Winning the World of Biosimilars: Commercial Strategies for European Market

By

Varun Reddy Thummala

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2015-2017

The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Sanganer, Airport
Jaipur 302029, Rajasthan
Ph: 0141 3924700, Fax: 3924738
Website: **www.iihmr.edu.in**

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Jaipur 302029, Rajasthan
Ph: 0141 3924700, Fax: 3924738
Website: www.iihmr.edu.in

INSTITUTE OF HEALTH
MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

TO WHOMSOEVERMAY CONCERN

This is to certify that **VARUN REDDY THUMMALA**, student of **MBA Pharmaceutical Management** from The IIHMR University, Jaipur has undergone internship training at **HETERO LABS LIMITED**, Hyderabad from **February 6, 2017 to May 5, 2017.**

The Candidate has successfully carried out the study designated to him during internship training and his approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish him all success in all his future endeavors.

Dr. Ashok Kaushik
Dean - Academics and Student Affairs
The IIHMR University, Jaipur

Dr. Nirmal Kumar Gurbani
Professor
The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Near Sanganer Airport, Jaipur- 302029, Rajasthan, India.
Ph.: 0141- 3924700, 2791431- 32, Fax: 0141 3924738, E-mail: iihmr@iihmr.edu.in, Web.: www.iihmr.edu.in

HETERO LABS LIMITED

"Hetero Corporate", 7-2-A2, Industrial Estates, Sanathnagar, Hyderabad - 500 018, Telangana, INDIA
Tel : 0091-40-23704923/24/25, Fax : 0091-40-23704035, 23813359
E-mail : contact@heterodrugs.com URL : http//www.heterodrugs.com
CIN : U24110TG1989PLC009723

05.05.2017

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This is to certify that **Mr. Varun Reddy Thummala (Regn No-IIHMR-U/01/2015-17/0050)** bonafied MBA (Pharmaceutical Management) student of "Institute of Health Management Research", has undergone project work on "*Winning the World of Biosimilars: Commercial Strategies for European Market*" in our **Corporate Office, Sanathnagar**, Hyderabad from **06-02-2017 to 05-05-2017**. He has shown lot of interest in collecting the data, and assisted to the department. He has successfully completed his project work. His conduct and behavior during the period of training is found to be good.

We wish him all the best.

For HETERO LABS LIMITED

S. V. Jayapal Reddy
DGM-HR

HETERO LABS LIMITED Hetero Corporate Hyderabad-18

Factory : Survey No.10, I.D.A., Gaddapotharam, Jinnaram Mandal, Sangareddy (District) - 502 319, TS., INDIA.
Phones : 0091-8458 277106, Fax : 0091-8458 277135.

IIHMR UNIVERSITY

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **"Winning the world of Biosimilars: Commercial Strategies for European Market"** and submitted by **Varun Reddy Thummala**, Enrollment No. **IIHMR-U/01/2015-17/0050** under the supervision of **Dr. Nirmal Kumar Gurbani** for award of **MBA in Pharmaceutical Management** in the University carried out during the period from **February 6, 2017 to May 5, 2017** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

T. Varun

VARUN REDDY THUMMALA

IIHMR UNIVERSITY

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that all ethical issues have been considered while collecting data for my dissertation titled **"Winning the world of Biosimilars: Commercial Strategies for European Market"**.

T. Varun

VARUN REDDY THUMMALA

ABSTRACT

Background: European Union delivers the immense potential of Biosimilars market to be tapped as a stride towards the Healthcare economical substantiality of the EU Member States. As the uptake of Biosimilars varies considerably by therapeutic area and case basis across the European Nations, the Companies striding towards the European Union should postulate its Go-to-Market considerations with the perspectives of the market drivers.

Objective: The objective of the study is to assess the Regulatory and Commercial considerations of Biosimilars in the European Union to edge the sustainable space in the market.

Methods: Researcher has deployed an exploratory study with the Dual approach system to establish the objectivity of the research sphere.

Findings: The uptake of biosimilars across EU is ascertained by the Stakeholders orbit based on the existing policies of the market sphere.

Conclusion: Therefore, unlocking the potential of Biosimilars across the EU necessitates the integrated approach of Regulatory and Commercialization considerations to counter the gray areas in the path and to edge the sustainable market space across European Union.

Key words: Biosimilars, European Union, Go-to-Market considerations, Stakeholders orbit, Gray areas.

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SYMBOLS

- **$ - US Dollar**
- **€ - Euro (EUR)**

ABBREVIATIONS

EMA	=	European Medicines Agency
EU	=	European Union
WHO	=	World Health Organisation
SBP	=	Similar Biotherapeutic Product
US FDA	=	United States Food and Drug Administration
BPCIA	=	Biologics Price Competition and Innovation Act
ICH	=	International Conference on Harmonization
PMDA	=	Pharmaceuticals and Medical Devices Agency
NICE	=	National Institute for HealthCare Excellence
NHS	=	National Health Service/System
EEA	=	European Economic Area
MAA	=	Marketing Authorisation Application
CHMP	=	Committee for Medicinal Products for Human Use
EC	=	European Commission
BMWP	=	Biological Monitoring Working Party
RMP	=	Risk Management Plan
EPAR	=	European Public Assessment Report
PSUR	=	Periodic Safety Update Report
HTA	=	Health Technology Assessment
INN	=	International Non-Proprietary Name
P&MA	=	Pricing and Market Access Policies
IPR	=	Intellectual Property Rights

1. Background

Biologics are therapeutic proteins, derived from genetically modified living sources like bacteria, yeast or mammalian cells.[1] Since the cell lines in a given source are unique and generate drug products via complex biological systems and production methods, the biopharmaceutical product manufactured by various companies other than the original biologic (innovator) are not considered to be as identical molecular copies, so the term biosimilars was created for those products which are similar, but not identical to the reference biologic molecules.

A **Biosimilar** is a biological medicinal product containing a version of the active substance of an authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.[2]

The complexity of establishing bio-similarity with reference biological product lies in the way of developing biosimilars and the development from laboratory scale to commercial scale generally consists of an iterative process, for being considering product quality and productive yield, as this is needed due to both regulatory requirements and productivity margin.

By 2020, the biologics are predicted to generate revenue of $290-$300 billions and comprises 27 percent of the Pharmaceutical market.[3] Forty-eight percent of sales come from 11 biologics that face Patent-cliff over the next seven years period.[4] The Patent-cliff issue along with the increasing global focus on improving healthcare access and the cost of healthcare burden generates an captivating opportunity for biosimilars market. The biosimilars market has the potential to disrupt the healthcare industry by exponentially increasing the market access to the patient population which cannot afford $100,000 therapies, thereby providing the affordable cost of treatment to them. It is expected that the global biosimilars market will reach $25-$35 billion by 2020[4] representing a CAGR of 62.1 percent[5], as the $50 billion global market of **RRABIT** is going off-patent by 2020.

The **European Medicines Agency** (EMA) has led the way in the development of regulatory guidelines for the development and assessment of biosimilars by providing an overarching regulatory approval framework and subsequently approving the first biosimilar in the following year in 2006.[6] Since then, the European Union (EU) has led the world in biosimilar development,

having approved 29 different biosimilar products as of February 2017 and these EU guidelines on biosimilars are updated in 2014.[6]

In 2009, World Health Organisation (WHO) developed a set of global acceptance standards to ensure the safety, efficacy and quality of similar biotherapeutic products (SBPs). These were mainly targeted to aid and ascertain regulatory authorities of all the nations to adhere to the worldwide standards. Ever since there has been a rapid evolution of guidelines and most of the countries have adopted the general framework of either EMA or WHO, while others have established their individual national guidelines based on either of these templates. For instance, Australia adopted the EU guidelines without any changes, while Singapore and Malaysia amended their guidelines mainly in accordance with the EMA guidelines. Brazil and Cuba chooses the WHO and Canadian guidelines as the basis for formulating the regulatory guidelines. However, there are considerable variations in accordance to definition, terminology, reference product for comparability, extent of data requirements and other related aspects. India has released the official guidelines on biosimilars in June 2012, prior to which 20 biosimilars were already approved for use within India under the provision of an ad hoc abbreviated process of approval.[7]

The US FDA was a late entrant in formulating the regulatory pathway for biosimilars. On March 23, 2010, the Biologics Price Competition and Innovation Act (BPCIA) were signed as part of the Patient Protection and Affordable Care Act, which created a new licensure pathway for biosimilars within the domain of US FDA. Biosimilar applications are to be submitted under section 351(k) of the Public Health Service Act and the FDA has issued 3 draft guidance documents in 2012, recommending a stepwise approach to establish the biosimilarity by laying importance on totality of evidence.[7] In March 2015, FDA approves the first biosimilar in the U.S, Zarxio (Filgrastim-sndz) by Sandoz.[8]

Japan has a clearly established approval pathway for biosimilars that is based on EU regulatory processes and was published in 2009 by its regulatory approval agency (Pharmaceuticals and Medical Devices Agency) and its regulatory body (Ministry for Health, Labour and Welfare). Also the biosimilar regulations principally follows the guidelines of the International Committee on Harmonization (ICH), particularly the guidelines Q5E and Q6B.[7] The PMDA has been supporting the biosimilar development in the nation by conferring with the Pharmaceutical

companies across. Japan's first biosimilar was approved in 2009 and approved 7 biosimilars subsequently as of February 2016.[8]

1.1 Biosimilars scenario in Europe

In fact, biologics have transformed the clinical outcomes for patients across Europe but their high cost factor has put a heavy strain on European healthcare systems. For example, in more than half of the European nations, the annual cost of a biologic product which is disease modifying anti-rheumatic drug (DMARD) exceeds the per capita GDP by 11 times and in UK, around 8 Breast cancer biologics with clinical outcome have been rejected between 2011 to 2014 by the National Institute for HealthCare Excellence (NICE) for reimbursement on the National Health System (NHS) because of the cost factor, concerning that the price is merely as much as safety, efficacy and quality. This issue has proved a burning topic in the European Society for Medical Oncology (ESMO) congress in 2014 at Madrid for nearly 20,000 oncology experts.[9]

Biosimilars improves patient access to treatment and are economical for European healthcare systems. This is for two main reasons; firstly, the development of biosimilar medicines builds on the scientific knowledge obtained with the reference biological medicine and not all the phases of clinical studies carried out with the reference biologic need to be repeated. Secondly, after launching in the market, biosimilars competes with the reference biologic for sustainability and as a result, they are offered at economical price value.

