# Biosimilar in Lymphoma Treatment

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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## Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
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.
4. I have acknowledged all main sources of help.

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# Approval

The project titled “Biosimilar in Lymphoma Treatment” submitted by Mehrin Haque Tanisha (17146020) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

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## Ethics Statement

This study does not involve any human or animal trial.

## Abstract

We are living in an era where the number of ageing population is increasing, as well as the demand for treating chronic conditions like cancer, cardiovascular disease, diabetes, etc. Considering the different types of cancer, lymphoma is one of the leading causes of death, with an estimated 259,793 deaths (2.6%) in 2020. Focusing on treatment with biosimilars, this review study aims to address the Rituximab biosimilars in lymphoma care. The patent of Rituximab has expired recently, resulting in concerns for patients with regard to accessibility particularly in countries with limited funding. These challenges stimulated the development and manufacturing of Rituximab biosimilars. The review also discusses the potential advantages and impacts of Rituximab biosimilars in lymphoma patients.



**Keywords:** Biosimilar; Cancer; Lymphoma; Rituximab

## Dedication

*Dedicated to my parents*

## Acknowledgement

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## List of Acronyms

| | |
|---|---|
| US FDA | The United States Food and Drug Administration |
| EMA | European Medicines Agency |
| EU | European Union |
| WHO | World Health Organization |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| TGA | Therapeutic Goods Administration |
| INN | International Non-Proprietary Names |
| REAL | Revised European-American Lymphoma Classification |
| BPCIA | The Biologics Price Competition and Innovation Act |
| PHS | Public Health Services Act |
| SEB | Subsequent Entry Biologics |
| CAGR | Compound annual growth rate |
| PK | Pharmacokinetics |
| PD | Pharmacodynamics |
| mAbs | Monoclonal Antibodies |
| ADCC | Antibody Dependent Cell-Mediated Cytotoxicity |
| CDC | Complement Dependent Cytotoxicity |
| HL | Hodgkin’s Lymphoma |

| | |
|---|---|
| NHL | Non- Hodgkin’s Lymphoma |
| DLBCL | Diffuse Large B-cell Lymphoma |
| FL | Follicular Lymphoma |
| RA | Rheumatoid Arthritis |
| CLL | Chronic Lymphocytic Leukemia |
| MALT | Mucosa Associated Lymphoid Tissue |
| NLPHL | Nodular Lymphocyte Predominant Hodgkin’s Lymphoma |

# Chapter 1

# Introduction

We are living in an era with an ageing population and growing demand for treating chronic conditions like cancer, rheumatoid arthritis, cardiovascular diseases, where biological therapy is on the rise. In this era, the introduction of biological similar AKA biosimilars has begun to revolutionize biological therapy by increasing access for patients in all the therapeutic arenas. This new class of drugs is intended to provide an acute and chronic therapeutic response similar to that of their biological counterparts but without any significant or substantial changes in effectiveness, potency, purity and safety of administration. Besides, in an environment now-a-days where health decisions are increasingly made based on value and cost, biosimilars are becoming an essential tool in the healthcare and biopharmaceutical industry by playing a vital role in improving patient access to needed medicines. They also started to generate huge global attention as safe biologic replacements in recent years. Expanding patients access and reduced healthcare expenditure remains to be the two major drivers of biosimilars' exponential rise including their rapid development in the biopharmaceutical industry (Chopra & Lopes, 2017). Biosimilars are the follow on biological products which are considered to be comparable in safety, quality and effectiveness to that of an existing authorized bio-therapeutic reference product. The introduction of biosimilars across gastroenterological, nephrological, oncological, hematological disciplines has a considerable scope to reshape biological therapy by improving access to patients (Khraishi et al., 2016). Biosimilars are developed globally, especially within the oncology segment, to meet heath care needs and to provide cancer patients more access to biological therapy as cancer imposes a massive threat on the healthcare system across worldwide. Many conventional supportive treatments indicate pharmaceutical agents for cancer patients. But in this era targeted biological therapies, drugs, biosimilars have begun to become an

increasingly core and important tool for cancer treatment (Verrill et al., 2019). Furthermore, biosimilars can improve access and provide low cost cancer treatment options. Among them, Rituximab is one of the most widely used biologics which has been indicated for the patients with CD-20 positive Non-Hodgins's Lymphoma (NHL) and its originator's patent has been expired in 2013 (in Europe) and in 2016 (in US). In the oncology segment of the healthcare, biosimilars have been currently approved for several drugs, in which the first biosimilar of Rituximab named as 'Truxima' has been authorized by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) with an indication for lymphoma treatment (Subramanian et al., 2017). Rituximab biosimilar authorization has reshaped B-cell Non-Hodgkin's Lymphoma (NHL) therapeutic choices and is now an indisputable treatment option. Thus, the Rituximab biosimilars play a major role in optimizing patient outcomes in the lymphoma treatment in order to improve access to biological therapy.

## 1.1 Aim of the Study

As biosimilar drugs have begun to dominate pharmaceutical companies' pipelines all over the world, particularly in the oncology sector, it is needed to comprehend and acknowledge the idea about the development and regulatory framework of biosimilars, as well as the need for the integration and uptake of biosimilars in the oncology segment around worldwide in the current perspective for the healthcare providers, researchers, patients, clinicians. To address this need, this study seeks to provide a comprehensive discussion about biosimilar development, its needs, increased integration in the global market along with its clinical and global regulatory considerations. Besides these, it is estimated at 19.3 million new cases of cancer worldwide and nearly 10.0 million deaths of cancer occurred in 2020. The global cancer burden is projected to be 28.4 million, with a 46% rise in transitioning countries (64% to 95%) by 2020 compared to those in transitioned countries (32% to 56%) due to

demographic changes, although increasing risk factors associated with globalization and growing economy may further exacerbate this. More than 100 types of cancer, lymphoma remained one of the leading causes of cancer death, with an estimated 259,793 deaths (2.6%) in 2020 which led to the study of the treatment options available for lymphoma. Focusing on lymphoma treatment with biosimilars of Rituximab, this review study aims to address the features and benefits of Rituximab biosimilars and their potential roles and boons in lymphoma treatment.

## 1.2 Objectives of the Study

This study's primary objective is to emphasize the integration of biosimilars in oncology treatment paradigms, need for the biosimilars in the current perspective along with its development and regulatory guidance, and in particular to specify the impact of Rituximab biosimilar in oncology segment. The review also explored the possible areas for which Rituximab biosimilar in the near future is likely to continue as a core component in lymphoma care choices.

# Chapter 2

# Methodology

This review involves a comprehensive overview on different aspects of biosimilars particularly the biosimilar Rituximab used in lymphoma treatment. Secondary data for this review paper was collected from peer-reviewed research articles (indexed in PubMed, Elsevier, Web of Science, Scopus, etc.), news articles, academic published papers, and web sites. Furthermore, articles from distinguished journals such as, Springer, Nature, Cells, The Lancet, MDPI, Frontiers, Bio drugs, Taylor and Francis were analysed for this study. Information and data were gathered from many publications with their insights which helped to identify the need of biosimilar in the oncology segment. All the information were compiled and appropriately referenced thus providing better understanding of biologics and biosimilars and the use of Rituximab in lymphoma treatment. Attempts were taken to identify missing information or gaps within the existing literature.

# Chapter 3

# Biosimilars

The increased costs and complexities involved in developing novel biotech products and recent expirations of originator patent of several widely used biologics prompted pharmaceutical companies to try to replicate existing products in order to maintain a constant stream of such biologics in the development pipeline. These follow-on biological products, also regarded as biosimilars, have been identified as products similar in terms of safety, purity, quality, efficacy to a licensed reference bio-therapeutic product. The biosimilar industry is expanding rapidly, and with the implementation of more biologically similar or bio-like medications, the patients' advantage for access and regulation of health care costs will continue to thrive. Biosimilars also achieve a major industry revival, with biosimilars released in 2019-2020 reaching 20-42 percent of their initial year's market share. These findings indicate that the uptake and adoption rate of newly launched biosimilars would be higher and more likely than was shown with earlier biosimilars and it will be attributed to increased education, familiarity, and expertise knowledge about biosimilars among health providers and patients (*Biologics & Biosimilars | PhRMA*, 2020).

## 3.1 Biologics and Biosimilars

Biologics are large, complex molecule obtained from living organisms using recombinant DNA methods or regulated gene expression that resemble natural biologics such as hormones, e.g., monoclonal antibody (Trastuzumab, Infliximab), soluble receptors (Etanercept) or recombinant DNA technology products such as human analog insulins and growth hormones. These are polypeptides, glyco-proteins and/or nucleic acids with much more complex molecular features than typical chemical drugs. Biologics are widely employed for treatment of diseases and therapeutic problems of multidisciplinary practices.

On the other hand, after the expiration of the patent(s) on first approved bio-drug products, copying and marketing of these biologics can be made accessible which will minimize the costs to the patients and will increase access to targeted treatment field? However, biopharmaceuticals or biologics are made by living cells. Owing to the inherent complexity and because of the two cell lines which have not been formed independently, biologics cannot be identically copied and replicated. As a consequence, it has added to the definition of 'biosimilar' recognizing that although biosimilars are close to the original product, they are not identical. Biosimilars are the drugs similar to the biological drugs that already have been licensed, hence similar but not identical, and therefore specific regulatory requirement for approval apply to biosimilars. So, a biosimilar is often termed a 'similar biological medicine' or a 'follow-on biologic' (in Japan, in USA) considered as drug which is similar to an already approved reference biopharmaceutical (Declerck, 2012; Pittman et al., 2019).

## 3.2 What are Biosimilars?

A biosimilar drug is characterized as highly similar to a licensed biologic reference drug including small changes in clinically inactive ingredients, for which there are no clinically significant disparities in quality, effectiveness and safety between the two drugs. Though the definition of the term 'Biosimilar' is not internationally standardized across regulatory bodies, a comparison of how regulatory authorities interpret the definition of biosimilar shows clear correlations and substantial resemblance among the agencies.

- Biosimilars are described by the FDA as biological products, which are quite similar to an approved FDA licensed reference product and lack clinically significant variations.
- The EMA defines biosimilar as a drug product very close to a biological medicine that has already been authorized.

- Biosimilar is characterized by the World Health Organization (WHO) as a bio-therapeutic product, equivalent in terms of its quality, safety, efficacy to an approved bio-therapeutic product comparison.
- Therapeutic Goods Administration (TGA) acknowledges biosimilar as the already registered version of biologic medication which, based on extensive comparability studies, shows similarities in the physical, biochemical and immunological characteristics, efficacy and potency.
- Pharmaceuticals and Medical Devices Agency (PMDA) describes biosimilar as the result of biotechnology, a product that is manufactured by another company, and that is equivalent to the licensed biotechnologically derived product.

The parallel between the meanings of biosimilar defined by these regulatory agencies can be broken down into two major themes: They are not generic products and copies of already licensed products which demonstrate a similarity to the reference product and it must need to be similar to that of a licensed or authorized biological product in respect of efficacy, quality and safety (Agbogbo et al., 2019).

Better affordability and thus, greater access to patients in contrast with biologics make a biosimilar significantly appealing (Rugo et al., 2016). As a result, of recent technological advancements, emerging legislation in the biopharmaceutical sector and cost problems, the concept of biosimilar has gained prominent support (Epstein et al., 2014).

## 3.3 Comparison between Biosimilar and Generic Drugs

Even though, biosimilars and generic drugs share the same commercial base, which means that they are commercialized after the expiry of the patent of original drug, still they are two distinctly different products when it comes to their structure, development, and regulatory

authorization. The comparison between biosimilars & generic drugs are given below (Table 1).

