controlled groups observed (Hyland et al., 2016). 13 of the patients had changes in their liver enzymes. Additionally, 5 patients had injection site reactions. All the groups had the same types of adverse events. Overall, during the studies, no deaths, lupus-like structures, or cardiac failures were observed.

6.1.2 Efficacy and Safety in Moderate to Severe Rheumatoid Arthritis (RA)

A double-blind, randomized, controlled equivalence study was conducted between ABP-501 and adalimumab RP to observe the similarities of safety, efficacy, and immunogenicity in patients having moderate to severe rheumatoid arthritis (Argollo et al., 2019). All the patients were divided into 2 groups where the first group had gotten adalimumab RP and another group had gotten ABP-501.On day 1, all patients got 40 mg SC adalimumab RP or ABP-501 and then the next 2 weeks until the 22nd week. At week-24, the primary endpoint of the study was determined. At week 16, safety and efficacy studies were conducted (P. E et al., 2018). The primary efficacy endpoint of the study was to achieve 20% of ACR improvement from baseline in week 24. The secondary efficacy endpoint was to achieve ACR 20% of ACR 20, 50% of ACR 50, and 70% of ACR 70 improvement at different points throughout the study (Cohen et al., 2017). A total of 526 randomized patients were involved in the study. At week 24, among the 526 patients, 74.6% of ABP-501 and 72.4% of adalimumab RP receiving patients met ACR 20 response criteria as Figure 07 states (Kaur et al., 2017b).

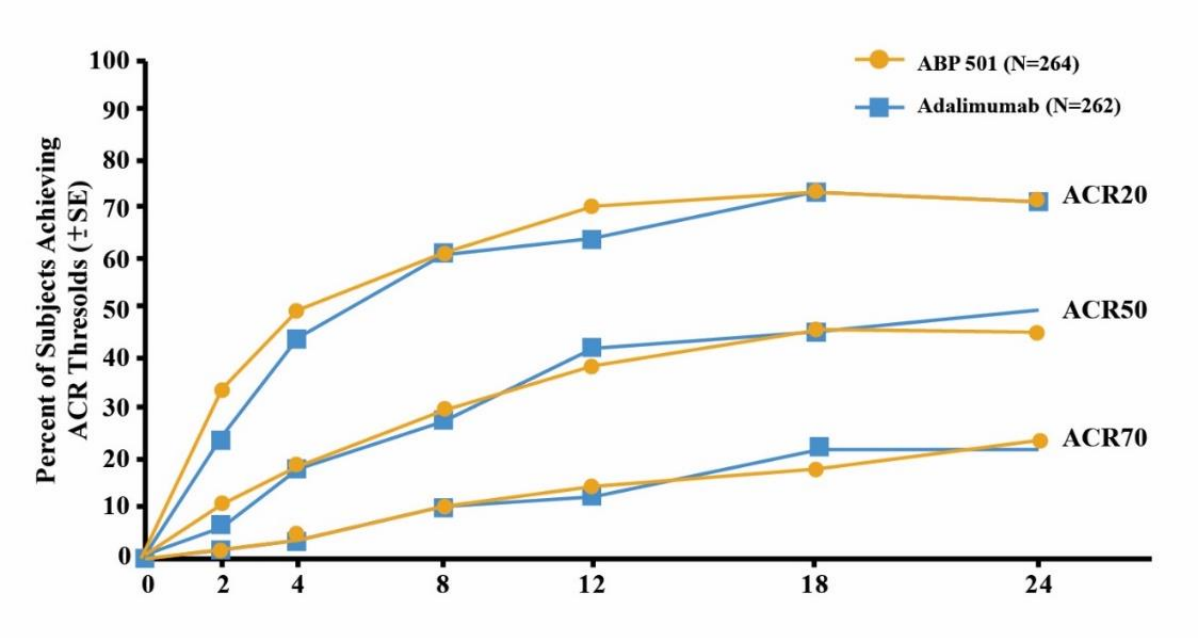

Figure 11: Phase 3 clinical data of patients with moderate to severe RA: number of patients achieving ACR-20. ACR-50 and ACR-70. (Markus et al., 2019a)

90% CI was achieved from the study which states the similarity between adalimumab RP and ABP-501. Again, a similar number of patients met ACR-50 and ACR-70 criteria at week 24. From the above graph, it had been clear that ACR-50 and ACR-70 responders were similar between the patients during the study (Rahalkar et al., 2021).

The overall data demonstrated TEAEs in the patients using ABP-501 was 50%. On the contrary, in patients who had taken adalimumab RP, the TEAEs were 54.6% as mentioned in Table 12.