A company chooses to develop a biological medicinal product claimed to be "similar" to the reference biological medicinal product, which has been granted a marketing authorisation in the European Economic Area (EEA) on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. For this scenario, the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I to the said Directive lays down the requirements for the Marketing Authorisation Applications (MAAs) based on the demonstration of the similar nature of the two biological medicinal products. Comparability studies are required to generate evidence validating the similar nature in terms of quality, safety and efficacy of the similar biological medicinal product and the chosen reference biological medicinal product authorized in the EEA.[10]

The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning the scientific data to be provided to validate the claim of similarity used as the basis for a Marketing Authorisation Application (MAA) for a biological medicinal product and is defined in Section 3.2.1.1, Part I, Annex I to Directive 2001/83/EC, as amended. The legal basis for similar biological applications are found in Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC, as amended. The dossier requirements for similar biological medicinal products are found in Part II, Section 4 of the Annex I of Directive 2001/83/EC, as amended. Along with these, Guidelines on similar biological medicinal products comprising biotechnologically derived proteins as active substance: Quality issues (EMA/CHMP/BWP/247713/2012) and the Guidelines on similar biological medicinal products comprising biotechnology-derived proteins as active substance: Non-Clinical and Clinical issues EMEA/CHMP/BMWP/42832/2005 Rev) are to be focused for biosimilar approach.[10]

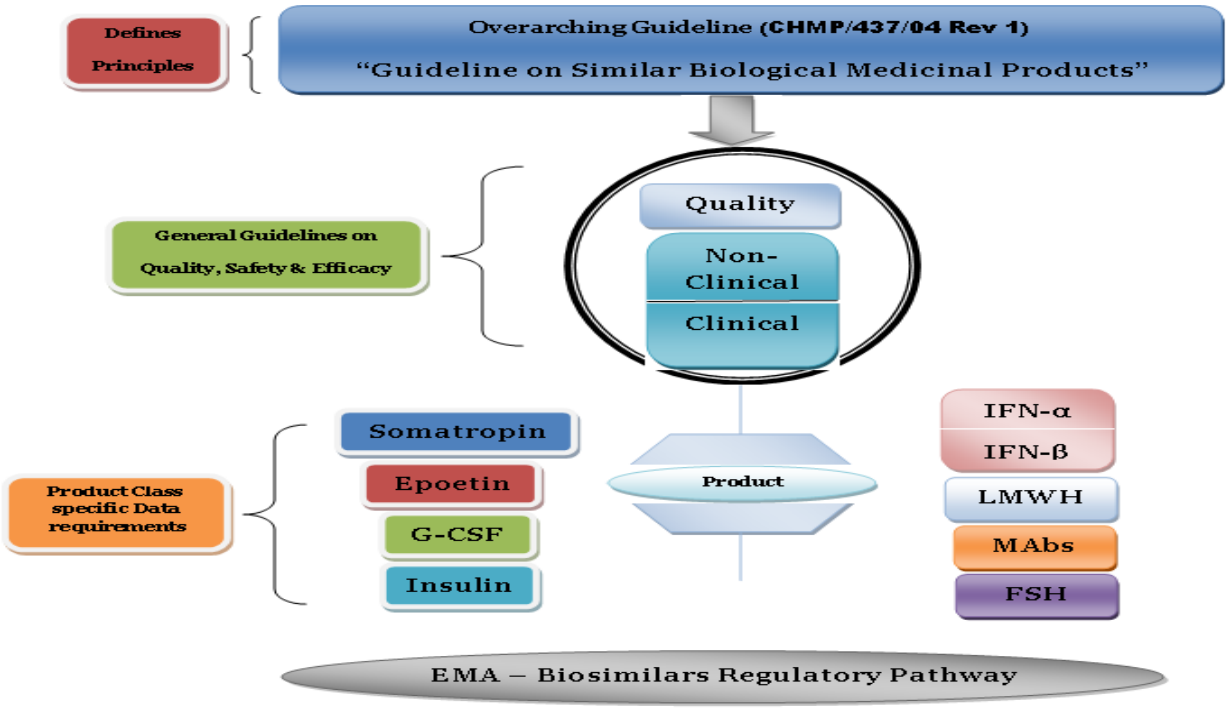

Figure 1.1.1: EMA – Biosimilars Regulatory Pathway

Omnitrope (Somatropin) by Sandoz was the first product to be approved in the Europe as a biosimilar in 2006 and till date, EMA has approved 29 biosimilars within the product category of Human growth hormone, Erythropoiesis stimulating agent, Granulocyte colony stimulating

factor, Insulin, Follicle stimulating hormone (FSH), Tumor necrosis factor (TNF) inhibitor and Parathyroid hormone for use in the European nations. Two biosimilar approvals have been withdrawn; One in April 2011 for Filgrastim and other in May 2012 for Somatropin, leaving a count of 27 biosimilars approved for use in Europe by February 2017.[11]

Product Name	Active Substance	Therapeutic Area	Authorization Date	Company
Abasaglar	Insulin glargine	Diabetes	9 September 2014	Eli Lilly & Boehringer Ingelheim
Abseamed	Epoetin alfa	Cancer, Anemia, Chronic Kidney Failure	28 August 2007	Medice Arzneimittel Pütter
Accofil	Filgrastim	Neutropenia	18 September 2014	Accord Healthcare
Amgevita	Adalimumab	Crohn's disease, Rheumatoid arthritis, Spondyloarthritis, Suppurative hidradenitis, Psoriasis, Psoriatic arthritis, Ulcerative colitis, Uveitis	26 January 2017 (CHMP positive opinion)	Amgen
Benepali	Etanercept	Axial Spondyloarthritis, Psoriatic arthritis, Plaque Psoriasis, Rheumatoid	14 January 2016	Samsung Bioepsis

		arthritis		
Bemfola	Follitropin alfa	Anovulation (IVF)	24 March 2014	Finox Biotech
Binocrit	Epoetin alfa	Anemia, Chronic Kidney Failure	28 August 2007	Sandoz
Biograstim	Filgrastim	Cancer, Haematopoietic Stem Cell transplantation, Neutropenia	15 September 2008	CT Arzneimittel
Epoetin alfa Hexal	Epoetin alfa	Anemia, Cancer, Chronic Kidney Failure	28 August 2007	Hexal
Filgrastim Hexal	Filgrastim	Cancer, Neutropenia, Haematopoietic Stem Cell transplantation	6 February 2009	Hexal
Filgrastim ratiopharm	Filgrastim	Cancer, Neutropenia, Haematopoietic Stem Cell transplantation	15 September 2008 (Withdrawn on 20 April 2011)	Ratiopharm
Flixabi	Infliximab	Ankylosing Spondylitis, Rheumatoid arthritis, Psoriasis, Psoriatic arthritis, Crohn's disease, Ulcerative colitis	26 May 2016	Samsung Bioepsis

Grastosil	Filgrastim	Neutropenia	18 October 2013	Apotex
Inflectra	Infliximab	Ankylosing Spondylitis, Rheumatoid arthritis, Crohn's disease, Psoriasis, Psoriatic arthritis, Ulcerative colitis	10 September 2013	Hospira
Movymia	Teriparatide	Osteoporosis	10 November 2016 (CHMP positive opinion)	STADA Arzneimittel
Nivestim	Filgrastim	Cancer, Neutropenia, Haematopoietic Stem Cell transplantation	8 June 2010	Hospira
Lusduna	Insulin glargine	Diabetes	4 January 2017	Merck (MSD)
Omnitrope	Somatropin	Pituitary Dwarfism, Turner syndrome, Prader-Willi syndrome	12 April 2006	Sandoz
Ovaleap	Follitropin alfa	Anovulation	27 September 2013	Teva Pharma
Ratiograstim	Filgrastim	Cancer, Neutropenia, Haematopoietic Stem Cell transplantation	15 September 2008	Ratiopharm

Remsima	Infliximab	Ankylosing Spondylitis, Rheumatoid arthritis, Crohn's disease, Psoriasis, Psoriatic arthritis, Ulcerative colitis	10 September 2013	Celltrion
Retacrit	Epoetin alfa	Anemia, Cancer, Autologous Blood transfusion, Chronic Kidney Failure	18 December 2007	Hospira
Silapo	Epoetin zeta	Anemia, Cancer, Autologous Blood transfusion, Chronic Kidney Failure	18 December 2007	STADA R&D
Solymbic	Adalimumab	Ankylosing Spondylitis, Rheumatoid arthritis, Crohn's disease, Psoriasis, Psoriatic arthritis, Suppurative hidradenitis, Ulcerative colitis	26 January 2017 (CHMP positive opinion)	Amgen
Terrosa	Teriparatide	Osteoporosis	10 November 2016 (CHMP positive opinion	Gedeon Richter

Tevagrastim	Filgrastim	Cancer, Haematopoietic Stem Cell transplantation, Neutropenia	15 September 2008	Teva Generics
Truxima	Rituximab	Chronic Lymphocytic Leukaemia, Non-Hodgkin's Lymphoma, Granulomatosis with polyangiitis, Rheumatoid arthritis	15 December 2016 (CHMP positive opinion)	Celltrion
Valtropin	Somatropin	Pituitary Dwarfism, Turner Syndrome	24 April 2006 (Withdrawn on 10 May 2012)	BioPartners
Zarzio	Filgrastim	Cancer, Neutropenia, Haematopoietic Stem Cell transplantation	6 February 2009	Sandoz

Source: EMA

Table 1.1.1: EMA approved Biosimilars

The positive opinion given by the EMA's Committee for Medicinal Products for Human Use (CHMP) on June 27, 2013 for the Infliximab biosimilars, Inflectra and Remsima was a landmark decision, proving that the biosimilar concept can be successfully implied to such a complex molecules like Monoclonal Antibodies and also the positive opinion given by the EMA's Committee for Medicinal Products for Human Use (CHMP) on July 26, 2014 for the Insulin glargine biosimilar came as a relief to diabetic patients in Europe, after the dissatisfactory

withdrawal of the applications for 3 biosimilar Insulin products by Marvel Life Sciences in November 2012.[11]

Between 2006 and 2014, biosimilar medicines have increased patient access by 44% overall within in the EU-5 countries.[12] Global biosimilars sales in 2015 reached about $1.7 billion, but by 2020 biosimilars penetration is expected to deliver from $11-$33 billion in savings across the EU[13] i.e., for instance, by 2020 biosimilar mAbs alone will shave €20 billion of the Europe's healthcare bill.[14]

1.2 Literature Review

A comprehensive literature survey was performed to retrieve the data from various databases describing the Biosimilars and their scenario in the European Union. The search strategy was done in the databases like European Medicines Agency (EMA), Generics and Biosimilars initiative (GaBI) Online, Organisation for Economic Co-Operation and Development (OECD) and other data sources provided by the Organization. The review was completed by retrieving the entropy of information from Gray literature and White papers along with other publications. The information was reviewed from the inception of regulatory pathway for Biosimilars in Europe to till date. Later, the data extracted was screened and tailored to evaluate the need and scope of the study and then the objectives were formulated for a way forward to the study.