*Table 1: Comparison between biosimilar and generic drugs (Lee Ventola, 2013; Tkaczuk & Jacobs, 2016).*

| **Features** | **Biosimilars** | **Generic Drugs** |
|---|---|---|
| Identity, resemblance and similarity with reference product | Not completely identical, but highly similar | Exact identical like the originator reference product |
| Production source or synthesis | Obtained from living cells, Recombinant DNA technology or regulated gene expression is used | Produced from chemical synthesis process |
| Structural characteristics | Complex structural features including primary, secondary, tertiary, post- translational changes | Simple and basic molecular structure |
| Stability | To maintain stability, monitoring of manufacturing and production conditions is needed | Usually stable molecules. |
| Chemical structural features | Identical amino acid sequence, glycosylation and protein folding differentials are expected | Chemically identical as the reference one |
| Nomenclature | Diverse international biosimilar naming scheme is being used currently; no harmonized scheme | Same international non-proprietary name (INN) as the originator product |

| | | |
|---|---|---|
| | has been approved yet | |
| Immunogenicity | To detect immunogenicity proper surveillance and immunological tests are needed | Usually, non-immunogenic |
| Interchangeability | This product may or may not be interchangeable with the reference product. | Interchangeable with the reference product |
| Analytical characteristics | The final construction might not be described by the current available techniques, extent of structural resemblance to reference product is therefore uncertain | There are existing approaches for confirming similarity of the compound to the reference product |
| Complexity in production and manufacturing procedure | Complex and several steps are needed for purification, production and validation | Simple and synthesized from chemical reaction |
| Impact of any changes during manufacturing | Small process alterations will modify the protein's final structure and function | Perhaps insignificant since the final product is identical |
| Legislation pathway | The Biologics Price and Competition and Innovation Act of 2009 establish a foundation for a streamlined approval process for biosimilars, and the FDA has | The Hatch-Waxman Act authorizes generic drug approval via Abbreviated New Drug Application (ANDA). |

| | | |
|---|---|---|
| | issued final guidance. | |

## 3.4 The Need of Biosimilar Drugs

Biological drugs have seen significant advances in the treatment of severe and persistent debilitating diseases such as rheumatoid arthritis, inflammatory bowel syndrome, tumours, cancer and hematological malignancies. However, this breakthrough has been costly for biological therapy. As a consequence, many countries around the world are struggling with their annual drug budget as pharmaceutical usage rises, and new medicine, in particular biopharmaceutical products, is highly expensive. Biological drug products can cost up to €100,000 or more per year which causes them a financial burden. In many countries, gross spending on biologics rises 5% to 10% per year and the recent expiry of few widely used biologics' patent also add burden on the healthcare sector (Aapro, 2014). In the healthcare systems this situation is unsustainable. Under these circumstances, biosimilars - a new class of drugs comes up with similarly safe and efficacious replacements to innovative biological drugs. Also, these alternative versions of biologic drugs are being launched after the market exclusivity expire, contributing to lower costs, more accessibility and develop a headroom for innovation (Vulto, 2019). It is undeniably true that biological products are widely utilized in the prevention and treatment of multiple diseases. However, because of their increasing costs, healthcare expenditures crises worldwide as well as the expiry of the originator biologic patents, biosimilars have come on to the market (Zalcberg, 2018). They are more economical but offer a comparable and similar safety, efficacy and toxicity profile and do not vary clinically to their biological reference products. Consequently, a biosimilar is required to minimize healthcare expenses and expand patient access to novel therapeutic alternatives (Konstantinidou et al., 2020). And since many biologics' imminent patent expiry has become a major problem for conventional treatment choices to patients, it has unlocked the way to

both the development and manufacturing of follow-on biologics or biosimilar drugs. Furthermore, the integration of biosimilars in the next 10 years could save consumers up to $250 billion and expand access for an additional 120 million patients by 2025 to biological treatments. This will extend the therapeutic choices for the patients suffering from acute or chronic disorders and will permit a larger usage of biologics in general by offering more affordable treatment options to individuals who in the past have either forgone treatment or settles for less costly medicines (*Why Biosimilars Are Important for Treating Patients*, 2020; Horn, 2020). Biosimilars are therefore needed for delivering enormous savings in healthcare system and for greater access to treatment in the future years as biologic medicines continue to lose patenting (Horn, 2020).

## 3.5 Uses of Biosimilars in Disease Management

The biologic drug has been an indispensable tool in modern medicine since it was first introduced the 1980s. Advances in biologic research and development have stretched science's limits and offered lifesaving care for patients with deadly disease including cancer. Biological treatments have also enabled patients to make great strides in the treatment of debilitating illnesses including asthma, rheumatoid arthritis, cancer, cardiovascular diseases. Biologics are an innovative therapeutic choice for patients afflicted by chronic and life-threatening diseases; however, it is also associated with high prices and restricted patient access (Abraham, 2013). Fortunately, more accessible and cost-effective alternatives are starting to come into the market for many patients who depend on biologic treatment. With the loss of biologics' patent exclusivity, biosimilars are highly alike or similar to a previously licensed comparative biologic on the market. Biosimilars also play a pivotal role as they can provide competition on the market and extend patients' access to essential pharmaceutical drugs, much like the advent of generic medications more than 35 years ago (*Why Biosimilars Are Important for Treating Patients,* 2020). Biosimilars are also safe, reliable and affordable

drugs for the management of several diseases for example, chronic skin and bowel disorders, asthma, kidney disorders, cancer, hematologic malignancies, diabetes and many more. Some examples are given below- Infliximab biosimilars and Adalimumab biosimilars are used to treat inflammatory bowel disease (IBD). Infliximab biosimilars and Etanercept biosimilar is licensed for multiple rheumatic disorders. Trastuzumab biosimilars are used to treat breast cancer, stomach cancer. Rituximab approved biosimilars are indicated to treat lymphoma. Thus, biologic similar or biosimilars are continuously playing an essential role in multidisciplinary therapeutic fields (Khraishi et al., 2016).

# Chapter 4

# Biosimilar Development and Regulatory Framework

For the approval, development and ready availability of effective and safe biosimilar drugs rigorous scientifically suitable and clinically acceptable regulatory criteria and development guidance are required. A biosimilar must meet and uphold rigorous requirements prior to and after approval to assure trust, safety, patient protection and credibility of the healthcare system. The same production, safety, feasibility, quality criteria would be applicable to the biological products, including biosimilars. This would promote faith in biosimilars and contribute to accelerate the adoption and integration of more biosimilar drugs in future as well (Christl & Regulatory, 2020).

## 4.1 Development Process of Biosimilar

The biosimilar development was due to the economic success in biological therapy and its inevitable “patent cliff”- a marked reduction in revenues as they came up to the expiry of their originally patented products (*BIOSIMILAR DEVELOPMENT - Approval of Biosimilar Medicines Through Totality of the Evidence*, 2019). The structural complexity and the method of development of biologics distinguish their “patent cliff” from that of chemically synthesized drugs. Thus, the concept of biosimilars has received support and gained attention in the biopharmaceutical industry because of emerging technical advances, new legislation, and cost considerations.

The development process of a biological similar or biosimilar is distinguished and varied from the processes which are applied during the development of any biologic product. The manufacturing process of an originator biologic is proprietary. Thus, a pharmaceutical industry which produces a biosimilars will analyze and use reverse engineering to produce

that with structural and functional characteristics which are highly resembling (Agbogbo et al., 2019).

Biological products are typically larger, complex proteins generated with biological processes which require production within living cells that are difficult to thoroughly characterize. Also small structural changes following the translation phase will influence biological drug clinical results. Therefore, there is also a need of considerable expertise and experience to develop and manufacture a possible bio-similar approach of biological production to properly characterize the product of the originator and produce a biological product of equal therapeutic efficiency and safety close to the originator's one (Vandivort et al., 2020). Although the biosimilars cannot be regarded as the generic alternatives of the originator, a comprehensive non-clinical analysis confirms the functional and structural resemblance of the originator. This range of analyzes does not overshadow the need for equal clinical effectiveness and safety. This guideline has been used to establish detailed recommendations for approval of biosimilars for many regulatory bodies. Although are minor discrepancies among the guidance given by different regulatory bodies, the process usually entails a systematic and a step-by-step approach to show comparable therapeutic effectiveness and safety compared with the originator (Greenwald et al., 2018; Patel et al., 2017).

Other important criteria of biosimilar development are bio-similarity which is verified when in spite of small variations in clinically inactive ingredients, that biological product is extremely comparable to the reference product and there are no clinically substantial variations in efficacy, purity, potency, and safety in the product. Bio-similarity compliance standards developed by different regulatory authorities including WHO, FDA, EMA and these standards are science-oriented and broadly close to each other. A detailed comparison between the proposed biosimilar and the biological reference product for assessing the similarity is needed for a biosimilar approval process (Figure1).

A step-by-step procedure starts with a systemic comparison including structural comparision, and *in vitro* trait analysis as well as *in vivo* (animal) toxicity testing. Each stage depends on the extent and kind of data processed in previous stages. Also, on a product-specific basis, the nature and quantity of the data deemed to be adequate to show bio-similarities are calculated. The final clearance is subject to comparative clinical trials, with at least one analysis showing the purity, quality, safety and therapeutic effectiveness of the biosimilar medication containing an evaluation of immunogenicity, and pharmacodynamics (PD) or pharmacokinetics (PK) (Greenwald et al., 2018).