	Phase 3 Study		OLE Study
	ABP 501	Adalimumab	ABP 501
	(n= 264)	(n =262)	(n=467)
Any TEAE	132 (50.00 %)	143 (54.6%)	297 (63.7%)
SAEs	10 (3.8%)	13 (5.0%)	46 (9.9%)
AEs leading to discontinuation	7 (2.7%)	2 (0.8%)	8 (1.7%)
Infections	61 (23.1%)	68 (26.0%)	190 (40.8%)
Malignancies	1 (0.4%)	1 (0.4%)	8 (1.7%)
Hypersensitivity	14 (5.3%)	10 (3.8%)	20 (4.3%)
Hematological reactions	5 (1.9%)	5 (1.9%)	5 (1.1%)
Liver enzyme deviations	13 (4.9%)	10 (3.8%)	25 (5.4%)

AE: Adverse Events
OLE: Open-Label Extension
TEAE: Treatment-Emergent-Adverse-Events
SAE: Serious Adverse Event

Figure 12: Adverse reactions in moderate to severe RA (Markus et al., 2019a)

Almost 3% of the total patients had TEAEs. For example, patients had several effects like cough (2.7% vs 3.1), nasopharyngitis (6.4% vs 7.3%), arthralgia (3% vs 3.4%) and headache (4.5% vs 4.2%). However, a total of 27 SAE cases were reported where 13 people were administered adalimumab RP and 10 people were administered ABP-501(Weise et al., 2014). Again, 2 patients had sepsis who were taking ABP-501 and they recovered end of the study. No patients had died throughout the study. Grade 1 & 2 adverse effects of interest were reported including hypersensitivity, infection, liver enzyme elevation, and malignancies (Pelechas et al., 2018b). Two types of malignancies were reported for a patient of the ABP-501 group, they are squamous cell carcinoma and basal cell carcinoma. On the other hand, a patient of the adalimumab RP group had reported squamous cell carcinoma of the skin (P. K et al., 2017). More than 2% reported hypersensitivity, including allergenic dermatitis, rash, erythematous, and rash. Total 5.0% of patients of the adalimumab RP group and 2.3% of patients of the ABP-501 group had suffered from injection site reactions. Finally, although some patients reported the elevation in liver enzymes, no patient had increased bilirubin in blood serum level (Puri et al., 2017).

6.1.3 Open-Label-Extension Safety and Efficacy Study in Patients with Moderate to Severe RA:

An extension of open-label study (OLE) was performed to compare treatments and accumulate secondary data about the long-term effects in the ABP-501 patient population. However, a phase-3 OLE study was performed to demonstrate the safety, efficacy, and immunogenicity between ABP-501 and adalimumab RP for 72 weeks with moderate to severe RA patients (Z. S et al., 2018). All patients who had completed the study for 22 weeks with ABP-501 were allowed for OLE study by taking 40 mg of ABP-501 SC per week. The primary outcomes for the study were SAEs, TAES, and, significant changes in clinical data (C. S et al., 2019).

From Figure 08, it is clear that ACR 20 response rate was 73.3% from the baseline and continued almost unchanged till week 72. Therefore, the proportion of ACR20 response rates were similar between the 2 groups (ABP-501 and adalimumab RP), and the efficacy was expected and the same as RP throughout the study (AL-Sabbagh et al., 2016).

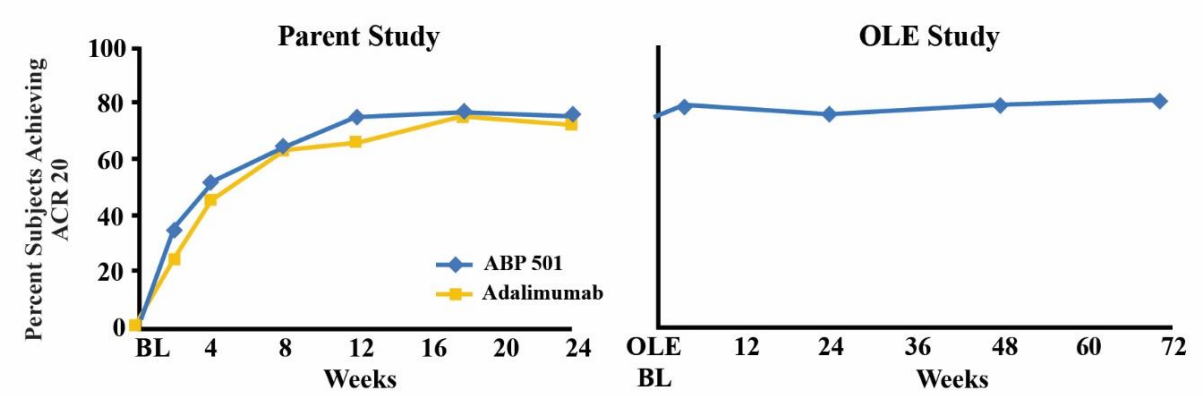

Figure 13: OLE trial for safety and efficacy evaluation of adalimumab RP and ABP-501(Markus et al., 2019a)

Throughout the study, a total of 63.7% of patients suffered from TEAEs. Though the TEAEs were similar between the 2 groups (Hung et al., 2017). Common TEAEs have occurred during the OLE study in more than 5% of patients including pharyngitis (47%), nasopharyngitis (9.2%), urinary tract infection (3.6%), bronchitis (6.4%), and upper respiratory tract infections (3.6%). A total of 59 SAEs were reported in 40 patients which were similar rates in ABP-501/ ABP-501 (10.9%), and Adalimumab Rp/ ABP-501 (8.9%). In addition, SAEs included more than one patients are osteoarthritis (5 patients), cataract (3 patients), RA (2 patients), and myocardial infarction (patients) (Moots et al., 2018). Common adverse events of interest were

hematological reactions, infections, liver enzyme elevations, and hypersensitivity. Most of the patients had reported nasopharyngitis as a common infection. Other infections that are included throughout the study were pharyngitis, pneumonia, upper respiratory tract infection, urinary tract infection tonsillitis, bronchitis, sinusitis, laryngitis, oral herpes, etc.(Hercogová et al., 2020).