In brief, the review of literature cites the information from some of the sources;

Most of the regulatory bodies and companies are looking at European track record for lessons learned on biosimilar launches and the market. The uptake of product varies widely based on the specific dynamics of the medication, regulatory framework, market competitiveness and stakeholders' landscape i.e. for example, even with substantial discounting of the erythropoietin biosimilar, the market in Europe is even prevailed by reference Erythropoiesis-Stimulating Agent (ESA) product. On the other hand, the launch of Enoxaparin, an anticoagulant biosimilar to Lovenox of Sanofi, in Europe has been more successful and boosted a differential share in the market.[15]

Companies must actively focus on their commercialization strategies for broader market access following the launch, although providers and few patients are familiar with the potential of

biosimilars, so educating these stakeholders about the safety and efficacy of biosimilars will requires nurturing the market as a whole. The key regulatory issues like Interchangeability and the International nonproprietary name (INN) will profoundly impact the biosimilars commercial strategies.[16]

The Analysts have forecasted that the global biosimilars market to reach $25-$35 billion by 2020. Since the first biosimilar in the European Union (EU) approved in 2006, there are now more than 450 biosimilars approved and around 250 in the pipeline globally. In EU, the regulators and payers have recognized the potential financial benefits of biosimilars and are driving the uptake. But the market uptake has been preceded slowly by physicians' skepticism and low awareness level among patients. Even tough, the EU market continues to have the highest number of biosimilar molecules filings compared to other developed markets.[17]

In spite of the challenges, biosimilars can be an attractive opportunity for companies looking to enter a therapeutic area or for existing players looking to foster their current status, as Europe can make an edge in terms of prospects; for patients by increasing access to medicines, for physicians & payers by promoting a stakeholder benefits model to enhance the market uptake and ultimately encouraging the stakeholders to work collaboratively to improve healthcare access.[18]

As the market for biosimilars proceeds to grow, many companies are trying to enter the space and are struggling to counter the challenges associated. The scenario requisites that an integrated strategy approach is must for the biosimilar development and commercialization phases. Along with it, the forces driving the biosimilar industry are milestones to reduce healthcare expenditures and so the booming market growth is accustomed for biosimilars.[19]

At last, by the information evoked, the need and scope of the study are defined and the objectives are framed accordingly for the purpose of proceeding with the study ahead.

1.3 Need and Scope of the Study

In Europe, Health spending accounts for around 11% of GDP.[20] Healthcare expenditure is high on the docket of every Member State of the European Union, with all governments being tasked to render the best and most up-to-date patient care, while at the same time trying to limit the

potentially huge increases in associated costs. The Biosimilars significantly increased access to greater number of patients at affordable cost thereby managing the healthcare budgets. These substantial benefits implied with biosimilars, however are achieved only if sustainable mechanisms are available to strengthen the entry into the market.

The uptake of biosimilars varies considerably by geography and therapeutic area across the EU countries.[12] i.e., the European Commission has acknowledged in the Workshop on Access to and Uptake of Biosimilars that the biosimilars uptake and competition varies across EU nations based on the therapeutic area of the biologics and the EU Member States policies. So, based on these considerations, the European Commission has given a call for better control of healthcare budgets and reduction of the health inequalities between and within EU Member States through an increasing competition between both reference biologic medicine and its biosimilar versions.[21] According to Scientific advisory panel of EMA, it is tenable to expect new filings and approvals for biosimilars in the years ahead, especially for biosimilars of Monoclonal Antibodies (mAbs) as many of the blockbuster mAbs are going off-patent.[22]

Majority of the companies are developing a framework to succeed in the biosimilars market, which involves addressing both strategic and tactical set of choices associated. The associated choices are addressed through the "Market Choice Strategy Cascade" Model and it aids a company to evaluate the strategic approach for specific product category and in this case, it is of biosimilar scenario.

The model postulates the market as the core implicitly the environment, value chain forces and stakeholders and depicts the relation between the vision, therapeutic area, competencies and strategy framework with each other and the market. It is represented as choice cascade because it elucidates the cascade of choices associated with the specific market to a company. This model can be engaged to have a strategic view of biosimilars in the market.

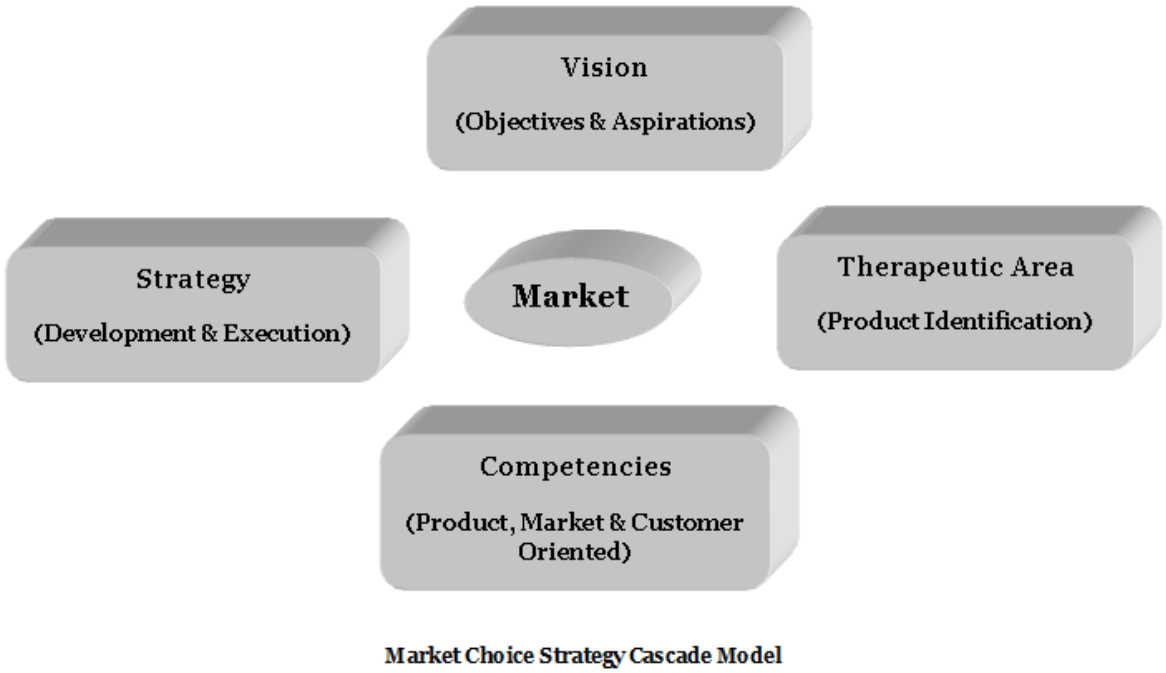

Figure 1.3.1: Market Choice Strategy Cascade Model

Along with this, the Companies quest to enter into or a sustained position within the biosimilar market must identify the requisite regulatory stipulations for European market to capture their interest and proceed further to establish their market value through an integrated commercialization strategy approach and the EU market delivers sustainability for the stakeholders through its functioning nature of competitive market.

1.4 Study Objectives

The objective of the study is to assess the,

1) Regulatory Challenges and apt Strategies
2) Commercialization Strategies
3) Impact of Regulations on Commercialization
   - of Biosimilars in the European Market.

The pillars of the study sphere are built on these objectives.

2. Methodology

The Methodology depicts the study approach i.e. the material and method employed.

2.1 Study Design

For this study, an Exploratory research approach was deployed with the perspective of formulating a commercialization oriented approach for Biosimilars in European Union. The exploratory study aims at gaining the familiarity with a phenomenon in order to formulate new insights.

This exploratory approach with qualitative outfit is a best suit, as the study entails the assessment of European regulatory framework and commercial strategies for biosimilars in to the market space. In fact, a qualitative research is apt as the study seeks to understand complex issues associated and addressing them by an integrated approach. Therefore, this approach was found to be more suitable than employing a quantitative method.

2.2 Study Duration & Context

The study duration is of 3 months i.e. time period between February 6, 2017 & May 5, 2017 and the study setting includes the European Union – Biosimilars market fabric postulating the stakeholders' scenario from commercial prospective. The stakeholders imply regulators, physicians, patients, payers and competitors in European nations under EMA.

2.3 Data Collection Procedure & Content Analysis

The Dual approach system is deployed to establish the objectivity of the research sphere. The first step, involves the retrieval of entropy of the information from various data sources like websites of WHO, EMA, FDA and other global regulatory authorities for regulatory publications on biosimilars, gray literature etc and is performed as the commentary was concerned with the entirety of the accessible data on biosimilars. The second step implies the Discussion-Framework technique, with the panel of experts of the domain to have a qualitative content emphasis and is transcribed to objective insight. Utmost, this dual approach is employed to have an integrated view of biosimilars market fabric in the European Union.