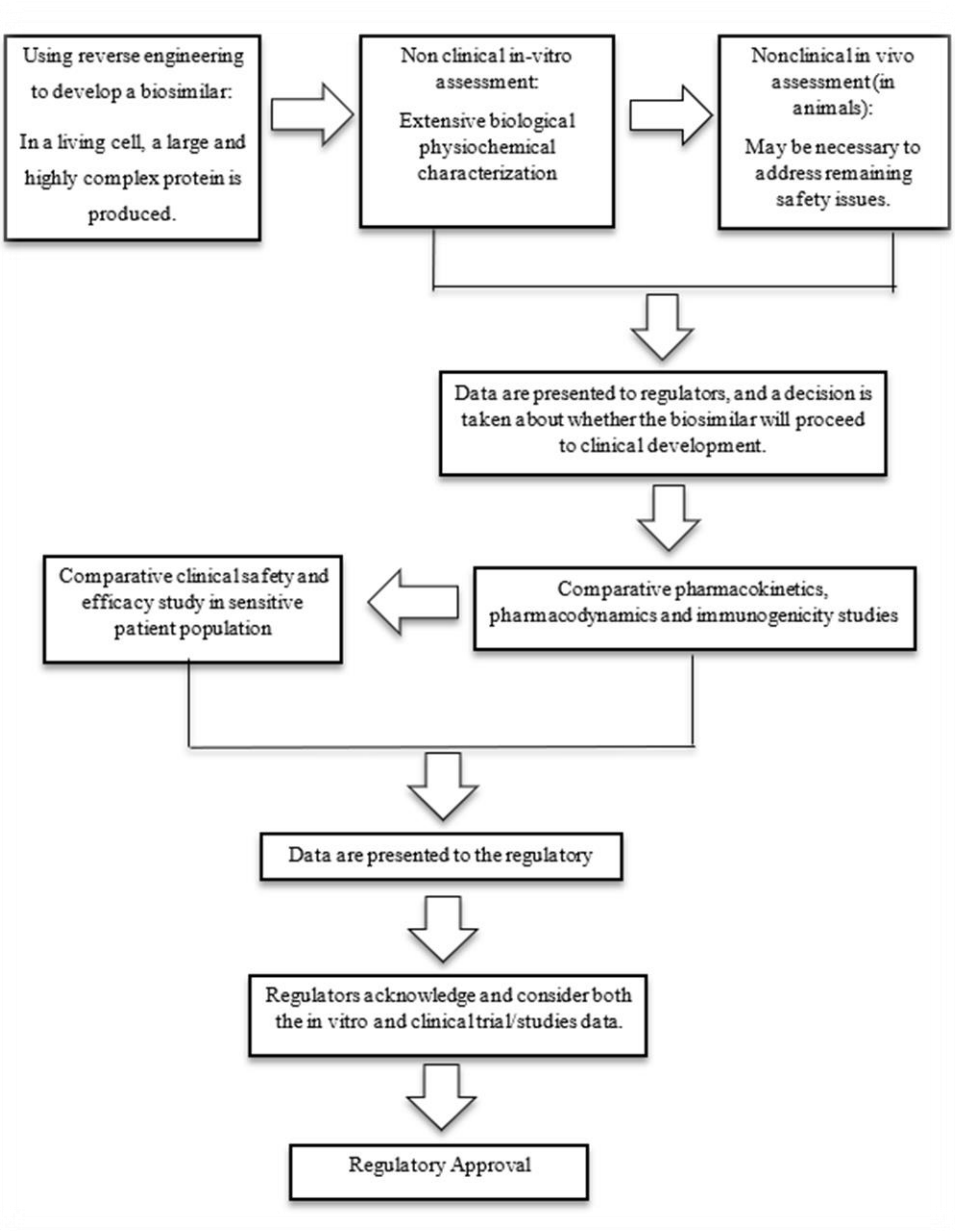


*Figure 1 : Biosimilar development process*

## 4.2 Clinical and Regulatory Considerations of Biosimilars

In the early 1980s, the development of biologics in the pharmaceutical industry started. However, the need for biosimilars became inevitable with their economic strain and patent cliff (a constant fall in revenue, as the biologics approach to the expiry of their patents). Several countries rigorously control their criteria of biosimilar approval, which guarantees their empirical alignment with scientifically agreed standards. The emergence of standardized

and harmonized global approval methods will make the acceptance of biosimilars simpler reduce the complexity of their regulatory framework. The adoption of internationally accepted regulatory guidelines will foster the interest of the patients and clinicians in prescribing and taking biosimilar drugs (Rathore & Bhargava, 2020).

The EMA was the first regulatory authority to set guidance on biosimilar drugs in 2005, a year before it was authorized for the first time. The European Union's (EU) states have the authority to enact any legislation relating to the manufacturing, processing, approval of biosimilars. This regulatory framework was followed by the WHO in 2009, which was already developed. Their legislation and regulation for biosimilars established internationally agreed standards for the launch of similar bio-therapeutic products (SBP) that are safe and effective. The primary aim of the WHO regulatory guidance was to support and assure the local regulatory authorities met global therapeutic production standards and guidelines. These standards were subsequently recognized by most nations, but only a few of them adopted their guidance on the basis of existing models.

The United States FDA was the late entrant into biosimilar enforcement with the Public Health Services Act (PHSA) allowing biologics. The Biologics Price Competition and Innovation Act (BPCIA) were already included in the Patient Protection and Affordable Care Act and later developed a modern biosimilar licensing process. BPCIA promised access to medicines at reasonable public prices and promoted creativity from businesses that produce originator biological products (Malhotra et al., 2015; Rahman Kabir et al., 2019; Rugo et al., 2016).

Moreover, biosimilars approval legislative criteria are broadly consistent across the EMA, WHO, and FDA guidelines. Although there are small variations, such terminology differences, establishing bio-similarities requires a step-by-step approach. Comparative

evaluations including analytical, non-clinical, and clinical trials are also included in these specified regulatory pathways. Apart from these, other regulatory authorities of different countries have also made their guidelines for biosimilars. A brief discussion about regulatory guidelines on bio similarity from different regulatory authorities around the globe is given below:

**European Medicines Agency (EMA) -** The EU is the forefather of the biosimilar sector, as shown by the number of approved products, market dimensions, guidelines promulgation, and so on. The EMA was the first regulatory body to introduce well-documented regulatory approaches to the approval of biosimilar products, which were different from generic products. In the guidance approved by the EMA, clear definitions have been defined in greater depth than generics about the analysis, pre-clinical and clinical evidence requirements. A comprehensive study of comparability between the same biologic and referencing products is detailed in the EMA Guideline. EMA published general guidance for quality issues, non-clinical and clinical concerns, covering quality, accuracy, production methods, safety, effectiveness issues.

**United States of America (US FDA) -** The FDA had become a late entrant to biosimilars regulatory pathway. In 2012, FDA published three draft guidelines proposing step-by-step approaches to prove bio-similarity, guidelines included analytical trials, animal trials, human clinical tests including measure of PK and PD, immunogenicity, safety and efficacy evidence, and equivalence studies that illustrate upper and lower margin comparability.

**World Health Organization (WHO) -** The WHO guidelines draw up some fundamental principles that are needed for the clearance of a biosimilar to guarantee the safety, efficacy, and consistency of bio-therapeutic products. This assures effective regulatory submissions in the most important pharmaceutical areas worldwide. It offers guidance on reference products,

quality, non-clinical evidence, pharmacovigilance, clinical trial, etc. Since the WHO guidelines were preceded chronologically by the EMA guidelines, they were not geographically specific and therefore, became a template for several other national regulators authority (NRA).

**Japan (Pharmaceuticals and Medical Devices Agency) -** The PMDA of Japan developed biosimilar regulatory approaches in early 2009. The regulatory framework is highly similar and quite close to EU. In Japan as well, the biosimilars legislation is mostly following the guidelines of the International Harmonization Committee, in particular, the Q5E guideline, dealing with improvement in the manufacturing process and comparability assessment, and the Q6B guideline about product comparability. Via consultations with pharmaceutical companies, PMDA has been promoting biosimilar developments in Japan and has also achieved fast growth in this field.

**Canada (Health Canada) -** Health Canada is the regulatory authority that evaluates the safety, quality and efficiency of biologics and follow-on biologics developed when the originator patents are expired. In 2010, Health Canada published 'Guidance for Sponsor: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)'. Similar to WHO, the Canadian guidelines recommends that the biologic drug that was authorized based on a complete clinical data package with sufficient safety and efficacy data could qualify as a suitable reference. In addition, specialized analytical tests should be conducted for thorough characterization and the product should follow the required specified criteria (Malhotra et al., 2015; Wang & Chow, 2012).

**Comparison of Biosimilar Development Process among Different Regulatory Authorities**

There are few differences which are noticed in the development guidelines given by different regulatory authorities like EMA, FDA, WHO etc. The differences among guideline in the development process of biosimilar are given below (Table 2).

*Table 2: Comparison of biosimilar development process among different agencies (Socinski et al., 2015)*

| | EMA Guidelines | U.S FDA Guidelines | Health Canada Guidelines | WHO Guidelines |
|---|---|---|---|---|
| *In-vitro* non-clinical trials or studies | Target binding; signal transduction, cells of relevance functional activity/viability | Functional analysis, structural studies | Cell-based or receptor-binding assays | Cell-based or receptor-binding tests |
| *In vivo* non-clinical studies | When *in vitro* comparison is acceptable and reasonable without factors blocking human entry directly, there might be | Except not listed by the FDA, checks for animal toxicity, animal PK and PD tests and animal immunogenicity | PD studies relevant to clinical application, toxicity (including toxic kinetic parameters), and | Relevant biological/pharmaco dynamics activity, toxicity study |

| | | | | |
|---|---|---|---|---|
| | no need for animal trials (risk-based approach) | should be provided | other relevant safety observations | |
| Clinical studies | Comparison with PK (and PD) with therapeutic effectiveness and safety trials, where appropriate | Assessment of immunogenicity, PK, PD to demonstrate safety profile | Safety, efficacy, quality studies by PK, PD and immunogenicity assessments | Includes pharmacodynamics and pharmacokinetics profile |
| Labelling | Labelling will copy label of reference product | Clinical evidence for all biosimilar and reference products would likely be used. | The product monograph must not be fully replicated, the assertion of product being a biosimilar, the core evidence used for a judgment on the marketing authorization | May involve characterizing and carrying out biologically similar studies, but as similar as possible to the reference product label |

## 4.3 Interchangeability

The US FDA released final guidelines for manufacturers aimed at showing the interchangeability of biosimilar drugs on May 10, 2019. The aim is to help the sponsors demonstrate that, the proposed therapeutic protein product may be interchanged with a reference product, to apply market application or supplements under section351 (k) of the PHSA. The ultimate objective of the manufacturer to determine its interchangeability is to show that in a given patient, biosimilar products will yield the same clinical effects as the reference product (Mckinnon et al., 2018; Olech, 2016).

FDA specifies interchangeability to imply that "the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product". Until the FDA approves the biosimilar as interchangeable, pharmacists may not replace the biosimilar for their reference product unlike the generic small-molecular drugs which are substituted after FDA approval (*New FDA Guidance On Biosimilar Interchangeability*, 2020). The final guidance defines the studies and data necessary to achieve this standard. The level of complexity of a product, its clinical expertise, risk analyses, and post-marketing data will influence the nature and amount of data required to support an interchangeability presentation.

Data needed to comply with section 351(k)(4)(A) may include:

- Identification and analysis of critical quality attributes,
- Mechanism of action analysis in any stage of usage,
- Study of pharmacokinetics (PK) among various patient groups,
- Assessment of some immunogenicity risk variation among various patient groups,
- Examination of any toxicity variations in each use and patient population status, and,
- Additional safety and efficacy factor information.

The FDA mandates that the sponsors conduct more than once drug switch trials to an interchangeable product and a referring product for the provision of 351(k)(4)(B), which measure treatment differences occurring in two or more alternate doses (interval switching) (Mckinnon et al.,2018; *New FDA Guidance On Biosimilar Interchangeability*, 2020). In addition, to replacing the clinical research/ trials needed to show bio-similarity, the switching studies focuses on the clinical impacts of a switch between a reference product and its similar. Finally, because of the complexities of biological products and the distinctive features of an interchangeability evaluation of individual products, sponsor should pursue initial consultation and, in any step of the process, should continue working closely with FDA to ensure an efficient and accurate process to show the interchangeability of a biological product selected (*ASHP Issue Brief: Biosimilar Interchangeability Guidance*, 2019).

## 4.4 Immunogenicity

Several biosimilars have been used clinically, with many under trial run. As other biological products, biosimilars can induce unwanted immune responses, which can significantly impact therapeutic efficacy. Therefore, an essential aspect of the head-to-head immunogenicity assessment of biosimilars and their benchmarking biologics should be included in a biosimilar development process. Regulators must be capable to interpret the immunogenicity finding in an assay-specific context and also in terms of clinical pharmacology, efficacy, and safety to completely realize its clinical significance (Markus et al., 2017).

Several regulatory bodies including EMA, WHO, and US FDA have released guidelines for the development of biosimilars. In the last decade, several additional countries have also introduced national standards which focus on the same concepts as EMA, WHO and FDA. The development of biological similarities comprises a step-by-step method for showing

similarity with reference biological products and head-to-head comparability studies focused on the entirety of evidence of the scientific, clinical and non-clinical trial results.

Head-to-head clinical immunogenicity monitoring in an adequately sensitive study population as part of this development pathway (i.e., the patient population in which the study biologics are most likely to elicit an immune response is recommended by the EMA, WHO, and FDA as a key criterion for the regulatory evaluation of bio-similarity, or assess clinical immunogenicity, a fully-validated, tiered approach for detection of Antidrug antibodies (ADAs) is recommended. The four main assessment stages involve: Antidrug antibody screening, ADA confirmation assays, ADA characterization and titration, and assessment of neutralizing capacity. Each of these stages may be performed using a variety of bioanalytical platforms, and the results of these evaluations can be viewed as part of the integrated pharmacology, reliability, and efficacy review that is required to determine the clinical validity of immunogenicity evidence (Schreitmüller et al., 2019).