Chapter 7

7.1 Immunogenicity of ABP-501 with Adalimumab

In total 3 clinical studies, immunogenicity tests were carried out. Binding and neutralizing antibody production were similar between adalimumab RP and the ABP-501 population in both diseases PsO and RA. The data are presented below:

Immunogenicity of ABP 501 vs. adalimumab RP in moderate to severe RA and PsO									
	Moderate to severe RA				Moderate to severe PsO				
	Phase 3 study		OLE study		Phase 3 study: 16-week		Phase 3 study: post rerandomization		
	ABP 501 (%)	Adalimumab RP (%)	ABP 501 (%)	Adalimumab RP (%)	ABP 501 (%)	Adalimumab RP (%)	ABP 501/ABP 501 (%)	Adalimumab RP/Adalimumab RP (%)	Adalimumab RP/ABP 501 (%)
Binding antibody	38.3	38.2	54.1	48.9	55.2	63.6	68.4	74.7	72.7
Neutralising antibody	9.1	11.1	14.4	13.9	9.8	13.9	13.8	20.3	24.7

Figure 14: Immunogenicity data in moderate to severe RA and PsO (Markus et al., 2019a)

Also, in PsO studies, when patients were switching from adalimumab RP to ABP-501 at week 16; the generation of binding and neutralizing antibodies between patients for the entire 52 weeks was similar (DG et al., 2020). Therefore, antibody production was similar to the reference product from baseline to end of the studies. Also, in the OLE study, when patients transferred from adalimumab RP to ABP-501, the ratio of the production of antibodies was similar. From the aforementioned table, it is proved that the rate of the incident in binding antibodies and neutralizing antibodies in the phase-3 RA study was similar across the treatment groups for 52 weeks (Smolen et al., 2019). But, for ABP-501, the development of binding antibody and neutralizing antibody increased compared to the reference product. However, throughout the study, the rate of development was maintained, with no significant differences with adalimumab RP. Overall, there were no remarkable differences observed with ABP-501 throughout the 2 years of total study (Markus et al., 2019a).

Chapter 8

8.1 Conclusion

The discovery of new biosimilars for different biologics has brought numerous treatment options for long-term incurable diseases and cut the extra cost of biologics (G et al., 2019). The potentially expanding market of biosimilar leads to the accessibility of high-quality medications to patients from all over the world. Different regulatory agencies like EMA, and FDA ensure that biosimilars have a similar mechanism of action like their reference product by supporting the evidence of manufacturers. The results of the analytical study stated that the ABP-501 and reference Humira have the same physicochemical properties and biological activities. After that, the phase 1 single-dose, single-blind, parallel-group Pk comparison study result demonstrated similar serum concentrations between the patients who had taken adalimumab RP and ABP-501 in both mild to moderate PsO and RA. Moreover, phase 3 pharmacokinetic studies of ABP-501 exhibit clinical equivalence to Humira by reaching primary endpoints. During the study, the patients also had similar TEAE like oropharyngeal pain, nasopharyngitis, and sinus conjunction. Next, the phase 3 randomized, active-controlled, and, double-blind safety and efficacy studies were conducted among healthy volunteers and patients having long-term RA and PsO for getting detailed and accurate results among different populations. The study results concluded that ABP-501 is equally safe and effective as its reference Humira and there were no clinically meaningful differences between the ABP-501 with reference adalimumab product. The nonclinical toxicology studies stated similar adverse events like cough, nasopharyngitis, arthralgia among the treatment and control groups where no deaths were reported during the overall phase 3 safety and efficacy study. The results of the total 3 clinical and OLE studies of ABP-501 demonstrate high similarities to the reference Humira in terms of safety, efficacy, and immunogenicity in moderate to severe PsO and RA. Therefore, after all the investigation, FDA approved the interchangeability of ABP 501 with Humira in conditions like moderate to severe RA and PsO.

8.2 Future Directions

- Conduct extensive research focusing on FKB-27 (Huilo) and PF-06410239 (Abrilada/Amsparity).

References

A, B. (2006). Early development of therapeutic biologics--pharmacokinetics. *Current Drug Metabolism*, *7*(1), 15–21. https://doi.org/10.2174/138920006774832604

A, E., MB, O., R, G., S, B.-O., TN, D., LE, B., MK, R., & L, S. (2018). Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *The British Journal of Dermatology*, *178*(2), 509–519. https://doi.org/10.1111/BJD.16102

A, I.-W., & T, K. (2019). Biosimilarity assessment of biosimilar therapeutic monoclonal antibodies. *Drug Metabolism and Pharmacokinetics*, *34*(1), 64–70. https://doi.org/10.1016/J.DMPK.2018.11.004

AB, A., & A, M. (2016). Understanding the biosimilar approval and extrapolation process-A case study of an epoetin biosimilar. *Critical Reviews in Oncology/Hematology*, *104*, 98–107. https://doi.org/10.1016/J.CRITREVONC.2016.04.016

AG, V., & OA, J. (2017). The process defines the product: what really matters in biosimilar design and production? *Rheumatology (Oxford, England)*, *56*(suppl_4), iv14–iv29. https://doi.org/10.1093/RHEUMATOLOGY/KEX278

AL-Sabbagh, A., Olech, E., McClellan, J. E., & Kirchhoff, C. F. (2016). Development of biosimilars. *Seminars in Arthritis and Rheumatism*, *45*(5), S11–S18. https://doi.org/10.1016/J.SEMARTHRIT.2016.01.002

Argollo, M., Fiorino, G., Gilardi, D., Furfaro, F., Roda, G., Loy, L., Allocca, M., Peyrin-Biroulet, L., & Danese, S. (2019). Biosimilars of Adalimumab in Inflammatory Bowel Disease: Are we Ready for that? *Current Pharmaceutical Design*, *25*(1), 7–12.