3. Findings & Discussion

The European Union (EU) was first to have a constituted policy and legal framework for the approval of biosimilar products in the world. The EMA in concert with the Committee for Medicinal Products for Human Use (CHMP), the Biotechnology Working Party (BWP) and the Working Party on Similar Biological Medicinal Products (BMWP) released specific guidelines to deal with all the facets of biosimilars. This was done in consultation with the stakeholders' perspectives.[23]

The authorisation of biosimilar medicines in the EU requisites the comparability data set ascertaining the biosimilarity with the reference biologic medicine and in fact, that a company developing a biosimilars has no data on the critical in-process controls and about the intermediates in the development process of the innovator biologic (because the data is of confidential information) and as a result exhibits subtle differences, so it add challenges to the situation at the regulatory prospect in displaying the biosimilarity to the reference biologic.[22]

3.1 Regulatory Challenges for Approval of Biosimilars in the European Union

The biosimilars poses substantial challenges to the companies for regulatory authorisation. These include the following;

3.1.1 Establishing Biosimilarity in line with Reference Biological Product

Biosimilarity is to be established to denote the comparability between a biosimilar and its reference biological product. The marketing authorisation of a biosimilar is on the grounds of regulatory assessment that the applicant has demonstrated the product's similarity to the reference biologic as outlined in the Committee for Medicinal Products for Human Use (CHMP) of EMA - Scientific Guidelines on Biosimilar Medicines. **Comparability** is the core principle for a biosimilar development to ascertain quality, safety and efficacy.[23]

Extrapolation of clinical efficacy studies to other indications of the reference biologic, which are not specifically studied during the clinical development process of the biosimilar product is achievable on the ground of overall evidence of comparability (for validation of biosimilarity) rendered with suffice scientific justification.[23] The comparability exercise with reference to innovator biologic is executed in **3 steps** to ensure biosimilarity.[10] It is as follows;

a) First step: Quality comparability studies (Physicochemical and Biological comparability)

b) Second step: Non-Clinical comparability studies

c) Third step: Clinical comparability studies.

3.1.2 Assessment of Immunogenicity

All the biologics demonstrate a greater capacity to elicit an immune response as they are protein derived compounds and therefore might be recognized by the human immune system as antigens. The immunological response is complex as it triggers antibody formation and leads to events like activation of T-cell, thereby contributing to loss of effect of the biologic medicine and any potential adverse effect in the patients. However, in majority of patients, an immune response does not lead to any clinical consequences. Immunogenicity may be influenced by factors relating to the biologic development process, the individual susceptibility of a patient i.e. Leukocyte antigen expression, co-morbidity and any early exposure cases, the disease case and the treatment method. These factors are to be evaluated in the development process of biologics (both the reference biologic and biosimilars). However, the immunogenicity of biologics cannot be often assessed completely during the development process and in clinical studies, because the patient-specific immunogenicity may sometimes emerge only after extensive usage and exposure, therefore further immunogenic studies are required after marketing authorisation too. So, the assessment of immunogenicity is also a part of **post-approval Risk Management Plan** (RMP) i.e. Pharmacovigilance activities.[22]

These challenges are to be figured out to attain the marketing authorization for biosimilars in the respective market.

3.2 Strategies to Address the Regulatory Challenges for Marketing Approval in EU

The **totality-of-evidence** approach has to be deployed for demonstrating the biosimilarity to the reference biologic, as to obtain the regulatory approval for market authorization. The approach involves the streamlining of clinical development process by endearing **ABCE** of biosimilars and ascertaining the totality of evidence in the **registration Dossier** of marketing authorization.

The totality of evidence establishes the analytical and biological relation data points and adhere the data extrapolation in line with the reference biologic[24] by endearing the ABCE path.[25] The ABCE of biosimilars are;

A - Accuracy of Analytics (Analytical demonstration and Biological characterization)
B - Bridging of Clinical data points
C - Curb the expectation of Clinical trials in every indication
E - Embrace Extrapolation.

Table 3.2.1: ABCE of Biosimilars

The approach exploits the variations by analytical demonstration and justifies the biosimilarity via the clinical development process as a whole. Even tough, through the analytical characterization, it is evident that the variations exist between the biosimilar and the reference biologic, the clinical process establishes the biosimilarity of the product justifying that the variability stays within the lines of specific quality parameters and is not substantial.

The analytical characterization and clinical trial process is imbibed as the comparability studies as a whole in line with reference biologic. The Quality comparability aspect is to have a comprehensive analytical characterization with regards to molecular structure and functional prospects. The Non-Clinical and Clinical comparability studies entails the evidence that any variations observed at the quality comparability level have no impact on the safety and efficacy of the biosimilars in line with the reference biologics in a robust head to head comparative way.

Each biosimilar application will be assessed on the individual basis and the EMA has released both the general and product specific guidelines in terms of quality, non-clinical and clinical issues and immunogenicity for every biosimilar product category[6] i.e. for example,

- Guidelines on Similar Biologic Medicinal Products - CHMP/434/04 Rev 1
- Guidelines on Similar Biological Medicinal Products comprising Monoclonal Antibodies: Non-Clinical and Clinical issues - EMA/CHMP/BMWP/403543/2010
- Guidelines on Immunogenicity assessment of Monoclonal Antibodies intended for In-Vivo Clinical use - EMA/CHMP/BMWP/86289/2010.

The analytical characterization quality attributes imbibed as comparability quality data is as follows;

Attributes	Key Considerations
Product-related	Percent Protein content, pH, Osmolarity, Excipients composition
Structure of Active Ingredient	Primary Structure must match the reference product and any differences in higher order structure need to be justified robustly as having very low or no impact at all.
Impurities	Process-related impurities like host cell proteins, trace solvents and leachable and the Product-related impurities depending on percent content, activity level may not impact the biologic activity, but may affects the immunogenicity profile.
Biological Activity	Potency and Receptor binding (for mAbs, both target antigen and Fc binding)

Table 3.2.2: Key Quality Attributes for Analytical Characterization

Besides it, the clinical development strategies should focus on patient selection, recruitment and appropriate clinical endpoints. The patient and sample size selection and recruitment is accelerated on case to case basis and incorporating appropriate clinical endpoints including validated biomarkers of efficacy and any surrogates (on case basis) with an integrated protocol design as a part of clinical trial design is a requisite to establish biosimilarity with the reference biologic.[19]

All these ensures the totality of evidence approach and ascertaining the same in the registration dossier filing for marketing authorization provides the comparability data establishing biosimilarity for approval purpose by the regulatory agency – EMA.

The registration dossier for a biosimilar comprises of a data package based on the scientific guidelines as per EMA. The dossier filed is accessed via the centralized procedure involving the two autonomous assessment teams from two member states and scientific experts from all the other member states.[22] The data package imbibed in the dossier should ensure the biosimilarity, and then the biosimilar receives the marketing authorization from the European Commission.

Quality Data	Data points on manufacturing process, process controls, analytical tests and stability data i.e. analytical demonstration data.
Non-Clinical Data	Data on In-Vitro studies and in case of exceptionality, it implies PK & PD studies along with tolerability case models.
Clinical Data	Data of both positive and negative results of clinical trials and also postulates the data on Immunogenicity.
Pharmacovigilance	Data on the Risk Management Plan (RMP) and Pharmacovigilance system postulating the Periodic Safety Update Reports (PSURs).

Table 3.2.3: Data Package imbibed in Dossier for Marketing Authorization by EMA

A summary pertaining to the biosimilar data and its assessment is made accessible in the public domain as European Public Assessment Report (EPAR) by EMA, after the issue of marketing authorization by the European Commission. The Risk Management Plan (RMP) is imbibed in the EPAR after authorization of the biosimilar product and is to be updated throughout the lifetime as a part of Pharmacovigilance system to have a view of immunogenicity issues.[22]

Through the totality of evidence approach in alignment with the ABCE of biosimilars and ascertaining the evidence data points in the registration dossier for marketing authorization, streamlines the regulatory challenges buckled for the marketing approval of biosimilars in the European nations. As soon as the European Commission has cleared the path for marketing authorization, the companies then should focus on the commercialization strategies to ensure the

biosimilar product in the market space and thereby to render the patient access for economical treatment as par with healthcare access program.

3.3 Commercialization Strategies to have an Edge in Biosimilar Market Space

Once the biosimilar sponsors/companies overcomes the regulatory hurdles and gains marketing authorization are to define the commercial strategies to be deployed in order to enhance the uptake of biosimilars with the perspective of stakeholders and maximizing the market potential. As identified, the level of uptake of biosimilars varies across the EU nations based on the existing policies in each individual nation and also on product category/case to case basis.

One of the major key influential factors for the biosimilar market penetration in EU is **Payer environment** as a part of **Health Technology Assessment** (HTA) Committee under **National Health System** (NHS) of European Commission and **Four** unique payer models/approaches[8] have been evolved across the Europe for the uptake of both reference biologics and biosimilars (as the lever to drive the adoption of biosimilars is Price). The four payer models are as follows;

- **Tender Model** - Based on the principle that the government plays the role of payer and negotiates with the supplier. The model is in practice in the nations like Poland, Norway and Hungary (to an extent). The influence of the model has bought in to focus by the entry of the 1st monoclonal antibody i.e. Infliximab in the Europe in September, 2013. The monthly uptake of the biosimilar mAbs has been 46 % in Poland and 36 % in Norway respectively, between December 2014 and February 2015.[26]
- **Hospital Plan Purchasing Approach** – It is typically in use, when the national purchasing does not occur and relies on the ability of hospitals plan to negotiate with the competitors of biological products (biosimilar with reference biologic) with or without payers involvement. In this, discounts from list price can be achieved, particularly when negotiating is done at a regional level and in addition to it, there is discretion in the planning among hospitals, pharmacies and payers to implement their own tender models, which can have a significant impact on biosimilar adoption. This approach is implemented in the nations like Italy, Spain, Germany and U.K.
- **Competition-Driven Free Market:** It involves either a minor portion of direct involvement or no direct involvement at all by the payer in setting or even negotiating the

prices. In fact, the product companies are free to set their own price in order to drive the free-market competition. The nations that have adopted this approach include Belgium, Finland and Switzerland.