## 4.5 Naming

The word biosimilar is a regulatory term which is different to the international non-proprietary name (INN) of the biologics issued by the World Health Organization (WHO). While the INN system, first adopted 50 years ago, establishes global pharmaceutical nomenclature rules, biosimilar naming is being debated in many fields. Universal harmonization on biosimilar names is not possible, since pharmacovigilance affects the recognition of biosimilars. The WHO recommendation for biosimilar identification indicated that the INN of the reference product should not include in non- glycosylated biosimilars.; where areas Greek letter suffixes must be added to INN of glycosylated biosimilars. WHO suggests every biologic (not only biosimilars) should have a two- part name. The first half is INN and the second part is a 4-letter code (not INN) for the identification of biological

prescribing, dispensing, pharmacovigilance drugs. This would help also in identifying biological substances. Some countries have adopted their biosimilar naming policies. On this naming concern, FDA issued a draft guideline document 'Non-proprietary Naming of Biological Products' in January 2017 (FDA, 2017; Socal et al., 2020). Nevertheless, in March 2019, FDA published new guidelines on biologics and biosimilars naming convention defined as the "Non-Proprietary Naming of Biological Products: Update Guidance for Industry". It described the rationale of the FDA on the designation of biological products that does not include the FDA-designated suffixes approved under section 351 of the Public Health Services Act (PHS). To achieve the goals of the naming convention mentioned in the previous guideline, the non-proprietary names of these products must not be revised. The FDA claims this approach is appropriate for the implementation of the naming convention to 1) To promote pharmacovigilance for origin biological products, associated biosimilar products, and interchangeable products where other means are not readily available to trace a particular dispensed product, 2) Enable the accurate identification by health care practitioners and patients of these biological products, 3) aid to avoid inadvertent biological substitution (FDA, 2017; *Nonproprietary Naming of Biological Products: Update Guidance for Industry | FDA*, 2019).

The names of biosimilars must be conveniently distinct from those of the reference products and those of other biosimilar medicines, in accordance with the Directive issued by the Japanese Pharmaceutical and Medical Devices Agency (PMDA). In Europe, approved biosimilars share the INN according to their reference and EMA recommends that the terms for the trade, appearance and packaging should differ. Although these regulatory authorities vary in the naming guidelines for biosimilars, most of them agree that to develop and maintain effective pharmacovigilance systems, they should have a distinct brand name and/or a distinct non-proprietary biosimilar name (Grampp & Felix, 2015).

## 4.6 Post-Approval Surveillance

Manufacturing difficulty and subtle discrepancies between biologics and associated biosimilars result in product-related, procedure, or host-related issues. Different comparative studies, which concentrate on preclinical immunogenicity assessments, should therefore be designed. Besides, biosimilar manufacturers must implement long term pharmacovigilance trials following biosimilar authorization (Rathore & Bhargava, 2020). Clinical experiments required for biosimilar clearance are often conducted in a small sample group, making it difficult to pinpoint any potential adverse effects, especially uncommon and delayed ones. Robust post-approval monitoring, therefore, remains the key to identifying, assessing, and barring harmful events and others questionable issues, such as elucidating interchangeability. The proper involvement of healthcare experts in monitoring documents, and in surveillance can also be seen as a significant contributor to safety and other associated issues that take into consideration biosimilars. It is also imperative to serialize biosimilars and to identify safety and consistency issues in each box in the same batch, taking into consideration that biosimilars and biologics are extremely light sensitive, elevated temperatures, and are susceptible to microbial and viral contaminations. Even small changes in manufacturing processes or devices, the handling, and the closure of products could affect the safety, quality, effectiveness of biosimilar drugs (Halimi et al., 2020; Grampp & Felix, 2015). Therefore, strong post-approval monitoring remains a key component of detection, assessment, and prohibition of adverse effects of biosimilars.

## 4.7 Challenges in Adoption and Use

The adoption of biosimilar provides a breakthrough for manufacturer and expands alternative options for payers, doctors, and patients by providing a cheaper variant of biologics that have proved useful therapy options for chronic patients. Despite the fact that biosimilars claim to be reliable and safe alternatives to biologics, a number of obstacles impede their adoption and

use. Several difficult issues surround biosimilar adoption, including regulatory pathways, safety, quality issues, cost-benefit analysis, and comparability. To develop the catalyst for biological innovation and competitiveness on the market and to lower expense, the WHO, FDA, EMA, and other regulatory authorities have developed an abbreviated pathway for biosimilars' regulatory approval. Challenges for the adoption of therapeutic biosimilars persist in the world, including lack of targeted education for clinicians and patients, residual questions about effectiveness and safety, and activities including 'pay for delay' (Epstein et al., 2014; Markus et al., 2017).

Other obstacles include designing suitable clinical tests with relevant comparability endpoints, generating clinical/patient interest in enrolment for this studies, limited guidelines on extrapolation of an authorized biosimilar, possibility of immunological activities in the research patient, interchangeability with the originator product, lack of skill and expertise among healthcare professionals and patients about the potency and safety of biosimilars, etc. (I. Chopra et al., 2018; R. Chopra & Lopes, 2017). The usage of biosimilar still has become influenced by many problems, mostly related to costs of care, including the cost of medication, patient accessibility, and inclusion into the formulary and algorithms for treatment management. While biosimilar drugs may serve as an affordable alternative for brand-name drugs or biologics, these are the possible challenges to their usage and path of adoption.

# Chapter 5

# Cancer and Biosimilars

Cancer puts a significant and growing strain on health systems across the world. About 20% of cancer patients and family members expend about $20,000 annually in gross out-of-pocket costs on the treatment and care of cancer. Fortunately, there as advanced therapeutic category of biological therapy, including biosimilar drugs, which has the potential to expand access to more people diagnosed with cancer and to promote better outcomes. This new class of drugs AKA biosimilars- are quite close and similar variants of licensed biologics – have been seen to be capable of creating cost efficiency for individuals, healthcare facilities as a whole since the United States first introduced them in 2015 (*Biosimilars in Cancer Care: Insights From 2020 and Expectations for 2021* - *Cancer Therapy Advisor,* 2021). Over the last year, we have begun to see the momentum in the oncologic biosimilar industry and the real opportunities it can provide. The forthcoming patent of some widely used biological oncology products has opened the doors for the development and manufacture of subsequent biologic similar or biosimilars. Increasing biosimilars adoption in oncology sector thus provides a vital approach to reduce healthcare expenses and expanding patient access to effective cancer therapies (Aapro, 2014). Until now, only a few licensed and authorized cancer biosimilars exist, but many more of them will soon enter the market (Konstantinidou et al., 2020).

## 5.1 Cancer and Types of Cancers

Cancer is a debilitating illness that affects millions of people every day. Cancer is a broad group of diseases that can originate in nearly every organ or tissues in the body if abnormal cells develop uncontrollably, reach beyond their natural limits, or infiltrate the adjacent areas in the body. Also, this process is called metastasizing and is a major cause of death from

cancer. Cancer arises by consecutive mutations in genes that alter cellular function (Hassanpour & Dehghani, 2017). In all forms of cancer, certain cells of the body tend to differentiate without halting and spread to adjacent tissues. One out of every five individuals globally develop cancer during their lives, and one out of eight men and one in eleven women die because of it. It is a crucial problem impacting the welfare of all communities across worldwide.

The highest proportion of cancer arises in men respectively in the prostate, lungs, colon, and rectum. In women, breast, lung and bronchus cancer, colony, uterine corps and thyroid are the most often seen occurrence of cancer. About 100 cancers are identified. Types of cancer are usually referred to the organ or tissue of cancer in which it occurs. For instance: Lung cancer begins in the lung cells, brain cancer begins in the brain cells. Cancer may also be defined as a kind of cell, such as epithelial cells or squamous cells. Examples of certain cancer divisions beginning with specific cell types are: Carcinoma, squamous cell carcinoma, lymphoma, melanoma, myeloma and others (*What Is Cancer? - National Cancer Institute*, 2021).

## 5.2 Global Scenario of Cancer

In any nation, cancer is a major cause of death and a significant deterrent to rising life expectancy. Cancer is the first or second leading cause of death before the age of 70 in 112 out of 183 nations, and places third or fourth in a further 23 countries, according to figures given by the WHO in 2019. Cancer accounts for around 15% of all deaths globally per year (Renner et al., 2013). According to the International Agency for Cancer Research (IARC), in 2020 the worldwide prevalence of cancer is estimated to be 19.3 million new infections and 10.0 million deaths (Sung et al., 2021).

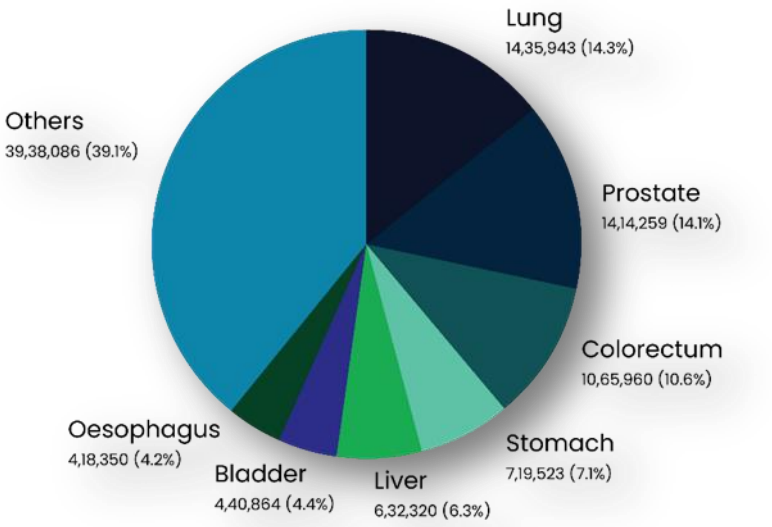


*Figure 2 : Estimated numbers of new cancer cases in male in 2020 (GLOBOCAN 2020: New Global Cancer Data | UICC, 2020)*

Figures 2 and 3 shows the estimated numbers of new cancer cases according to gender in 2020. It is now anticipated that 1.9 million additional diagnoses of cancer and 608,570 more mortalities would only arise in the USA in 2021 (Siegel et al., 2021). Worldwide cancer deaths are expected to begin rise, with a predicted 11.5 million deaths in 2030 with the global prevalence of cancer estimated to be 28.4 million in 2040 (Fan, 2009).