AS, R., H, C., & A, B. (2021). Approval of biosimilars: a review of unsuccessful regulatory filings. *Expert Opinion on Biological Therapy*, *21*(1). https://doi.org/10.1080/14712598.2020.1793954

Bellinvia, S., Cummings, · J R Fraser, Ardern-Jones, M. R., Christopher, ·, Edwards, J., & Edwards, C. J. (123 C.E.). Adalimumab Biosimilars in Europe: An Overview of the Clinical Evidence. *BioDrugs*, *33*, 241–253. https://doi.org/10.1007/s40259-019-00355-4

Biologics: Definition, Side Effects, Uses & Drug List. (n.d.-a). Retrieved September 2, 2021, from

https://www.medicinenet.com/biologics_biologic_drug_class/article.htm#what_are_the_medical_uses_for_biologics

Biologics: Definition, Side Effects, Uses & Drug List. (n.d.-b). Retrieved September 2, 2021, from https://www.medicinenet.com/biologics_biologic_drug_class/article.htm

Biologics for Rheumatoid Arthritis (RA): What To Expect. (n.d.). Retrieved September 2, 2021, from https://www.webmd.com/rheumatoid-arthritis/biologics

Biosimilar and Interchangeable Products | FDA. (n.d.-a). Retrieved November 11, 2021, from https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

Biosimilar and Interchangeable Products | FDA. (n.d.-b). Retrieved September 25, 2021, from https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#biosimilar

BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence. (n.d.). Retrieved September 2, 2021, from https://drug-dev.com/biosimilar-development-approval-of-biosimilar-medicines-through-totality-of-the-evidence/

Biosimilars_ A Multidisciplinary Perspective | Elsevier Enhanced Reader. (n.d.). Retrieved August 2, 2021, from https://reader.elsevier.com/reader/sd/pii/S0149291816300923?token=02119342A5D217EB028547B28266F6D3683FF995850E000D90EC73E3ED0C2469AFFA11A753C9003DFB6760998F6343AD&originRegion=eu-west-1&originCreation=20210802092320

Calvo, B., & Zuñiga, L. (2012). The US approach to biosimilars: The long-awaited FDA approval pathway. *BioDrugs*, *26*(6), 357–361. https://doi.org/10.2165/11635830-000000000-00000

CHMP. (2014). *Committee for Medicinal Products for Human Use (CHMP) Guideline on similar biological medicinal products*. www.ema.europa.eu/contact

Chung, S. W., Hil-Lal, T. A., & Byun, Y. (2012). Strategies for non-invasive delivery of biologics. *Journal of Drug Targeting*, *20*(6), 481–501. https://doi.org/10.3109/1061186X.2012.693499

Cingolani, L., Barberio, B., Zingone, F., Ferronato, A., Bertani, L., Costa, F., Bodini, G., Demarzo, M. G., Melatti, P., Gubbiotti, A., Massimi, D., Casadei, C., D'incà, R., & Savarino, E. V. (123 C.E.). Adalimumab biosimilars, ABP501 and SB5, are equally

effective and safe as adalimumab originator. *Scientific Reports* |, *11*, 10368. https://doi.org/10.1038/s41598-021-89790-4

Cingolani, L., Barberio, B., Zingone, F., Ferronato, A., Bertani, L., Costa, F., Bodini, G., Demarzo, M. G., Melatti, P., Gubbiotti, A., Massimi, D., Casadei, C., D'Incà, R., & Savarino, E. V. (2021). Adalimumab biosimilars, ABP501 and SB5, are equally effective and safe as adalimumab originator. *Scientific Reports*, *11*(1). https://doi.org/10.1038/S41598-021-89790-4

Coghlan, J., He, H., & Schwendeman, A. S. (2021a). Overview of Humira® Biosimilars: Current European Landscape and Future Implications. *Journal of Pharmaceutical Sciences*, *110*(4), 1572–1582.

Coghlan, J., He, H., & Schwendeman, A. S. (2021b). Overview of Humira® Biosimilars: Current European Landscape and Future Implications. *Journal of Pharmaceutical Sciences*, *110*(4), 1572–1582. https://doi.org/10.1016/J.XPHS.2021.02.003

Cohen, S., Genovese, M. C., Choy, E., Perez-Ruiz, F., Matsumoto, A., Pavelka, K., Pablos, J. L., Rizzo, W., Hrycaj, P., Zhang, N., Shergy, W., & Kaur, P. (2017). Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: A randomised, double-blind, phase III equivalence study. *Annals of the Rheumatic Diseases*, *76*(10), 1679–1687.