- **Prescribing, Substitution, Switching Guidelines and Mandates:** This approach can be implemented as a stand-alone policy or in combination with the other three models. In this model, a biosimilar may be mandated as the first choice of therapy or the prescribing guidelines may recommend its use as the first choice of treatment. As of October 2014, Denmark has effectively implemented this approach to influence biosimilar prescribing.[12] Across the Europe, decision on prescribing policies like substitution are made at the national level and in the countries like Germany and Italy, biosimilars are specifically excluded from the list of products entailed for substitution, but in other countries where substitution is permitted only for International Nonproprietary Name (INN) prescriptions, the physicians prescribe biologics by brand.[27] So in 2013, France has passed a law in its territory permitting the restricted form of substitution, wherein the pharmacists may dispense a biosimilar for a patient who is initiating the therapy for the first time and has been prescribed with the reference product.[28]

The Health Technology Assessment and Reimbursement Process crusades the Payer policies towards the market access of the Pharmaceutical products i.e. in this case, Biosimilars across the European Nations, thereby substantiating the companies with the operative pace towards the market space. The Overview of Pharmaceutical HTA & Reimbursement Process across EU5 is as follows;

Pharmaceutical HTA & Reimbursement Process
Germany **Regulatory Agency:** EMA or Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM (German Federal Institute for Drugs and Medical Devices). **Decision-makers:** G-BA (Gemeinsamer Bundesausschuss – Federal Joint Committee) **Decision-making Process Influencers:** Ministry of Health, Federal Institute for Drugs and Medical Devices, German Institute for Health Technology Assessment (DAHTA), Institute for Quality and Efficiency in Healthcare (IQWIG), The Social Insurance Organisation (Bismarckanian Social Insurance System – Social Health Insurance) and Federal Association of Statutory Health Insurances (GKV-Spitzenverband). **Pricing & Reimbursement approval:** Federal Joint Committee (G-BA). **Reimbursement:** Statutory Health Insurances (SHIs). **Cost-Benefit Assessment:** Institute for Quality and Efficiency in Healthcare (IQWIG) – Efficiency Frontier technique.
France **Regulatory Agency**: EMA or Agence Française de Securité Sanitaire des Produits de Santé – AFSSAPS (French Medicines Agency). **Decision-makers**: HAS (Haute Autorité de Santé) – Technical Assessment by SMR & ASMR committees, CEPS (Comité Economique des Produits de Santé) – Pricing and UNCAM (Union Nationale des Caisses d'Assurance Maladie) – Reimbursement rate fixation. **Decision-making Process Influencers**: French Medicines Agency (AFSSAPS). **Pricing**: CEPS **Reimbursement Decisions**: Governed by Health Ministry. **Reimbursement**: National Health Insurance Fund (CNAM - Caisse Nationale d' Assurance Maladie). **Cost-Benefit Assessment**: SMR (Medical Benefit Assessment) and ASMR (Improved Medical Benefit Assessment) Committees – Incremental Cost Effectiveness Ratio technique.
UK **Regulatory Agency**: EMA or MHRA (Medicines and Healthcare Products Regulatory Agency). **Decision-makers**: England - NICE (National Institute for Healthcare Excellence), Scotland - SCM (Scottish Medicines Consortium), Wales - AWMSG (All Wales Medicines Strategy

Group) and Northern Ireland - HPSS (Department of Health, Social Services and Public Safety). **Decision-making Process Influencers**: NICE and NCCHTA (National Coordinating Centre for Health Technology Assessment) in UK. **Pricing and Reimbursement**: NICE across United Kingdom. **Cost-Benefit Assessment**: NICE – Incremental Cost Effectiveness Ratio technique.
Spain **Regulatory Agency**: EMA or Agencia Espanola del Medicamento y Productos Sanitarios – AEMPS (Spanish Medicines Agency). **Decision-makers**: Central and Regional Governments' Health Ministry Department, with the decision making process at 3 Levels of HTA (National level for common benefit package excluding Pharmaceuticals, National level for Pharmaceuticals and Regional level). **Decision-making Process Influencers**: National Health Service (SNS - Sistema Nacional de la Salud). **Pricing and Reimbursement approval**: Inter-territorial Councils of Spanish Government. **Reimbursement**: National level – 4 (AEMPS, AETS, DGFPS and CIPM) and Regional level – 5 (AATM, AETSA, AVALIA-T, OSTEBA and UETS). **Cost-Benefit Assessment**: SNS - Incremental Cost Effectiveness Ratio technique.
Italy **Regulatory Agency**: EMA or Agenzia Italiana del Farmaco – AIFA (Italian Medicines Agency). **Decision-makers**: Ministry of Health, Italian Government. **Decision-making Process Influencers**: SSN (Servizio Sanitario Nazionale - National Healthcare System). **Pricing and Reimbursement approval**: CPR (Pricing and Reimbursement Committee). **Reimbursement**: CTS (Comitato Scientifico e Tecnico – Reimbursement Organization). **Cost-Benefit Assessment**: CPR - Incremental Cost Effectiveness Ratio technique.

Source: ISPOR

Table 3.3.1: Overview of Pharmaceutical HTA & Reimbursement Process across EU5 Nations

The biosimilars provides the opportunity of savings to the healthcare system and the potential savings by biosimilars comes to European payers, at the time of implied budgetary pressures

specifically. The constrained environment of payers is stimulating a orbit of initiatives designed to constrain rise in healthcare budgets, especially with the target of Pharmaceutical budgets.

Constrained Payer Environment
France The 2016 draft social security finance law (PLFSS - projet de loi de financement de la sécurité sociale) employs an orbit of initiatives designed to reduce the deficit of the social security system (excluding pensions) from €9 billion to €6 billion in 2016. The annual growth rate target of healthcare expenditure (ONDAM - Objectif National de Dépenses d' Assurance Maladie) is 1.75 percent in 2016. In order to achieve this, the legislation portraits the healthcare sector savings of €3,410 million, inclusive of €1,580 million of Pharmaceuticals.
Italy As per the Stability law, 2015, the healthcare savings of €2.3 billion to be achieved in 2015, based on the measures implemented at the regional level.
Spain As per the reports, by October 2014, six autonomous communities (CAs) – Baleares, Canarias, Cataluña, Extremadura, Valencia and Murcia had exhausted their Pharmaceutical budgets for 2014 and had to rely upon the funding which is on the basis of credit line from central government to pay the invoices of Pharmacy. Later, in January 2015, the Treasury is of concern that the seven CAs – Castilla-La of Mancha, Extremadura, Castilla y León, Cataluña, La Rioja, Valencia and Murcia were at the risk of being incapable of paying the Pharmaceutical invoices for the year, as the Pharmaceutical budgets are lower than the official estimates of total spending in 2014.
UK The report by NHS (National Health Service) England and the Health Services regulator for England (Monitor) in October 2014 warned that the UK faces substantial annual funding deficit of GBP 30 billion by 2020 as the NHS in the UK facing significant challenges over a period of time.

Source: IMS Institute for Healthcare Informatics

Table 3.3.2: Constrained Payer Environment

The extent, to which payers are capable of redirecting the expenditure towards budgetary relief, new generations of innovative treatment and greater patient access, by substantiating the net savings from biosimilars, depends on their policy approaches towards the biosimilars market space. The general payer policies and market access regulations for uptake of biosimilars across European Union are as follows;

European Nations	General Payer Policies & Market Access Regulations across EU
France	**Pricing & Market access process** o Similar to reference biologic processes of Medical Benefit Assessment, but the review is typically shortened. **Hospital setting** o Mandatory price cut for reference biologic (at least by 10%) o Biosimilar price must be ≤ to the price of reference biologic and same dispensation status with reference biologic. **Retail setting** o Mandatory price cut of reference biologic by 15-20% o Biosimilars needs to be priced at 25-35% less relative to that of innovator's initial price.
Germany	**Pricing & Market access process** o AMNOG (Arzneimittelmarkt-Neurordnungsgetz) process, is not applicable for biosimilars pricing and market access. **Reference Biologic Pricing** o No specific rules & regulations, but in case of FRP (Fair and Remunerative Price) group, the innovator's list price will be usually adjusted to have a full reimbursement with the FRP level. **Biosimilar Pricing** o Free pricing for biosimilars, however the major demarcation from reference biologic price is expected by the payers.
Italy	**Pricing & Market access process** o Process is similar as reference biologic.

	Reference Biologic Pricing o No mandate of discount for reference biologic after Loss of Exclusivity period. But, the AIFA (Agenzia Italiana del Farmaco) has started re-negotiation of prices for reference biologics, only in case of reimbursement has not yet filed for biosimilars by companies. **Biosimilar Pricing** o AIFA mandates a price reduction of 20% to that of reference biologic.
Spain	**Pricing & Market access process** o Process is similar to reference biologic but is typically shortened. **Reference Biologic Pricing** o No mandate of discounts either after Loss of Exclusivity or Biosimilar entry, unless the creation of FRP group. **Biosimilar Pricing** o 25-30% discount to reference biologic.
United Kingdom	**Pricing & Market access process** o Standard pricing and market access policies framed by NICE (National Institute for Healthcare Excellence) and has issued its latest guidance and advice on biosimilars in January 2015, stating that biosimilars should either subject to MTA (Multiple Technology Appraisal) together with the reference biologic or to lesser prescriptive as the summaries of evidence. **Reference Biologic Pricing** o No defined rules of pricing after launch of biosimilar medicines. **Biosimilar Pricing** o Free pricing for biosimilars and is included under the control of Pharmaceutical Prices Regulation Scheme (PPRS) system.

Norway	**Pricing & Market access process** o Similar pathway as that of other Pharmaceutical products. But the Stepped Price model implied for generics is not authenticated to biosimilars as they are not observed as interchangeable with the reference biologic. **Biosimilar Pricing** o 9% of discount is mandated for biosimilars with that of reference biologics in order to be listed by the Norwegian Drug Procurement operation (LIS).
Poland	**Pricing & Market access process** o Similar pathway as that of other Pharmaceutical products, but the AOTMiT (The Agency for Health Technology Assessment & Tariff System) process is excluded. **Reference Biologic Pricing** o As per the Reimbursement Act of 2012, the reference biologic losing their exclusivity should cut down their price by 25% to be eligible for renewal of reimbursement policy. But in reality, due to the confidential contracting agreements, this is not observed effectively. **Biosimilar Pricing** o 25% of price discount to that of reference biologic is mandated.