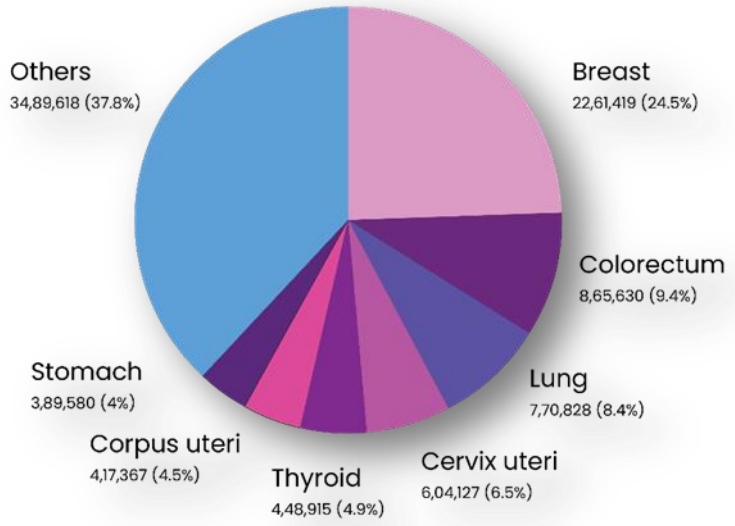


*Figure 3 : Estimated numbers of new cancer cases in female in 2020 (GLOBOCAN 2020: New Global Cancer Data | UICC, 2020)*

Furthermore, the IARC's estimate showed that more than 50 million individuals had been diagnosed with cancer in five years. Globally aging demographics and socio-economic risk factors remain among the major factors driving the rise. Thus, the prevalence of cancer continues to rise globally, exerting enormous physical, mental, and financial pressure on patients, households, governments, and healthcare services. Many health services in low and middle incoming countries are less able to cope with this challenge and many cancer patients worldwide do not have access to prompt diagnostics and treatments. The complexity of the treatment of cancer demands innovative approaches since the existing health care infrastructure faces obstacle to tackle the continuing burden of cancer. The lack of understanding of cancer, education and ability among health professional, lack of access of life-long therapy and palliative treatment, high cost of anti-cancer drugs, patent expiry of biologics are also causing difficulties in the health care sector. Any substantial decrease in the

cost of drugs, and biologically similar therapeutic agents (biosimilars) will therefore ensure the benefit of patients and will give more accessibility to cancer treatment (Renner et al., 2013).

## 5.3 Rationale for Development of Biosimilar in Cancer Care

The prevalence of cancer is growing considerably in almost all countries which puts a major strain on healthcare services across the world. The expenses of cancer drugs are rising, mainly propelled by the advent of modern, innovative cancer therapies. This creates concerns regarding the potential viability of cancer care and poses major obstacles for decision-makers in supplying patients with access to drugs and effective cancer therapies. Also, the effects of the COVID-19 pandemic not only affected cancer services; it also strengthened the need to make more effective use of existing health care infrastructure (Zinzani et al., 2019). Under these conditions, biosimilars will play a vital role in alleviating our overburdened healthcare system and ensuring that millions of patients can continue to provide access to life- changing biotherapy thus driving the much-needed efficiency and sustainability of cancer treatment (Remus, 2020). Moreover, biosimilars are set to start the new era of cancer care. As appropriately manufactured and used, these drugs allow health services around the world to provide safe and effective medication for more people with cancer than ever before. In short, biosimilars deliver an incredible opportunity for safe and effective drug choices that increases the sustainability and affordability of cancer treatment (*Biosimilars Create Opportunities for Sustainable Cancer Care*, 2017).

- **Impact of Oncology Biosimilars on the Sustainability of Healthcare System**

With several biosimilars for Trastuzumab, Rituximab, and Bevacizumab already approved by several regulatory authorities and many more currently under trial, the inclusion of biosimilars into oncology therapy offers a unique opportunity for cost-savings. Economic

benefits of biosimilars usage should be anticipated within a comparatively short period, with economic modelling finding that the launch of biosimilars for the top three oncology agents is projected to make savings of up to €2 billion on all European markets by 2021 alone. There may be assumed to be significant cross-country (and internal) heterogeneity affected by awareness, approval, and national agreements on pricing/substitution recommendations by practitioners or patients (thus affecting prescription). The balance between the timing and the effects of biosimilars on the market (and thus on healthcare budgets) depends on three major criteria: evidence availability (in both regulatory and realistic safety and effectiveness), efficient coordination by health care workers and patients, opportunity for investments in an acceptable prospect of benefit. The competition for biosimilar development is growing which influences the marketplace dynamics (Henry & Taylor, 2014). The challenge is to retain and align a vigorous economy with the race to achieve the lowest possible costs. The concept of sustainability is also becoming extremely relevant. It is also necessary to avoid the pitfall of a biosimilar capturing a significant market share through substantial cost decreases, leaving little space for maneuvers for newly arrived biosimilars to maintain the sustainability of the healthcare sector (Wolff-Holz et al., 2018).

## 5.4 Global Market Share of Biosimilar in Oncology Segment

Cancer is recognized worldwide as the second leading cause of death. Naturally, pharmaceutical firms have increased the supply of cancer therapy medicines to cope with such a huge pool of patients. Since the biological medicines cost a lot, the stage for in the introduction of biosimilar drugs is set. Based on these projections, the demand for oncology biosimilars is aiming for a promising future with a compound annual growth rate (CAGR) of 29.4 percent in 2022. The market of biosimilar is segmented by applications (blood disorders, growth hormone deficiency, oncology and others). In particular, the oncology segment dominates the global biosimilar market because of the high incidence of lungs, liver,

colorectal, and blood cancer. It is predicted that the oncology sector would hold the largest economy in the biosimilars market and the growth of the market analyzed over the expected period would be driven by a rising number of cancer cases worldwide. In particular, over the forecast timeframe (2019-2024), the blood cancer category is expected to grow at an incredible 33.0 percent of CAGR (Figure 4). This is largely due to the number of novel drugs in the pipeline of the manufacturers. More than 1/5 of the overall oncology biosimilars market is projected to capture by blood cancer segment.

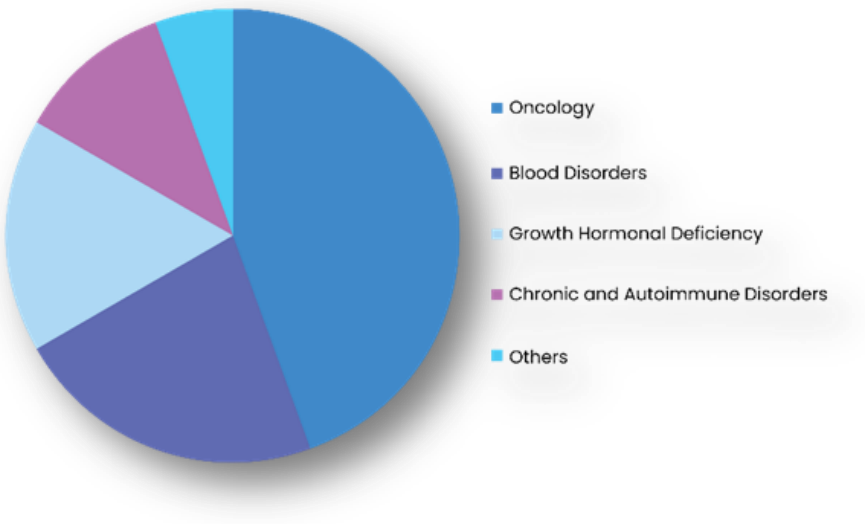


*Figure 4 : Biosimilar Market by revenue share (%) by application, Global (Biosimilars Market Size & Share | Industry Report, (2018-2025), 2018)*

In addition, the research initiatives from key players and enhanced regulatory approvals are expected to fuel the analysed market growth. As a result of the aforementioned factors, the biosimilar market in the oncology segment is expected to see substantial growth over the upcoming years (*Biosimilars Market | Growth, Trends, and Forecast (2019-2024)*, 2019).

- **Examples of FDA and EMA approved Biosimilars for Cancer**

Biosimilars licensed by the FDA could be used for the treatment of breast, liver, blood, colorectal, and other cancers. Few examples of cancer related biosimilars information are given below-

- FDA approved first biosimilar, Figrastim-sndz (Zarxio) in March 2015 which helps body to fight against any infection. It stimulates the body to produce more white blood cells. Its reference drug name is Figrastim (Neupogen).
- FDA licensed Trastuzumab-dkst (Ogivri), Trastuzumab-anns (Kanjinti), Trastuzumab-pkrb (Herzuma), Trastuzumab-qyyp (Trazimera), Trastuzumab-dttb (Ontruzant) to treat breast cancers and certain stomach cancers. Their reference product is Trastuzumab (Herceptin).
- The FDA approved Rituximab-abbs (Truxima) in November, 2018 as the first biosimilar to treat patients with NHL. Its reference drug is Rituximab (Rituxan). Rituximab-pvvr (Ruxience) also got approval from FDA for same indications.
- Herceptin's biosimilars - Ontruzant, Trazimera, Kanjinti became approved by the FDA in 2019 to treat patients with breast or meatsatic stomach cancer.
- Ruxience - the second biosimilar to Rituxan (Rituximab) also approved to treat adult patients with CD20 positive B-cell NHL as a single agent or as a combination therapy along with chemotherapy.
- The FDA approved Pfizer's Nyvepria (Pelfigrastim-apgf), a biosimilar of Amgen's Neulasta, Nyvperia to treat patients with neutropenia.
- On December, 2020 U.S FDA approved Riabni - third approved biosimilar to Rituxan (Rituximab), for the treatment of adult patients with NHL, Chronic lymphocytic

leukaemia (CLL), Microscopic Polyangitiis (*Biosimilar Product Information | FDA*, 2020; Franceschetti & Caldeira, 2018).

Some examples of EMA approved biosimilars to treat cancer are given below-

- EMA approved Epoetin alfa (Abseamed) for cancer on 27 August 2007. It also approved Filgrastim (Accofil) for neutropenia on 17 September 2014.
- EMA approved Bevacizumab (Aybintio) indicating for breast neoplasms, colorectal neoplasms, non-small-cell lung carcinoma, ovarian neoplasms, uterine cervical neoplasms on 19 August 2020.
- EMA approved Bevacizumab (Aybintio) indicating for breast cancer on 19 August 2020. It approved Rituximab (Blitzima) for NHL, CLL in 2017.
- EMA approved CT-P10 Truxima (Rituximab) for the treatment of the patients with NHL, and for other indications which were also indicated for the biologic 'Mabthera' in February, 2017.
- It also approved Pegfilgrastim (Cegfila) for neutropenia on 19 Dec 2019. EMA also approved rituximab (Truxima) indicating NHL, chronic lymphocytic leukaemia (CLL), Granulomatosis with polyangiitis on 17 February, 2017.
- EMA approved Rituximab (Ruxience) indicating NHL, CLL on 1 April, 2020.
- It also approved Trastuzumab biosimilar for breast cancer treatment (*Biosimilars Approved in Europe / General / Biosimilars / Home - GaBI Online - Generics and Biosimilars Initiative*, 2021).

# Chapter 6

# Lymphoma and its Types

One of the most complex and heterogeneous disorder sets in a single form of malignancy is lymphoid malignancies. Lymphoma includes a subset of haematologically differentiated lymphocytic malignancies arising from B and T lymphocytes. Usually, they are classified as Hodgkin's and Non-Hodgkin's lymphoma. Hodgkin's lymphoma (HL) comes from B cells or their progeny and Non- Hodgkin's lymphoma (NHL) are identified in 21 subtypes of B cells and 15 subtypes of T cell malignancies by the WHO, which account for about 80-90% of lymphomas. Our increasingly developing understanding about lymphoma in recent years has provided us new ways to stratify patients, and would possible contribute to more reasonable tailoring of treatment which has offered us the chance to treat these conditions more precisely (Fisher, 2008; *Lymphoma - an Overview | ScienceDirect Topics*, 2013).

## 6.1 What is Lymphoma?

Our immune system usually defends us from any kind of harm. In lymphoma, however, the elements of the immune system switch against us and become a malignant force. Lymphoma is a heterogeneous lymphoid malignancy marked by the proliferation of a lymphoid cell or its precursor. They are a heterogeneous group of hematopoietic malignant tumors, which are distinguished by the aberrant spread of mature lymphoid cells or their precursors (Storck et al., 2019). In other terms, lymphoma can be referred to as a cancer of the lymph (or lymphatic system) which is important functional part of our immune system. It usually defends our body from any infections and diseases and also, gathers, kills invading species such as bacteria, virus, and irregular cells (Shanbhag & Ambinder, 2018).