Cohen, S., Pablos, J. L., Pavelka, K., Müller, G. A., Matsumoto, A., Kivitz, A., Wang, H., & Krishnan, E. (2019). An open-label extension study to demonstrate long-term safety and efficacy of ABP 501 in patients with rheumatoid arthritis. *Arthritis Research and Therapy*, *21*(1). https://doi.org/10.1186/S13075-019-1857-3

Comparing U.S. and E.U. Biosimilar Regulations | RegDesk | Professional. (n.d.). Retrieved September 6, 2021, from https://www.regdesk.co/comparing-us-eu-biosimilar-regulations/

Crespi-Lofton, J., & Skelton, J. B. (2017). The growing role of biologics and biosimilars in the United States: Perspectives from the APhA Biologics and Biosimilars Stakeholder Conference. *Journal of the American Pharmacists Association*, *57*(5), e15–e27. https://doi.org/10.1016/J.JAPH.2017.05.014

Daller, J. (2016). Biosimilars: A consideration of the regulations in the United States and

European union. *Regulatory Toxicology and Pharmacology*, *76*, 199–208. https://doi.org/10.1016/J.YRTPH.2015.12.013

de Mora, F. (2019). Biosimilars: A Value Proposition. *BioDrugs*, *33*(4), 353–356. https://doi.org/10.1007/S40259-019-00360-7

DG, R., GP, C., R, P., M, V., GM, S., M, M., & M, A. (2020). Effectiveness and safety of adalimumab biosimilar ABP 501 in Crohn's disease: an observational study. *Revista Espanola de Enfermedades Digestivas : Organo Oficial de La Sociedad Espanola de Patologia Digestiva*, *112*(3), 195–200. https://doi.org/10.17235/REED.2020.6693/2019

Dixit, R., Iciek, L. A., McKeever, K., & Ryan, P. C. (2010). Challenges of general safety evaluations of biologics compared to small molecule pharmaceuticals in animal models. *Expert Opinion on Drug Discovery*, *5*(1), 79–94. https://doi.org/10.1517/17460440903443410

Dos Reis, C., Teixo, R., Mendes, F., & Cruz, R. S. (2016). Biosimilar medicines - Review. *International Journal of Risk and Safety in Medicine*, *28*(1), 45–60. https://doi.org/10.3233/JRS-160672

E, P., PV, V., & AA, D. (2018). ABP 501 for the treatment of rheumatoid arthritis. *Expert Opinion on Biological Therapy*, *18*(3), 317–322. https://doi.org/10.1080/14712598.2018.1430760

E, W.-H., K, T., C, V., & M, W. (2019). Evolution of the EU Biosimilar Framework: Past and Future. *BioDrugs : Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy*, *33*(6), 621–634. https://doi.org/10.1007/S40259-019-00377-Y

ER, K., SS, M., & MK, S. S. (2019). The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy. *Biomolecules*, *9*(9). https://doi.org/10.3390/BIOM9090410

F, de M. (2015). Biosimilar: what it is not. *British Journal of Clinical Pharmacology*, *80*(5), 949–956. https://doi.org/10.1111/BCP.12656

Fda, & Cder. (n.d.). *The Purple Book*. Retrieved October 26, 2021, from http://www.fda.gov/cdersmallbusinesschronicles

Fda, Cder, & TerrieCrescenzi. (2016). *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product: Guidance for Industry*. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/defa

ult.htmand/orhttp://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

FDA Promotes Efficient Biosimilar Approval. (2018). *Cancer Discovery*, *8*(10), 1200. https://doi.org/10.1158/2159-8290.CD-NB2018-113

Frazier-Mironer, A., Dougados, M., Mariette, X., Cantagrel, A., Deschamps, V., Flipo, R. M., Logeart, I., Schaeverbeke, T., Sibilia, J., Le Loët, X., & Combe, B. (2014). Taux de rétention de l'adalimumab, de l'étanercept et de l'infliximab en 1reou 2eligne de biothérapie chez les patients atteints de polyarthrite rhumatoïde en pratique courante. *Revue Du Rhumatisme (Edition Francaise)*, *81*(6), 483–490. https://doi.org/10.1002/14651858.CD008794.PUB2

G, F., D, G., C, C., F, F., G, R., L, L., M, A., M, A., L, P.-B., & S, D. (2019). Biosimilars of adalimumab: the upcoming challenge in IBD. *Expert Opinion on Biological Therapy*, *19*(10), 1023–1030. https://doi.org/10.1080/14712598.2019.1564033

GR, B., & U, M.-L. (2015). [Biosimilars]. *Zeitschrift Fur Rheumatologie*, *74*(8), 670–671. https://doi.org/10.1007/S00393-014-1490-0

Hercogová, J., Papp, K. A., Chyrok, V., Ullmann, M., Vlachos, P., & Edwards, C. J. (2020). AURIEL-PsO: a randomized, double-blind phase III equivalence trial to demonstrate the clinical similarity of the proposed biosimilar MSB11022 to reference adalimumab in patients with moderate-to-severe chronic plaque-type psoriasis. *British Journal of Dermatology*, *182*(2), 316–326. https://doi.org/10.1111/BJD.18220

Hung, A., Vu, Q., & Mostovoy, L. (2017). A Systematic Review of U.S. Biosimilar Approvals: What evidence does the FDA require and how are manufacturers responding? *Journal of Managed Care and Specialty Pharmacy*, *23*(12), 1234-1244b. https://doi.org/10.18553/JMCP.2017.23.12.1234

Hyland, E., Mant, T., Vlachos, P., Attkins, N., Ullmann, M., Roy, S., & Wagner, V. (2016). *Comparison of the pharmacokinetics, safety, and immunogenicity of MSB11022, a biosimilar of adalimumab, with Humira ® in healthy subjects*. https://doi.org/10.1111/bcp.13039

International Conference on Harmonisation. (1994). ICH S3A - Note for guidance toxicokinetics: a guidance for assessing sistemic exposure in toxicology studies.