Source: Simon-Kucher & Partners

Table 3.3.3: General Payer Policies & Market Access Regulations across European Nations

The factors that affect the sustainability of biosimilars market access are Payers (External factor) and Company (Internal factor) i.e. the payer's policies and the companies approach for the market access respectively. Ideally, the sustainability criteria rely on both payers and companies' perspectives in a market.

The United kingdom (UK) and Germany have evolved as the markets for the sustainable biosimilar access because of the pricing and market access policies (P&MA) deployed in the nations respectively.

Pricing and Market Access policies employed for sustainable Biosimilar Market	
UK	○ Four Regional Tender system ○ National/Regional Guidance – NICE and CCGs ○ Gain sharing – Clinical Commissioning Groups (CCGs) and Hospital level.
Germany	○ Target Agreements – Biosimilar Quotas ○ Sick Funding system – Tendering and Open-house Contracts ○ Bio-like initiative – Information and Education program ○ Gain sharing – at the Physician level i.e. KV Westfalen-Lippe and Sick fund Barmer GEK.

Source: Simon-Kucher & Partners

Table 3.3.4: P&MA Policies Employed for Sustainable Biosimilar Market

Pricing and Market Access policies are sustainable in the case, where payers are able to ascertain focused monitoring of their implementation and subsequently incentivizing physicians to adhere to the policies. Effective orientation of these policies in regards to physician and patient access programs ensures the dynamic and sustainable biosimilar market across EU.

The **Physician** and the **Patient** prospects are the other key influential factors for the biosimilar uptake in achieving the successful **Go-to-Market** phenomenon. So, as the market awaits the price shakeout with the policies, the sole is the physician and patient support programs towards the value proposition and in ascertaining it, there is an outstanding contend of anecdotal information to be disseminated in the Physician community in order to support the patient access.

Primarily, the **Physicians** have concerns about the clinical evidences of biosimilars in prospect of safety and efficacy.[16] The companies should disseminate the clinical evidences to counter the issues regarding the safety and efficacy data of biosimilars by educating the physicians by providing the data centered on clinical pharmacology in line with the reference biologic and thereby making them as a core in patient supporting programs for biosimilar orientation. The Physician role as a driver of biosimilar adoption comes in to play by upfront investment of real world data evidences and education programs especially aligned with the Key Opinion Leaders (KOLs) in the community.

The Physicians and Pharmacists to be provided with the insights of biosimilars, as these healthcare providers are riddled with myriad of questions to be resolved by the companies[29] like;

- Does the biosimilar is as safe and efficacious as the reference biologic?
- Does a biosimilar have all the indications of a reference biologic?
- Does the biosimilar indications approved through clinical trials or extrapolation?
- Does the dosing and administrative device of biosimilar are equivalent to the reference biologic?
- Does the biosimilar ensure patient compliance?
- Does the biosimilar have been designated as interchangeable by the policies in the region and the labeling discloses it?

  Does the biosimilar to be prescribed by the INN or with a Brand name specific to a company?
- Does the formulary barrier exist in therapeutic case of biosimilar choice for the patients?
- Does there is reimbursement support policy by the payers to the patient with biosimilar therapy?

Even the medical history of the patient is also a factor that is imbibed as an issue to prescribe i.e. in majority of the cases, the patients with chronic diseases may be stabilized on a particular biologic product and the physician may choose to maintain the patient on the same product, thereby influences the physician choice of decision to prescribe a biosimilar.[8] Utmost, navigating the list of requisites incur the substantial level of education for a physician to make a reliable informed choice.

Physician at the Heart of Decision-Driving
Norway The Norwegian Drug Procurement Cooperation (LIS) panels comprises of Physicians and delegates from all the 4 healthcare region of the country. The panel evaluates the tenders for the medicines procurement for state hospitals and the physicians' takes into count an orbit of factors such as clinical and cost related, while deciding to award a tender to a specific product. As a result, Physicians drive the biosimilars in the market.
Denmark The Council for the Use of High Cost Hospital Medicines (RADS) has a similar approach as the Norwegian LIS system.
Spain There is a system of prescribing indicators in some regions of Spain and these enacts as the target for physicians in prescribing the biosimilars. The Physicians are financially incentivized and other benefits like training is provided on reaching the indicated target.
Italy A unique approach is deployed in Italy, i.e. a system in which 50% of the savings generated from the biosimilar uptake are reallocated in order to intensify the budget by 20% allotted for the coverage of reference biologics.
Germany The Physicians association (KV – Kassenärztliche Vereinigung) and the Statutory Health Insurers are proactive in reaching to physicians via discussion forums to equip the concept of biosimilars and ensure the prescribing quota by enforcing the "Dear Doctor Letters" (Ärztebriefe). The KV enforcement has highlighted the savings potential of biosimilars, thereby substantiated to be a tool to boost the competition and intensify the biosimilars uptake.
Eastern Europe The uptake of Biologics has been historically low, due to the cost factor. Even tough, these markets have encountered progressive uptake of versions of biologics i.e. biosimilars as the locus is Physician and as a whole the prescribing pattern of physicians in order to avail their patients, the cost effective treatments.

Source: IMS Institute for Healthcare Informatics

Table 3.3.5: Physicians at the Heart of Decision-Driving for the Uptake of Biosimilars across EU

The **Patient awareness** is the other key influential driver of biosimilars uptake and the patients receives the information regarding healthcare aspects from variety of sources, but the **Physician** often remain as their primary point of contact. It marks the clear implications for patient education by the physicians to ensure the adoption of biosimilars from the point of companies.

Patients might be reluctant to switch to a biosimilar, in the case of achieving satisfactory outcomes with the therapy by reference biologic and is covered with the healthcare reimbursement plan. The awareness among them is provided by the physician by equipping with the suffice knowledge about the therapy with biosimilars and switching. However, it depends on the national/regional policies across the Europe for the patients for those are already on the treatment with the reference biologics and in case of naive patients, the physicians can prescribe the biosimilar, provided the patient equipped with the information about the biosimilars and thereby adheres to the patient access support programs.[16] The companies and the payers' needs to work collaboratively to formulate the plan to establish value added services for the patients to ensure the uptake of biosimilars.

Unlocking the potential of biosimilars requisites a focused approach for commercialization and to counter the impact of regulations on it, thereby orienting towards the market access. The Gray areas of commercialization need to be addressed and the value proposition is to be framed for the stakeholder orbit to ascertain the patient access and thereby to sustain the edge in the market space.[30] The success in overcoming the gray areas necessitates a unique Go-to-Market consideration to encompass the biosimilar market uptake by stakeholders.

3.4 Gray Areas of Commercialization across EU

The regulatory issues like Interchangeability, Naming and Pharmacovigilance aspects and the other issues like IPR & Trade Secrets and Innovator/Competitors orientation towards the market space enacts as the gray areas of commercialization.

One of the major regulatory issues is **Interchangeability** in the European Nations. The EMA had announced that the member nations are solely responsible to decide upon the issue and the nations have framed their policies on interchangeability as par with EMA guidelines[16] and the policies differ across the EU.

Interchangeability Regulatory Landscape
France France has passed the legislation in 2014, allowing the automatic substitution i.e. interchangeability is allowed with the informed choice of the patient.
Germany No authorized legislation regarding interchangeability, but the pharmacist can substitute a biosimilar in consultation of physician i.e. switching depends on physician.
UK Interchangeability is not allowed, but the physician is allowed to switch depending on the case.
Spain Interchangeability is not allowed and the switching depends on the physician as a part of economic prescribing pattern.
Italy Interchangeability is not allowed and the AIFA (Agenzia Italiana del Farmaco) has stated that the physicians can prescribe biosimilars for the patients naive to the therapy case.

Source: Monitor Deloitte

Table 3.3.6: Interchangeability Regulatory Landscape across EU5

The **Name Game** has revolved around **INN** (International Non-Proprietary Name) to the biosimilars in Europe, while many industry leaders favor in giving a unique INN to biosimilar versions corresponding to reference biologic, but the EMA in 2009, has stated that the biosimilars are referred by their unique trade/brand names rather than INN system and the INN of a biosimilar is identical to its reference biologic. For instance, the European packaging of Zarzio (Filgrastim Biosimilar) by Sandoz denotes the product by its trade name.[31]

The **Labeling and Public Information** of biosimilars should aims to provide an orbit of information on safety and efficacy and about dosing and administration pattern in line with reference biologic. The innovator biologic companies are of the strong opinion that specific rules should be deployed by EU for the biosimilar companies, to clearly denote their product is a biosimilar to the innovator biologic and also the biosimilar labeling should denote the way in which every indication has been approved by EMA, thereby demonstrating safety and efficacy. In the recent years, these components are notified in the European Public Assessment Report

(EPAR) by EMA and also to an extent, in the product literature of biosimilar. In support to this, the UK Medicines and HealthCare Products Regulatory Agency has announced that Biosimilars will carry a Black Triangle symbol, to specify as biosimilars and that should be monitored for the emergence of any adverse events. In March 2013, the European Commission adopted the symbol for the biosimilar products.[32]

The aspect of **Pharmacovigilance** is related to Immunogenicity issue of biosimilar and any other adverse events. The immunogenic potential as stated might be inherent to the product, patient and therapy regimen. The risk of immunogenicity is to be monitored by surveillance of biosimilars via patient health records. The innovator biologic companies in their marketing campaign, claiming that the biosimilars are having poor safety profile. As the biosimilars are marketed, the companies should prepare reports on regular basis to review the data on safety parameter and are called as Periodic safety Update reports (PSURs). Along with this, Post-Authorisation Safety Studies (PASS) are also a requisite and to ascertain the safety profile of biosimilars, the EU Pharmacovigilance legislation has stated that biosimilars should include a Black symbol along with the sentence inviting the reporting of adverse effects/events, these are to be included in the summary of product literature as well as patient information leaflet. The identification of adverse reaction with regards to manufacturing is of crucial one for biosimilars, so the EU legislation requisites the name of the biosimilar as well as its Batch number to be included in the adverse drug reaction (ADR) report. The **EudraVigilance** system ensures the reporting of adverse reactions to the National Competent Authorities (NCA) or EMA either by biosimilar companies, physicians, nurses and patients or can be retrieved from the scientific literature through the continuous screening and evaluation and finally, the data obtained from all the avail sources are collated for effective Pharmacovigilance system.[22]

The market entry of biosimilars is determinately blocked by **Patent** (IPR) rights as well as the **Trade secrets** (as a part of Data exclusivity) of reference biologics. The data exclusivity poses the delay in development process and once after the development stage, the biosimilar is to be validated in line with reference biologic. Along with it, the entry is restricted by patent extensions by gaining approval for another therapeutic indication etc. For example, the market entry of Infliximab biosimilar is delayed even after the authorisation because of gaining the approval for Pediatric use of Infliximab by Innovator company (Remicade® - Reference

Biologic by Johnson & Johnson) for 6 months period and the patent rights are territorial across EU and this further delayed the entry of biosimilar.[33] Along with it, the innovators offer competitive non-transparent rebates to all the stakeholders to sustain their market.