The lymph system is the formation of lymphatic hubs and vessels which transport lymph fluid throughout the body. It comprises disease battling white blood cells. Lymph nodes are

used to trap and annihilate microscopic pathogens and infections to deter the transmission of the disease. Although the lymph framework usually protects our body, lymph cells called lymphocytes may become harmful. The terms of malignant growth that arise in the lymphatic system are known as lymphomas. It is a form of cancer that begins in infection-fighting cells of the immune system known as lymphocytes. Lymphocytes are at the center of the lymphatic system; lymph, spleen, bone marrow, thymus and other parts. Right when anyone develops lymphoma, lymphocytes start changing and become out of control. They start dividing abnormally and do not die when they should. Furthermore, when anyone has lymphoma, abnormal lymphocytes can collect nearly everywhere in his body (Sethi, 2020). It commonly develops in the lymph nodes in the neck, armpit, or in the groin. It may also develop in lymphatic nodes and tissues deeper inside our body. Lymphoma also exists inside the bone marrow of certain individuals. Some regions of the body, such as the breast, belly, scalp, intestine, liver are less often affected by lymphoma (Walter, 2013; Zain & Kwak, 2017).

## 6.2 Different Forms of Lymphoma

Lymphoma is one of the most prevalent type of cancer in the world. There are a variety of common forms of lymphoma. There are also a large number of recognized subtypes of lymphoma. It can have several symptoms based on the form and subtypes and where it is in the body. A number of classification schemes for lymphoma have been established to indicate the different forms of it. The WHO classification released in 2001 and modified in 2008 was focused on the foundation laid down in the 'Revised European-American Lymphoma Classification' (REAL). This system distinguishes lymphoma by cell types and defines molecular, cytogenic features. The five groups classified by this scheme are given below-

1. Mature B cell neoplasms,

2. Precursor lymphoid neoplasm,
3. Mature T cell and natural killer (NK) cell neoplasm,
4. Hodgkin's Lymphoma,
5. Immunodeficiency-associated lymphoproliferative disorders.

These five groups also consists of several subtypes (Lymphoma association, 2020). There are a vast variety of known subtypes of lymphoma among these groups, and it is beyond the reach to address each of them separately. Among these variety subtypes of lymphoma, the major subtypes comprise HL and the most common NHL which would the centre of our focus in this study.

**Hodgkin's Lymphoma:** HL is an unusual hematopoietic neoplasm characterized by cancerous Reed-Sternberg cells**.** Nearly,15% of all lymphoma is HL (Boyne, 2008). In the United States, about 9000 people are diagnosed with HL per year and 2000 HL patients are diagnosed annually in the United Kingdom. The bimodal distribution of HL is initially highest among young adults from 20-24 years of age and the latter peak is second among adults aged 70 to 80, but this may take place at all ages. In men, with an occurrence ratio 1.2:1, the disease is slightly more common. It is not clear what the cause of HL is, but it is strongly related to Epstein- Barr virus infection, which in 45% cases is involved with HL. It is more likely in immune-compromised patients and an 11-fold increase in risk of HL is associated with HIV infection. Furthermore, HL is classified into classical HL (cHL) and nodular lymphocyte predominant HL (NLPHL) dependent on morphology and immunohistochemistry (Shanbhag & Ambinder, 2018).

**Non-Hodgkin's Lymphoma:** About 90% of lymphoma patients have Non-Hodgkin Lymphoma (NHL). NHL is a heterogeneous group of lymphocytic malignancy that are far less predictable than HL and therefore far more likely to spread in extra nodal places. Diffuse

large B-cell lymphoma (DLBCL) (about 30%) and follicular lymphoma (FL) (about 20%) are by far the most common form of NHL. Many other NHL subtypes are more than 10 percent prevalent.

NHL is the sixth most frequent cause of cancer- related mortality in the United States behind kidney, breast, lungs, colorectal, and bladder cancer (Singh et al., 2020). NHL that is slow growing is known as indolent or low-grade and which is fast-growing is called aggressive or high grade.

Slow-growing or indolent NHL consists of subtypes of

- Follicular Lymphoma (FL)
- Lymphoplasmacytic lymphoma
- Cutaneous T-cell lymphoma
- Marginal zone lymphoma
- Mucosa associated lymphoid tissue (MALT) lymphoma,

Fast-growing or aggressive NHL includes subtypes of-

- Diffuse large B-cell lymphoma (DLBCL)
- Anaplastic large cell lymphoma
- AIDS- associated lymphoma
- Lymphoblastic lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Mucosa associated lymphoid tissue (MALT) lymphoma (transformed)

## 6.3 Prevalence of Lymphoma Cases Worldwide

During the last decade, the prevalence of lymphoma cases has been constantly increasing globally. The most prevalent form NHL ranks 5$^{th}$ to 9$^{th}$ most frequent type-e of cancer around the world, representing around 4-6% of all cancer cases. A projected number of 544,352 individuals was anticipated to be diagnosed with lymphoma in 2020 around worldwide and 259,793 were projected to die because of it in 2020 across the globe according to the global cancer statistics (*GLOBOCAN 2020: New Global Cancer Data | UICC*, 2020).

In the United States, 178,520 people were expected in 2020 to have diagnosed leukemia, lymphoma and myeloma (Figure 5). Among them, 85,720 additional cases of lymphoma in the United States were reported to be diagnosed (8,480 cases of HL, 77,240 cases of NHL), where a total US population of 20,910 (19,940 NHL and 970 HL) were anticipated to die from lymphoma in 2020 (*Facts and Statistics | Leukemia and Lymphoma Society*, 2020).

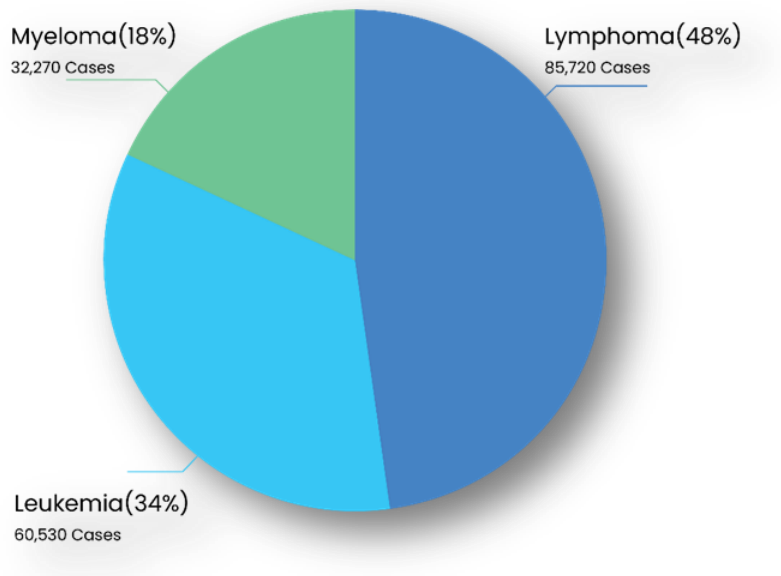


*Figure 5 : Estimated New Cases of lymphoma, leukemia, myeloma in 2020 (Facts and Statistics | Leukemia and Lymphoma Society, 2020)*

In addition, predictions for the NHL by the American Cancer Society in 2021 are:

- NHL would be diagnosed with about 81,560 individuals (45,630 males and 35,930 females). Adults and children are included. About 20,720 people will die from this cancer.

Estimates for HL in the US for the American Cancer Society are also given below:

- Approximately 8830 new cases (4,830 in males and 4,000 in females) and 960 fatalities are anticipated in this year (Siegel et al., 2021).

Thus, the prevalence of lymphoma cases continues to grow globally and exerts burden on healthcare system.

## 6.4 Treatments Options of Lymphoma

Cancer drugs (chemotherapy, steroids and selective therapies), radiation treatment or stem cell transplantation can be used to cure lymphoma. The treatment is focused on the type and level of lymphoma, recovery disorders, and other medical problems, such as reduced red cell counts, asthma, cardiac and kidney problems. Different treatment options are also available for NHL as well. The treatment options of lymphoma are discussed below:

- Chemotherapy- Combination chemotherapy with involved field radiation therapy represents the most effective treatment for HL. It employs high-energy rays for HL cell targeting. In some patients with widespread HL radiation free chemo is also being used. It is normally offered for several weeks in "cycles." There are several cycles required. Therapy will take six to ten months. In certain patients with NHL, it acts as an effective therapeutic alternative. Chemo can be used on its own or in combination with other therapies, including immunotherapy or radiation therapy, depending on the form and stage of the lymphoma. Many chemo drugs are useful in treating

lymphoma. Some examples include Alkylating agents (Cyclophosphamide), Corticosteroids (Prednisone), Purine analogues (Fludarabine) etc.

- Stem Cell Transplantation- A transplantation of stem cells (enables doctors to use chemotherapy and radiation treatment in extra doses, sometimes). Although only a small group of lymphoma patients are seen with this therapy, this figure is increasing.
- Radiation Therapy- It might be used to treat NHL in some different situations. Any NHL types are identified early (stage I or stage II), can respond to radiation very well. In addition, it is used for advanced lymphoma and for more aggressive lymphomas, along with chemotherapy. Radiation treatment may be used to alleviate (palliate) lymphoma signs spreading to internal organs or to alleviate a tumor inducing inflammation as it presses nerves.
- Immunotherapy –It is a procedure that either improves the patient's immune response or uses monoclonal antibody (mAbs) to inhibit or delay lymphoma cell development. mAbs can aim to find, attach and attack the substances on the lymphocyte and it can strike that specific target. NHL is treated with a number of monoclonal antibodies (mAbs). Among them, Rituximab is the mostly used CD-20-targeted mAb used to treat follicular, CD20-positive, DLBCL, NHL. In addition, Tafasitamab (Monjuvi) an antibody targeted to the CD19 antigen, immunomodulating drugs, are also used to treat various types of lymphoma.

Moreover, several targeted therapies, clinical trials of drugs blood transfusion, surgical procedure are also applied with an intent to treat lymphoma (Franceschetti & Caldeira, 2018; Walter, 2013).

- **Treatment of Lymphoma with Biosimilar**

The US FDA has licensed the first biosimilar 'Truxima' drug to treat adults with NHL. Truxima (Rituximab-abbs) is a mAb, a form of immunotherapy and is an authorised biosimilar to Rituxan (Rituximab). Loss of patent exclusion and limited access to Rituximab has helped to develop well-defined, safe biosimilar to Rituximab (Jurczak et al., 2019). Truxima acts like Rituxan works. Truxima targets the CD20 antigen, a compound on the surface of the B- lymphocytes, for patients with CD20-positive, B-cell NHL. Depending on particular lymphoma diagnosis, it should be used either with or on its own chemotherapy. It can be used along with chemotherapy or on its own, depending on the individual lymphoma diagnosis. Rituximab (MabThera/Rituxan, Roche/Genentech) is a mAb also approved by the EMA for the treatment of NHL, CLL, RA, Wegener's syndrome, and microscopic polyangitiis. In addition, two biosimilars of Rituximab for the treatment of lymphoma are currently licensed by the EMA:GP2013 (Sandoz, Brand name- Rixathon/Riximiyo ) and CT-P10 (Celltrion, Brand name- Truxima/Rituzena/Blitzima) (Greenwald et al., 2018; Subramanian et al., 2017; Vital et al., 2013).