International Conference on Harmonization, November 1994. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S3A/Step4/S3A_Guideline.pdf

J, C., H, H., & AS, S. (2021). Overview of Humira® Biosimilars: Current European Landscape and Future Implications. *Journal of Pharmaceutical Sciences*, *110*(4), 1572–1582. https://doi.org/10.1016/J.XPHS.2021.02.003

J, L., T, E., C, L., S, C., & S, K. (2016). Assessing Analytical Similarity of Proposed Amgen Biosimilar ABP 501 to Adalimumab. *BioDrugs : Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy*, *30*(4), 321–338. https://doi.org/10.1007/S40259-016-0184-3

J, O., SP, B., M, B., JM, M., & BT, G. (2019). Regulation of biosimilar medicines and current perspectives on interchangeability and policy. *European Journal of Clinical Pharmacology*, *75*(1). https://doi.org/10.1007/S00228-018-2542-1

Jacobs, I., Petersel, D., Isakov, L., Lula, S., & Lea Sewell, K. (2016). Biosimilars for the Treatment of Chronic Inflammatory Diseases: A Systematic Review of Published Evidence. *BioDrugs*, *30*(6), 525–570. https://doi.org/10.1007/S40259-016-0201-6

Jha, D., Mishra, R. K., & Pandey, R. (2013). Biosimilars: Current regulatory perspective and challenges. *Journal of Pharmacy & Bioallied Sciences*, *5*(1), 80. https://doi.org/10.4103/0975-7406.106569

JJ, D., J, A., & AS, K. (2020). FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA*, *323*(2), 164–176. https://doi.org/10.1001/JAMA.2019.20288

JS, S., J, G., M, Q., F, B., & JY, L. (2019). Era of biosimilars in rheumatology: reshaping the healthcare environment. *RMD Open*, *5*(1). https://doi.org/10.1136/RMDOPEN-2019-000900

K, B., & R, W. (2012). Disposition of biologics. *Advances in Pharmacology (San Diego, Calif.)*, *63*, 257–277. https://doi.org/10.1016/B978-0-12-398339-8.00007-0

K, P., H, B., A, C., P, F., M, G., P, K., J, N., S, P., L, S., J, W., N, Z., & B, S. (2017). Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *Journal of the American Academy of Dermatology*, *76*(6), 1093–1102.

https://doi.org/10.1016/J.JAAD.2016.12.014

Kaur, P., Chow, V., Zhang, N., Moxness, M., Kaliyaperumal, A., & Markus, R. (2017a). A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Annals of the Rheumatic Diseases*, *76*(3), 526–533. https://doi.org/10.1136/ANNRHEUMDIS-2015-208914

Kaur, P., Chow, V., Zhang, N., Moxness, M., Kaliyaperumal, A., & Markus, R. (2017b). A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Annals of the Rheumatic Diseases*, *76*(3), 526–533. https://doi.org/10.1136/annrheumdis-2015-208914

Kesik-Brodacka, M. (2018). Progress in biopharmaceutical development. *Biotechnology and Applied Biochemistry*, *65*(3), 306–322. https://doi.org/10.1002/bab.1617

Kim, K. S., Choi, Y. H., Moon, A., & Kim, S. G. (2020). Body Weight as a Determining Factor in the Predominance of Adverse Drug Reactions Induced by Fixed-Dose Adalimumab Injections in Female Patients in a Korean Hospital Setting. *Journal of Clinical Medicine*, *9*(2). http://www.ncbi.nlm.nih.gov/pubmed/32046138

L, S.-R. (2018). Approval Process: An Overview of Biosimilars in the Oncology Setting. *Clinical Journal of Oncology Nursing*, *22*(5), 13–18. https://doi.org/10.1188/18.CJON.S1.13-18

L, Z., & B, C. (2010). Biosimilars approval process. *Regulatory Toxicology and Pharmacology : RTP*, *56*(3), 374–377. https://doi.org/10.1016/J.YRTPH.2009.11.004

Liu, J., Eris, T., Li, C., Cao, S., & Kuhns, S. (2016). Assessing Analytical Similarity of Proposed Amgen Biosimilar ABP 501 to Adalimumab. *BioDrugs*, *30*(4), 321–338. https://doi.org/10.1007/S40259-016-0184-3

Lu, X. Q., Hu, R., Peng, L., Liu, M. S., & Sun, Z. (2021a). Efficacy and Safety of Adalimumab Biosimilars: Current Critical Clinical Data in Rheumatoid Arthritis. *Frontiers in Immunology*, *12*.