The **Market Orientation** of companies (Innovator/Competitors) imposes barriers in biosimilars uptake. For example, Roche has developed 2 drugs of biologic origin, named Perjeta® (Pertuzumab) and Kadcyla® (Adotastuzumab emtansine) to replace its own biologic market, Herceptin®, as the EU patent of it expires in 2014.[34] In order to strengthen the market position, Roche has developed a **Bio-better** version of its own biologic, Rituxan® called Gazyva® with premium pricing strategy. The bio-better improves the market access proficiency for an innovator to be more successful than the biosimilar in captivating the market share and space as well.[4]

Unlocking the potential by overwhelming the gray areas of commercialization requisites the Pharmacovigilance surveillance along with the differentiation approach, which is not only in terms of pricing/cost effectiveness therapy but also in offering the perceived value added services to all the stakeholders on the basis of real world evidence approach and branding in order to ensure the sustained market space for biosimilars.

3.5 Commercial Success Approach Model for Biosimilars

The Bio-Pharmaceutical companies' quests to enter the space are striving to sweep over the unique challenges at the regulatory level and optimal access of market space for biosimilars. From navigating the complex EMA regulatory landscape to ascertaining optimal market access, the roadmap for biosimilars is riddled with the possession of "Decision-Devising Model". The model postulates the Regulatory and Commercial considerations.

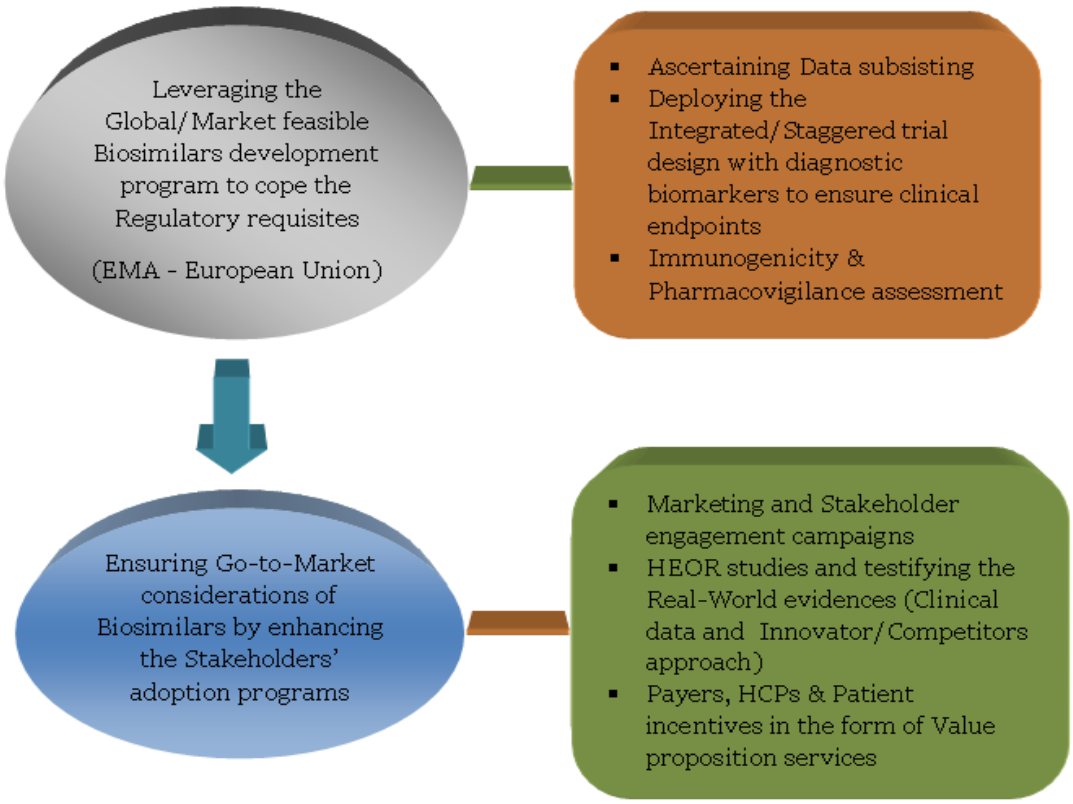

Figure 3.5.1: Decision-Devising Model

Along with it, a concurrent work stream should be tackled to assess payer and physician willingness to pay and prescribe respectively for the potential biosimilars. The cases in which reimbursement policies and system appear challenging, then the biosimilar companies should design the market oriented program in a way to elucidate real-world evidences and thereby the market and price have to play in the scenario.

On the basis of Decision-Devising model, the companies can evaluate its competencies in order to approach the market by performing SWOT model analysis of itself and the market of commercialization, PESTLE and Porter five force analyses of the market, Operating capacity and financial stability of self and the Stakeholders' sustainability. By considering these, the companies approach the market with divergence and the approach of the companies is categorized in to 4 segments orientation.[19]

Companies Approach	Segment Sustainability	Example of Companies
Companies with Innovative Biologics deploying the approach of Bio-better version	Defending their market share and space from Biosimilars	Roche (Gazyva® - Bio-better version of Rituxan®)
Companies developing and marketing the Biosimilars, while maintaining the Innovative Biologics portfolio	Gaining maximum space in the market with diversified portfolio	Sandoz (Novartis AG) – Zarzio (Infliximab Biosimilar) Amgen – Solymbic (Adalimumab Biosimilar)
Companies of Generic leaders leveraging their expertise in the development and marketing of Biosimilars	Diversifying in to new markets as a part of globalization and thereby access in to the market space	Hospira – Nivestim (Filgrastim Biosimilar)
Companies with either CRM expertise or of diverse industry entrant in to the market	Diversifying their expertise to have an access of market space	Celltrion – Truxima (Rituximab Biosimilar) Samsung Bioepsis – Flixabi (Infliximab Biosimilar)

Table 3.5.1: Four Segment Orientation of Companies to derive the Biosimilars Market Space

Besides, the type of approach deployed by the companies to derive a market space, the commercial success is attributed by the companies' decisions towards the orientation of space and the stakeholders in the market for biosimilars. The commercial success model attributes for biosimilar companies' performance is;

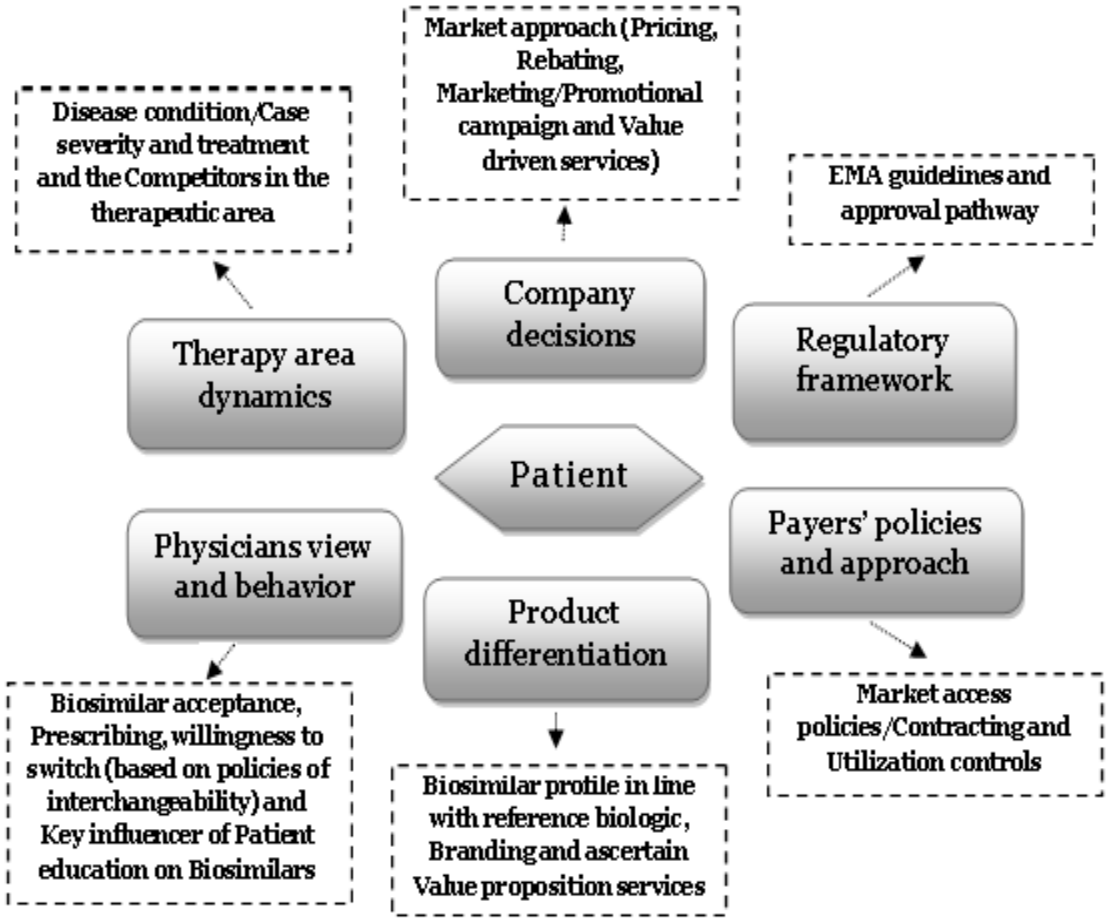

Figure 3.5.2: Commercial Success Approach Model for Biosimilars in EU

The model attributes the performance of biosimilar companies and drives the market space in view with stakeholders, with the company specific market oriented approach to derive space in the EU biosimilars market.