# Chapter 7

# Rituximab Biosimilar in Lymphoma Treatment

In view of the demands on the market and pending expiration of patents, a range of pharmaceutical industries have been developing biosimilar monoclonal antibodies (mAbs). Among them, the lymphoma treatment was revolutionized by Rituximab, an anti-CD-20mAb. The development and manufacturing of Rituximab was propelled by patent expirations and patient demands (Rioufol & Salles, 2015). Due to the expirations of Rituximab in Europe (2013), and the United States (in 2016), the production of Rituximab was able to succeed in the last five years. The plethora of biosimilars that has already become accessible as Rituximab's patent expires represents a significant revolution in targeted lymphoma care. EMA licensed first Rituximab biosimilar Rixathon, manufactured by Sandoz, Holzkirchen, Germany and Truxima, developed and manufactured by Celltrion, Metropolitan City, Incheon, South Korea in 2017, following the expiry of the originator of the Rituximab patent in Europe in 2013. Further, in 2018 Truxima (Rituximab-abbs) was approved by the US FDA to treat CD20-positive NHL patients, B-cell NHL as a single agent or combined with chemotherapy, as the first biosimilar to Rituxan (Rituximab) (Otremba et al., 2020).While Rituximab itself is likely to remain widely used, its biological resemblances or biosimilars will improve global access to therapy.

## 7.1 Rituximab – Introduction

Rituximab is chimeric, anti-CD20 mAb which is widely used to treat patients with malignancies in B cell, of which therapeutic results has been improved (Makita & Tobinai, 2017). The EMA and the US FDA have authorized Rituximab (MabThera/Rituxan, Roche/Genentech) for the treatment of CD20-positive, B-cell NHL, CLL, Wegener's syndrome. Rituximab has created a significant landmark in the age of immunotherapy, being

licensed for first mAb of oncology care and is used to treat most B-cell NHL as monotherapy or in conjunction with conventional lymphoma therapy. Its usage has significantly increased the therapeutic result for all patients with B-cell lymphoma. In addition, Rituximab has dramatically improved B-cell NHL treatments since its first approval and significantly improved therapeutic responses, as seen by improved response rates (Jurczak & Długosz-Danecka, 2020). In the USA, it was authorized as Rituxan in 1997 and licensed as MabThera in 1998 in the EU. It has showed enhanced outcomes after initial approval in 1997 for all malignancies of the B-Cell, including DLBCL, FL and CLL. Its broad variety of oncological indications make it unique among bio-pharmaceutical products (Baer et al., 2014).

Moreover, Rituximab is also one of the first therapeutic mAb in oncology to confront the competition from biologic similar at the expiry of its patent. The latest expiry (2013 and 2016 in Europe and the United States) of the patent and the economic importance of Rituximab as a leading oncology drug also prompted the development of a large number of Rituximab biological resemblances or biosimilars (Pierpont et al., 2018). Rixathon and Truxima were first authorized as Rituximab biosimilars in 2017 and in 2018 by the US FDA. Rituximab biosimilars have the ability to provide practical value clinically and enhance accessibility to lymphoma therapy by making it more affordable, which can enable more patients get optimal care. Table 3 gives the list of the FDA and EMA approved Rituximab biosimilars.

*Table 3: FDA and EMA approved rituximab biosimilars lists (Biosimilar Product Information | FDA, 2020; Jurczak et al., 2019).*

| **Reference Product** | **Biosimilar Name** | **Manufacturer Company** | **Approved By** | **Approval Year** | **Indications of approved Biosimilar** |
|---|---|---|---|---|---|
| Rituxan (Rituximab) | Truxima (Rituximab-abbs) | Teva and Celltrion | FDA & EMA | 2018 (FDA) 2017 (EMA) | NHL, DLBCL, CD-20 positive NHL, Follicular B cell NHL. Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent. |
| Rituxan (Rituximab) | Ruxience (Rituximab-pvvr) | Pfizer | FDA & EMA | 2019 (FDA) 2020 (EMA) | NHL, Relapsed, FL, refractory CD-20 positive NHL, previously untreated follicular B cell NHL in combination with |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | chemotherapy, Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CHOP chemotherapy, Previously untreated diffuse large B-cell, CD-20 positive NHL in combination with chemotherapies |
| Rituxan (Rituximab) | Riabni (Rituximab-arrx) | Amgen | FDA | 2020 | FL, CD-20 positive B-cell NHL |
| MabThera (Rituximab) | Rixathon | Sandoz | EMA | 2017 | FL and DLBCL |
| MabThera | Riximyo | Sandoz | EMA | 2017 | FL, DLBCL, B- |

| | | | | | |
|---|---|---|---|---|---|
| (Rituximab) | | | | | cell NHL. |

## 7.2 Mechanism of Action – Rituximab

Rituximab, the humanised, chimeric monoclonal anti-CD20 antibody, represents as an effective tool to combat B-cell malignancies and is approved to relapsed, chemo refractory, or follicular and other subtypes of NHL. It is a genetically engineered chimeric murine/human monoclonal immunoglobulin ($G1_k$ antibody) that targets the CD-20 antigen on B-cells. It attaches the CD-20 antigen with strong affinity to the surface of B cells (Greenwald et al., 2018). It targets CD-20 on B-cells, which is the only site binding to Rituximab. It has a unique mode of action which can lead to the death of CD20+ cells through many mechanisms. Rituximab's direct effect or mechanism of action include complement mediated cytotoxicity (CDC) and antibody dependent cell- mediated cytotoxicity (ADCC) and indirect actions include apoptosis, structural modifications, cancer cell sensitivity, to chemotherapies (Selewski et al., 2010).

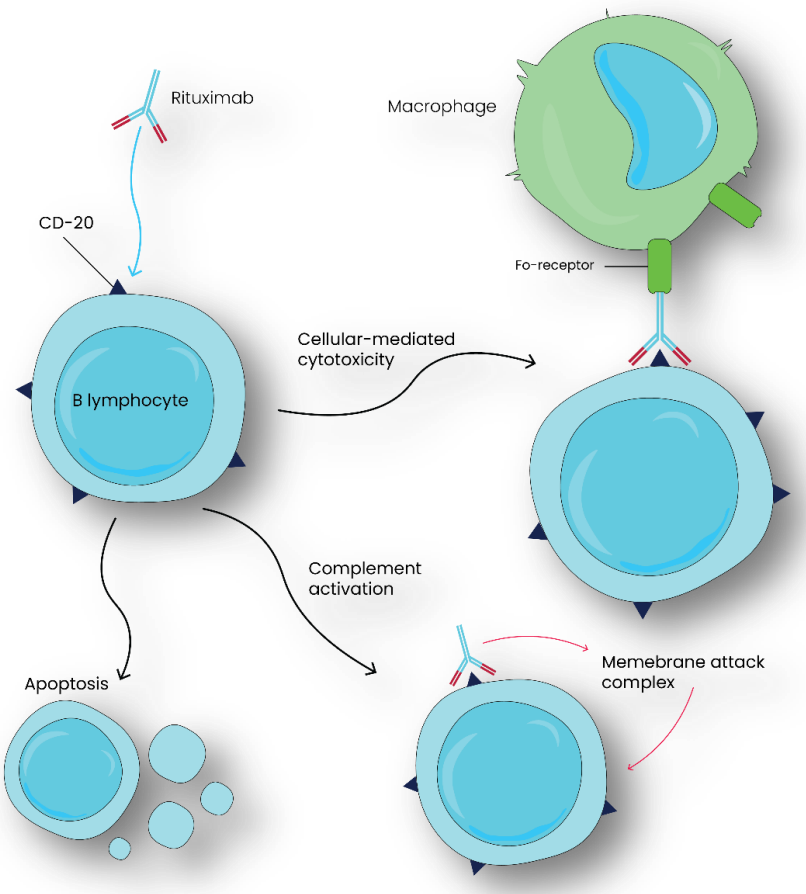


*Figure 6 : The three major mechanisms of action of Rituximab (D'Rozario & Bennett, 2019)*

Binding Rituximab to CD-20 results in B-cell degradation by triggering the activation of ADCC and CDC and also by inducing indirect effects which include apoptosis as well (Vital et al., 2013). Rituximab targets the specific moiety of CD-20 molecule as it is a comparatively short amino acid sequence and after binding it causes the redistribution of the CD-20 molecule inside the bi-lipid cell membrane and potentially induces ADCC and CDC. For Rituximab, the most likely dominant pathway in-vivo is CDC (D'Rozario & Bennett, 2019; Selewski et al., 2010).

## 7.3 The Role and Potential Advantages of Rituximab Biosimilars

Rituximab is a chimeric mAb that is intended for targeting B-cells specific antigen CD20 and has been the preferred therapy for the majority of lymphoid malignancy. Rituximab is

licensed and approved for the treatment of many conditions, including follicular lymphoma (FL), DLBCL and several subtypes as well. It is indicated for the treatment of almost all B-cell NHLs (Coleman et al., 2016). It is more often used in conjunction with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP), although it may also be used in other chemotherapeutic varieties, small molecule targeted therapies, as a monotherapy, or as maintenance therapy. However, in 2013, the originator patent of Rituximab covering in Europe (MabThera) expired and in 2018 it expired in the United States (Rituxan). Furthermore, the costly biological Rituximab in certain countries was also not readily accessible to patients and patient access in particular to Rituximab in countries with minimal financial resources became restricted as well (Nava-Parada et al., 2020; Pierpont et al., 2018). For instance, a report by 450 hematologists and oncologists from the USA, Mexico, Turkey, Russia, and Brazil found more than 50% of doctors in countries outside the United States observed, Rituximab as not readily accessible and would increase its usage if more affordable options for NHL therapy including DLBCL, were present (Nava-Parada et al., 2020).

In another recent study of oncologists, several physicians have found limitations and encountered barriers to access to Rituximab for the treatment of NHL patients. In geographic surveys and evaluations of patient care and cost-effectiveness, limitations or disparities in access to biologics like Rituximab were also found. The lack of patient access to Rituximab for lymphoma care can be implicated in a variety of considerations, including limiting treatment directives, regulatory barriers and financial considerations, for instance, insurance/public payer coverage for the biologic / patient refund and bill-out costs to the patients (Greenwald et al., 2018). Under these conditions, including the latest expiry of the originator Rituximab patents (2013 and 2016 respectively in Europe and America) and economic importance of Rituximab as one of the highest selling oncology medications has

propelled and enabled the production and development of several biologic similar of Rituximab.

The integration into health care systems of Rituximab biosimilars would significantly help to manage healthcare expenses to combat against hematological and lymphoid malignancies. As the patent of originator biologic of Rituximab came to its end of term, the accessibility of biological similar version of Rituximab biosimilars have begun to mitigate the overall cost of care with the prospect of introducing more accessible prescription choices and improve the access for patients to these essential treatments. Also, improved accessibility of biosimilar Rituximab would lower costs, render anti-CD20mAbs worldwide more available, and promote further research that could contribute to improved and more widespread treatment choices. Present Rituximab biosimilar prices around the world are sometimes less than half the Rituximab originator. And thus, Rituximab biosimilars have also become an enticing prospect for growth of companies in places like India, Japan and South Korea. Moreover, the increased availability of Rituximab biosimilars can be anticipated to minimize access barrier, to increase usage, to provide patients with a more accessible alternative, to contribute to the further delivery and earlier initiation of biologics in the disease process, and to the therapeutic outcomes for the patients. Rituximab biosimilars are expected to remain as mainstay of treatment for NHL as it will improve accessibility of Rituximab-based chemo immunotherapies to patients with lymphoma and potentially contribute to the cost-saving of healthcare systems (Jurczak et al., 2019; Vulto, 2019; Young et al., 2018).

## 7.4 Comparison of Biosimilar with Originator Rituximab

The advent of biosimilars offers patients in many countries more affordable alternatives that increase the access to expensive biological therapies. Several hemato-oncological

associations have recognized the beneficial effect of biosimilars on the financial viability of health systems.