Lu, X. Q., Hu, R., Peng, L., Liu, M. S., & Sun, Z. (2021b). Efficacy and Safety of Adalimumab Biosimilars: Current Critical Clinical Data in Rheumatoid Arthritis. *Frontiers in Immunology*, *12*. https://doi.org/10.3389/FIMMU.2021.638444

M, S., G, R., K, W., B, J., K, R., B, C., M, T., P, B., & J, M.-J. (2020). The Path Towards a Tailored Clinical Biosimilar Development. *BioDrugs : Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy*, *34*(3), 297–306. https://doi.org/10.1007/S40259-020-00422-1

Markus Helen McBride Monica Ramchandani Vincent Chow Jennifer Liu Dan Mytych Gary Fanjiang, R. J., & Markus Á J McBride Á M Ramchandani Á V Chow Á J Liu Á D Mytych Á G Fanjiang, R. H. (2019). A Review of the Totality of Evidence Supporting the Development of the First Adalimumab Biosimilar ABP 501. *Advances in Therapy*, *36*, 1833–1850. https://doi.org/10.6084/m9.figshare.7998434

Markus, R., McBride, H. J., Ramchandani, M., Chow, V., Liu, J., Mytych, D., & Fanjiang, G. (2019a). A Review of the Totality of Evidence Supporting the Development of the First Adalimumab Biosimilar ABP 501. *Advances in Therapy*, *36*(8), 1833–1850.

Markus, R., McBride, H. J., Ramchandani, M., Chow, V., Liu, J., Mytych, D., & Fanjiang, G. (2019b). A Review of the Totality of Evidence Supporting the Development of the First Adalimumab Biosimilar ABP 501. *Advances in Therapy*, *36*(8), 1833–1850. https://doi.org/10.1007/S12325-019-00979-6

Medicines Agency, E. (n.d.). *Biosimilars in the EU - Information guide for healthcare professionals*.

Misra, M. (2012). Biosimilars: Current perspectives and future implications. In *Indian Journal of Pharmacology* (Vol. 44, Issue 1, pp. 12–14). Wolters Kluwer -- Medknow Publications. https://doi.org/10.4103/0253-7613.91859

Moots, R. J., Curiale, C., Petersel, D., Rolland, C., Jones, H., & Mysler, E. (2018). Efficacy and Safety Outcomes for Originator TNF Inhibitors and Biosimilars in Rheumatoid Arthritis and Psoriasis Trials: A Systematic Literature Review. *BioDrugs*, *32*(3), 193–199. https://doi.org/10.1007/S40259-018-0283-4

New WHO advice on biosimilar medicines aims to increase access to quality treatment. (n.d.). Retrieved October 26, 2021, from https://www.who.int/news/item/22-03-2019-advice-on-biosimilar-medicines-aims-to-increase-access-to-quality-treatment

O'Callaghan, J., Barry, S. P., Bermingham, M., Morris, J. M., & Griffin, B. T. (2019). Regulation of biosimilar medicines and current perspectives on interchangeability and

policy. *European Journal of Clinical Pharmacology*, *75*(1). https://doi.org/10.1007/S00228-018-2542-1

Pelechas, E., Voulgari, P. V., & Drosos, A. A. (2018a). ABP 501 for the treatment of rheumatoid arthritis. *Expert Opinion on Biological Therapy*, *18*(3), 317–322.

Pelechas, E., Voulgari, P. V., & Drosos, A. A. (2018b). ABP 501 for the treatment of rheumatoid arthritis. *Expert Opinion on Biological Therapy*, *18*(3), 317–322. https://doi.org/10.1080/14712598.2018.1430760

Puri, A., Niewiarowski, A., Arai, Y., Nomura, H., Baird, M., Dalrymple, I., Warrington, S., & Boyce, M. (2017). Pharmacokinetics, safety, tolerability and immunogenicity of FKB327, a new biosimilar medicine of adalimumab/Humira, in healthy subjects. In *British Journal of Clinical Pharmacology* (Vol. 83, Issue 7, pp. 1405–1415). https://doi.org/10.1111/bcp.13245

R, M., HJ, M., M, R., V, C., J, L., D, M., & G, F. (2019). A Review of the Totality of Evidence Supporting the Development of the First Adalimumab Biosimilar ABP 501. *Advances in Therapy*, *36*(8), 1833–1850. https://doi.org/10.1007/S12325-019-00979-6

Rahalkar, H., Sheppard, A., Santos, G. M. L., Dasgupta, C., Perez-Tapia, S. M., Lopez-Morales, C. A., & Salek, S. (2021). Current Regulatory Requirements for Biosimilars in Six Member Countries of BRICS-TM: Challenges and Opportunities. *Frontiers in Medicine*, *8*. https://doi.org/10.3389/FMED.2021.726660

S, B., L, P.-B., & S, D. (2017). Clinical development of biologicals and biosimilars - safety concerns. *Expert Review of Clinical Pharmacology*, *10*(6), 567–569. https://doi.org/10.1080/17512433.2017.1293522

S, C., JL, P., K, P., GA, M., A, M., A, K., H, W., & E, K. (2019). An open-label extension study to demonstrate long-term safety and efficacy of ABP 501 in patients with rheumatoid arthritis. *Arthritis Research & Therapy*, *21*(1). https://doi.org/10.1186/S13075-019-1857-3

S, Z., L, C., E, M., & RJ, M. (2018). Review of Biosimilar Trials and Data on Adalimumab in Rheumatoid Arthritis. *Current Rheumatology Reports*, *20*(10). https://doi.org/10.1007/S11926-018-0769-6

Sauerborn, M., Brinks, V., Jiskoot, W., & Schellekens, H. (2010). Immunological mechanism

underlying the immune response to recombinant human protein therapeutics. *Trends in Pharmacological Sciences*, *31*(2), 53–59. https://doi.org/10.1016/j.tips.2009.11.001

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product | FDA. (n.d.). Retrieved October 26, 2021, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product

Smolen, J. S., Goncalves, J., Quinn, M., Benedetti, F., & Lee, J. Y. (2019). Era of biosimilars in rheumatology: reshaping the healthcare environment Rheumatoid arthritis. *Open*, *5*, 900. https://doi.org/10.1136/rmdopen-2019-000900

Su, J., Li, M., He, L., Zhao, D., Wan, W., Liu, Y., Xu, J., Xu, J., Liu, H., Jiang, L., Wu, H., Zuo, X., Huang, C., Liu, X., Li, F., Zhang, Z., Liu, X., Dong, L., Li, T., … Zeng, X. (123 C.E.). Comparison of the Efficacy and Safety of Adalimumab (Humira) and the Adalimumab Biosimilar Candidate (HS016) in Chinese Patients with Active Ankylosing Spondylitis: A Multicenter, Randomized, Double-Blind, Parallel, Phase III Clinical Trial. *BioDrugs*, *34*, 381–393. https://doi.org/10.1007/s40259-020-00408-z

U.S. Biosimilars Market Size, Growth | Forecast Report, 2028. (n.d.). Retrieved September 2, 2021, from https://www.fortunebusinessinsights.com/industry-reports/u-s-biosimilars-market-100990

U.S. Biosimilars Market to Display a CAGR of 27.0% till 2028. (n.d.). Retrieved September 6, 2021, from https://www.fortunebusinessinsights.com/press-release/u-s-biosimilars-market-9187

Uifălean, A., Ilieş, M., Nicoară, R., Rus, L. M., Hegheş, S. C., & Iuga, C. A. (2018). Concepts and challenges of biosimilars in breast cancer: The emergence of trastuzumab biosimilars. *Pharmaceutics*, *10*(4), 1.-13 o. https://doi.org/10.3390/PHARMACEUTICS10040168

US Biosimilars Market Size to Reach $22,996 Million by. (n.d.). Retrieved September 6, 2021, from https://www.globenewswire.com/news-release/2020/08/13/2077943/0/en/US-Biosimilars-Market-Size-to-Reach-22-996-Million-by-2027-Recent-Scientific-Discoveries-Have-Indicated-Signs-of-a-Promising-Future-says-Fortune-Business-Insights.html

V, S., J, G., TP, H., HE, J., L, M., & JD, I. (2020). Immunogenicity of Biosimilars for

Rheumatic Diseases, Plaque Psoriasis, and Inflammatory Bowel Disease: A Review from Clinical Trials and Regulatory Documents. *BioDrugs : Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy*, *34*(1), 27–37. https://doi.org/10.1007/S40259-019-00394-X

Velayudhan, J., Chen, Y. feng, Rohrbach, A., Pastula, C., Maher, G., Thomas, H., Brown, R., & Born, T. L. (2016). Demonstration of Functional Similarity of Proposed Biosimilar ABP 501 to Adalimumab. *BioDrugs*, *30*(4), 339–351. https://doi.org/10.1007/S40259-016-0185-2

Vulto, A. G., & Jaquez, O. A. (n.d.). *The process defines the product: what really matters in biosimilar design and production?* https://doi.org/10.1093/rheumatology/kex278

Weise, M., Kurki, P., Wolff-Holz, E., Bielsky, M. C., & Schneider, C. K. (2014). Biosimilars: The science of extrapolation. In *Blood* (Vol. 124, Issue 22, pp. 3191–3196). American Society of Hematology. https://doi.org/10.1182/blood-2014-06-583617

What are biologics? Definitions and potential benefits | Bioanalysis Zone. (n.d.). Retrieved September 2, 2021, from https://www.bioanalysis-zone.com/biologics-definition-applications/

What Are "Biologics" Questions and Answers | FDA. (n.d.). Retrieved September 21, 2021, from https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers

What Are Biosimilars? Top Facts You May Not Know. (n.d.). Retrieved September 2, 2021, from https://www.drugs.com/slideshow/biosimilars--1264

Wolff-Holz, E., Tiitso, K., Vleminckx, C., & Weise, M. (2019). Evolution of the EU Biosimilar Framework: Past and Future. *BioDrugs*, *33*(6), 621–634. https://doi.org/10.1007/S40259-019-00377-Y

X, B., M, Ø., LS, G., D, P., EY, L., U, K., R, M., H, S., A, R., & B, P. (2020). Comparison of the Effects of Secukinumab and Adalimumab Biosimilar on Radiographic Progression in Patients with Ankylosing Spondylitis: Design of a Randomized, Phase IIIb Study (SURPASS). *Clinical Drug Investigation*, *40*(3), 269–278. https://doi.org/10.1007/S40261-020-00886-7

Y, I., PM, C., I, M., T, G., F, A., & G, T. (2018). Safety of Biologics, Including Biosimilars:

Perspectives on Current Status and Future Direction. *Drug Safety*, *41*(11), 1013–1022. https://doi.org/10.1007/S40264-018-0684-9

Zhou, X., Chen, Z., & Bi, X. (2021). An Update Review of Biosimilars of Adalimumab in Psoriasis – Bioequivalence and Interchangeability . *Drug Design, Development and Therapy*, *15*, 2987–2998. https://doi.org/10.2147/DDDT.S317382