Several phases and step-by-step approaches need to be completed for the approval of a biosimilar and clinical comparability is considered as confirmatory and the last phase by the regulatory guidance on biosimilar development process. Based on comparisons of the detailed structural and functional product characterization, animal trial data, pharmacokinetics and pharmacodynamics data and immunogenicity and efficacy statistics, Rituximab biosimilar is now authorized by the US FDA and EMA. To meet the standards with no clinically significant differences, a Rituximab biosimilar manufacturer needs to demonstrate its absence of such differences from the reference product in terms of safety, purity and potency (safety and efficacy); this is usually shown through studies on human pharmacokinetics and pharmacodynamics, an evaluation of clinical immunogenicity, and by additional clinical studies. In the United States already three biosimilars of Rituximab have been approved where four biosimilars of Rituximab from different manufacturers have been approved by EMA (Lee et al., 2019). Furthermore, given that many biosimilar Rituximab have been developed and manufactured after the patent expires, it is important to thoroughly integrate and review the recent data to demonstrate the comparability between originator biologic and rituximab biosimilar to assure its safety and efficacy. Apart from the regulatory guideline wise comparability studies, several comparison studies have been conducted by researchers to demonstrate the comparability between the Rituximab biosimilar and originator Rituximab (Bankar et al., 2020; Candelaria et al., 2019).

For example, a recent systematic review compared biosimilar Rituximab to the originator drug in patients with NHL and RA. The research has been published in *BioDrugs* where researchers asked for head-to-head randomized controllable trials to closely compare originator and biosimilar Rituximab and queried the PubMed, EMBASE, Cochrane Library,

Google Scholar Databases for the trials. Safety results were measured in both NHL and RA cases by anti-drug antibodies (ADAs) and also by adverse events occurrences. On the other hand, efficacy outcomes were measured by the response rates for both cases patients and a secondary result was considered to be the pharmacokinetic profile data. The overall study composed of 11 trials of 3,163 patients: 1,744 RA and 1,419 NHL patients. The outcome of the study revealed that biosimilar Rituximab showed comparable characteristics including efficiency, safety and pharmacokinetic parameters with the reference drug across extensive assessments. This systemic study and meta-analysis showed the similarities of biosimilar Rituximab as a therapeutic option for RA and NHL patients therefore, the findings have backed the usage of biosimilar Rituximab on evidence basis (Lee et al., 2019).

A further study published in *Taylor and Francis Journal* showed a prospective, multi-centre, double-blind, randomized clinical analysis and trial (RTXM83-AC-01-11) for confirming comparable clinical performance (efficacy, PDs, PKs, immunogenicity, safety) of Rituximab RTXM83 versus MabThera (Rituximab originator) (NCT02268045), both in combination with CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) chemotherapy as first-line treatment in diffuse large B- cell lymphoma(DLBCL). This study involved the randomisation of 272 patients with a positive prognosis in 12 countries <65 years of age in (1:1) ratio, receiving either RTXM83 or MabThera. At least one dosage of the drug was received by all the patients. It has been demonstrated in the result segment that the development of anti-drug antibodies between the arms was comparable. In both categories, a comparable percentage of patients reported at least one adverse condition. Furthermore, the PK/PD secondary endpoint findings confirmed the compounds' similarity. Finally, the Rituximab biosimilar showed equivalent effectiveness and comparable safety/immunogenicity to originator one, rendering as an available and affordable treatment options for the patients with previously untreated DLBCL (Candelaria et al., 2019).

## 7.5 Global Market of Rituximab Biosimilar

The biosimilar market of Rituximab has been segmented by application into NHL, RA, leukemia and others. Increasing NHL occurrence is projected to lead and fuel the development of the Rituximab industry and thus rising NHL cases worldwide are expected to generate strong Rituximab biosimilar demand over the projected timeframe (2020-2030). In the projected timeframe, the Rituximab biosimilar demand is predicted to increase more quickly, since Rituximab has been one of the world's best-selling drug accounts for 2.1 million prescriptions globally since the introduction of the market. Additionally, increased demand for biosimilar drugs and new entrants in pharma markets also helped to accelerate the Rituximab biosimilar market growth. The biosimilar Rituximab sector reached a valuation of $1.6 billion dollars by 2020 with CAGR of 67.9% since 2015. The market is projected to expand at a 16.7 percent annual pace, from $1.60 billion in 2020 to $3.47 billion in 2025 and $5.72 billion in 2030 (*Global Rituximab Biosimilar Market Assessment Report*, 2021).

The global biosimilar Rituximab industry has a regional or geographical segmentation in Europe, Asia-Pacific, North America, Latin America, the Middle East and Africa. Europe is the largest contributor to the global biosimilar Rituximab market in terms of sales across all the countries. Due to the expiration of the Rituximab patent in 2013, Europe is the biggest contributor to the world market. Sandoz announced the first biosimilar of Rituximab in Europe in June 2017. Europe is led by North America, which is the second highest revenue producer over the projected timeframe. Factors such as the robust clinical trial/product pipeline increased research activities and drug discovery activity boosts Rituximab biosimilar market growth in North American region. Also, the third promising contributor to revenues, Asia Pacific, is predicted to rise fast in the coming year. Countries such as Japan, India and China are major contributors for this market. Evolving and large population-based nations

such as China and India have substantial market opportunities for Rituximab biosimilar with rising lymphoma incidence (*Global Rituximab Biosimilar Market Assessment Report*, 2021).

## 7.6 Cost Comparison between Rituximab Biosimilar and its Originator

The treatment of CD20-positive lymphoproliferative disorders was significantly changed after biologic Rituximab was accepted as an immunotherapeutic in 1997. But second-generation cost-effective molecules and biosimilars with biological benefit emerge worldwide two decades later. Biosimilar production costs are considerably less than those associated with the licensed innovator/reference product, as a result of lower clinical tests anticipated before market launch. Therefore, the spiraling high expense of cancer drugs worldwide can be partly minimized with the usage of suitable biosimilars. The global demand for biosimilars was projected to hit USD35 billion by 2020 and in the US as well, biosimilars are predicted to save the Medicare system by USD 9–12 billion in the next decade. Besides these, biosimilars of monoclonal antibody like Rituximab biosimilar are anticipated to add substantial budgetary savings to the lymphoma care arena, and thereby expand patients' access to biological lymphoma treatment. For e.g., Ruxience, Pfizer's biosimilar to Roche's Rituxan (Rituximab), has launched at a cost of $71.68 per 10 mg, entering the market at a 24 percent lower price than its originator Rituxan, while Truxima, the first licensed biosimilar of Rituximab, is just 9 percent cheaper than the biologic Rituxan (Bankar et al., 2020). Even, the average cost of Rituximab biosimilar has fallen by an average of nearly 50% in an Asian country like India relative to its innovator version (Jang et al., 2021).

Furthermore, a number of budgetary effects analyses were also carried out to compare the expense between Rituximab biosimilar and its originator. The budget impact study in 28 European countries demonstrated a substantial budget reduction for CT-P10 (Truxima, first introduced biosimilar of Rituximab) introduction within the European Union (EU), enabling

even more patients to receive Rituximab therapy. The study found that the implementation of CT-P10, which will provide 7,533 additional patients with Rituximab treatment, was related to the expected initial year savings of €90.04 million. It corresponded to a 6.4% growth in the number of patients treated with Rituximab. In a 3 years' time, the estimated costs of Rituximab-based treatment have been reduced by about €570 million, which increases accessibility to 47, 695 patients (Gulácsi et al., 2017). Another research paper released in the *Bio Drugs* journal mentioned that the adoption of Rituximab biosimilars would save net costs. In 5th year, overall Rituximab savings were between €4.05 million and €303.86 million. Potentially, these reductions could improve coverage for an extra 15,671 patients (Jang et al., 2021).

Moreover, according to another research study published in the *Dove Press* journal, an annual total savings of $46.59 million is planned from use of Rituximab biosimilar in the Middle East and North Africa. The cumulative savings in all 13 countries would bring the overall number of patients that profit from Rituximab treatment to 6,589 patients, an increase of 14 percent (Almaaytah, 2020). Thus, the world introduction of a biosimilar Rituximab corresponds with significant budgetary savings when compared with its source, enabling government health agencies, either through expanding their access to Rituximab or in other respects, to expend these economic benefits.

## 7.7 Challenges in Adopting Rituximab Biosimilar

The pace of biosimilar growth and development in oncological therapeutic arena will likely to increase as further patents on oncologic biologics continue to expire. Also in the oncology section, therapeutic choices for hematological malignancies are expected to increase in the future as more Rituximab biosimilars are accepted and licensed. Their acceptance and integration in the oncology sector still appears to be challenging. Several difficulties and

barriers must also be addressed and resolved to the usage of Rituximab biosimilars. Challenges involve physician and patient knowledge about biological and biosimilars, particularly in terms of approval; immunogenicity concerns; pricing; interchangeability, and replacement; costs and supply chain concerns issues (Dolan, 2018; Otremba et al., 2020). Barriers also involve the views of stakeholders (including patients and providers of healthcare), financial disincentives relating to compensation, and legislative policies (such as the interchangeability of reference products and biosimilars). In certain circumstances, prescribers are uncertain if scientific information on the interchangeability of biosimilars and reference drugs is accurate or if data extrapolation through indications is permissible. In addition, patients can be unwilling to switch from reference drugs to biosimilar products, because physicians lack confidence in prescribing biosimilar drugs (Jurczak et al., 2019). With a better knowledge of the biosimilars, Rituximab biosimilars would certainly surpass these challenges when they enter the market and provide more prospects for better lymphoma therapies.

## 7.8 Future Aspects

From this review study, it can be anticipated that there will be a greater use of Rituximab biosimilars for lymphoma treatment in the years ahead. As the biosimilar mAbs (Rituximab biosimilars) begin to enter the landscape of lymphoma care, it will become extremely important for doctors, patients, healthcare professionals, and researchers to consider the problems in biosimilar growth in order to make informed decisions as these drugs enter clinical practice. This review study could be considered a useful guide to resolving these challenges as well as in the effective uptake and incorporation of biosimilars in lymphoma care, expanding options for patients and physicians and increasing access to potentially helpful biological lymphoma care. Continued research study would also help to drive the

innovation of more biosimilars in oncology sector to broaden accessibility to affordable biological therapies.

# Chapter 8

# Conclusion

Over the past decade, biosimilars have gained widespread interest in the pharmaceutical sector and are now an exceedingly relevant field of focus for the pharmaceutical industry worldwide (Yuk et al., 2015). Many patents from the first biological product made from recombinant techniques have already expired, with more future in the years ahead. In this present context where budgetary pressures on the healthcare system are on rise and the patent expire on major biological therapies used in oncology is inevitable, biosimilar provide a significant potential for high quality, clinically efficient, safe medicine at a reduced cost. The goal of this study was to show how the production and implementation of biosimilars will save patients' healthcare costs, increase patients' access to biological therapy, and help ensure long-term sustainability of cancer care. The focus of this study was in particular on Rituximab biosimilars, which have already received EMA and FDA approval to use various types of lymphoma treatment. The enhanced accessibility and the rise Rituximab biosimilars for lymphoma care are expected to further decrease mAb therapy costs and thereby increase patient access to Rituximab based lymphoma therapy. In addition, their increased affordability will contribute to clinical advantages through earlier and more intensive therapeutic usage and release funds for clinical treatment to other places. In order to reduce health budgets and improve patients' access to biological lymphoma therapy, increasing the use of Rituximab biosimilar is a crucial solution, with the required legislation and surveillance (Jurczak & Długosz-Danecka, 2020; Nava-Parada et al., 2020). To conclude, the current review was done with the hope that health care providers and patients would be able to know about the various facets of Rituximab biosimilars in one document, ensuring their successful integration into oncology care.

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