Winning firms will establish an agile model that allows them to promptly integrate the data of market with real world evidences, translating into insights to enable decisive responses in view of stakeholders and the orientation towards the market space, thereby ascertaining the successful Go-to-Market phenomenon of Biosimilars commercialization across the European Nations.

4. Conclusion

Biosimilar companies seeking to enter in to the European market are struggling to sweep over the unique challenges at the regulatory level and gaining optimal access of market space for biosimilars. From navigating the complex EMA regulatory landscape to ascertaining optimal market access, the roadmap for biosimilars is riddled with the regulatory and commercial considerations, to craft a strategy that integrates the roadmap in compliance with regulatory framework and commercialization approach.

In order to ascertain the integrated prospects of regulatory approval, the unique challenges of it are to be addressed by streamlining the clinical development process and demonstrating the data of real world evidences. The regulatory strategies must address the specifications pertaining to the product, its indications and the market by deploying an approach called, totality-of-evidence for establishing the biosimilarity of the product in line with reference biologic, so as to gain the marketing authorization from the European Commission via EMA.

Ensuring the speed-to-market is by leveraging the Go-to-market considerations after the approval, in order to optimize the market access via stakeholder engagement approach in marketing campaign. Among the stakeholders, Payers execute the role of major driver of biosimilars uptake followed by Physicians and ultimately the Patients, as the market is of payer driven. Along with the payers, the physicians are the heart of decision driving for patient access/support programs enabling the cost effective therapy, thereby ensuring the market access of biosimilars.

The Biosimilars provides the opportunity of savings to the healthcare system by 2020 i.e. the penetration of biosimilars is expected to have deliver the savings from $11billion to $33 billion across the EU. The constrained environment of payers is stimulating an orbit of initiatives designed to constrain rise in healthcare budgets, especially with the target of Pharmaceutical budgets and the extent, to which payers are capable of redirecting the expenditure towards budgetary relief, new generations of innovative treatment and greater patient access, by substantiating the net savings from biosimilars, depends on their policy approaches towards the biosimilars market space across the EU nations. Pricing and Market Access policies are sustainable in the case, where payers are able to ascertain focused monitoring of their

implementation and subsequently incentivizing physicians to adhere to the policies, as the ultimate goal is to optimize the patient access and the return on investments in the EU market space.

Besides these, unlocking the potential of biosimilars to capture the market space relies on countering the gray areas of commercialization. It requisites the Pharmacovigilance surveillance along with the differentiation approach, which is not only in terms of pricing/cost effectiveness therapy but also in offering the perceived value added services to all the stakeholders on the basis of real world evidence approach and branding in order to ensure the sustained market space for biosimilars by Go-to-Market consideration approach across the EU.

However, the policies vary across the Europe for biosimilars, with prospect of Payer policies, Physician and Patient acceptance level on case to case basis and the overall environment of biosimilar uptake i.e. overall uptake is increasing but the adoption and usage varies on case basis across the nations.

EU5 Nations	Biologics Market	Regulatory dynamics	Payer policies	Physician acceptance	Patient acceptance	Biosimilars presence
France						
Germany						
UK						
Italy						
Spain						

High Moderate to High Moderate Low

Source: Monitor Deloitte and Quintiles IMS

Table 4.1: Overall Pattern of adoption & usage of Biosimilars on Case to Case basis by Stakeholders across the EU5 Nations

In fact, the therapy area to enter with in to the European market is solely relies on the companies' biosimilar product categories and competencies requisiteness for that particular market, but the impact of stakeholder advocacy persists dynamically on the companies' market approach.

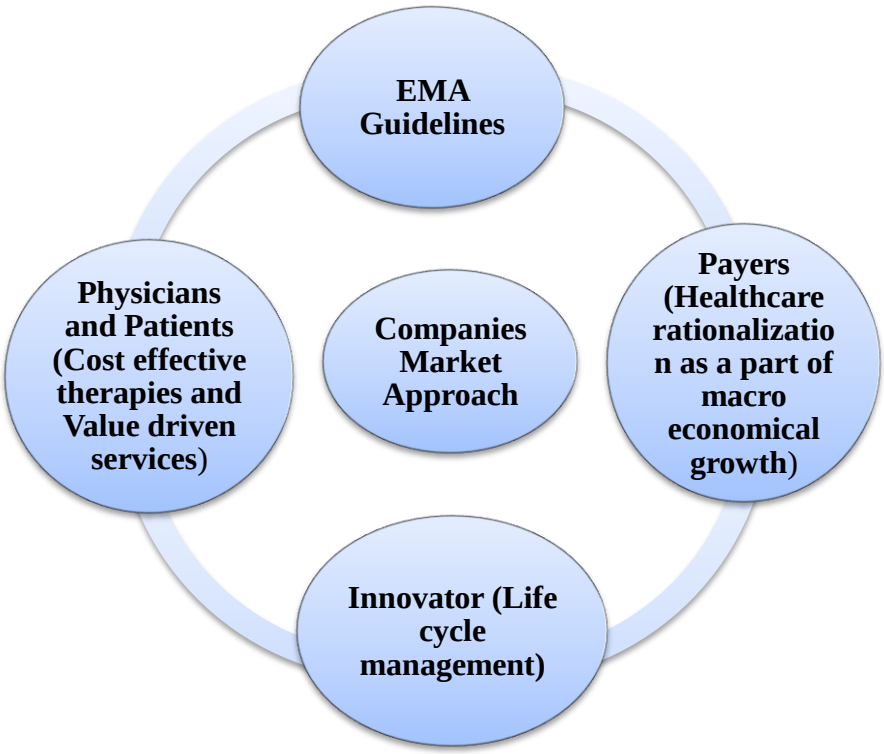

Figure 4.1: Stakeholder Advocacy of Biosimilars in Europe

Expediting the optimal market access across the European nations relies on the regulatory body (EMA), Payers, Physicians and Patients (however, the policies and level of acceptance varies respectively) across the EU. Yet, the market oriented approach relies on company to company entering in to the space on case to case basis.

Ultimately, the successful commercialization approach integrated with the regulatory roadmap and the Go-to-Market phenomenon by countering the gray areas of commercialization by deploying the market oriented approach (specific to each European nation) enacts as the winning strategy to gain the access in the market space, thereby unlocking the potential of biosimilars by the companies with the real world evidence and providing the therapy with value proposition to the patients across the European nations.

5. Bibliography

1. World Health Organization. Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Bio-therapeutic Products (SBPs). World Health Organization; October 23, 2009.

2. European Medicines Agency. Questions and Answers on biosimilar medicines (similar medicinal products). European Medicines Agency; September 27, 2012.

3. IMS Health. Searching for Terra Firma in the Biosimilars and Non-Original Biologics Market: Insights for the Coming Decade of Change; 2013.

4. Deloitte. Winning with Biosimilars: Opportunities in Global Markets; 2015.

5. Nitin Nayak et.al, 6 Factors Driving Global Biosimilar Market Growth. Biosimilar Development; 2016.

6. EMA Biosimilars [Accessed February 10, 2017]
   Available from:
   http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp.

7. Krishnan et.al, Global Regulatory Landscape of Biosimilars: Emerging and Established Market Perspectives. Dovepress; February 17, 2015; 5; 19-32.

8. Amgen. Trends in Biosimilars. Our Next Chapter in Health Care; 2016.

9. Quintiles IMS. Biosimilars in Europe; 2016. [Accessed February 15, 2017]
   Available from:
   http://www.quintiles.com/microsites/biosimilarsknowledgeconnect/biosimilarsbyregion/europe

10. Guideline on Similar Biological Medicinal Products – CHMP/437/04 Rev 1. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency; October 23, 2014.

11. Biosimilars Approved in Europe. GaBI Online; February 2017. [Accessed March 1, 2017]
Available from:
http://www.gabionline.net/Biosimilars/General/BiosimilarsapprovedinEurope

12. IMS Health. Assessing biosimilar uptake and competition in European markets; October 2014. [Accessed March 1, 2017]
Available from:
https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Assessing_biosimilar_uptake_and_ competition_in_European_markets.pdf.

13. Haustein R. et.al, Saving Money in the European Healthcare Systems with Biosimilars. Generics and Biosimilars Initiative Journal; 2012.

14. Gareth Mac Donald. Biosimilar mAbs to cut Europe's Healthcare Bill by €20bn by 2020. Marken; September 16, 2014.

15. Grabowski H. et.al, Biosimilar Competition: Lessons from Europe. Nature Reviews Drug Discovery; 2014; 13(2); 99–100.

16. KPMG International. How to compete and win in a world with biosimilars: Commercial launch strategies and defensive positioning for the U.S; September 2015.

17. Global Biosimilars Markets, Pipelines, Regulations and Major Players. Biosimilars Advisory Service. Decision resources Group; 2014.

18. Rohit Sood et.al, Five Strategic Considerations for Biosimilar Commercialization. OBR; October 15, 2014.

19. Quintiles. An integrated approach to biosimilar development & commercialization; 2014.

20. Health at a Glance: Europe 2016. State of Health in the EU Cycle. OECD; November 23, 2016. [Accessed March 5, 2017]
Available from: http://www.oecd.org/health/health-at-a-glance-europe-23056088.htm

21. Cécile Rémuzat et.al, Key Drivers for Market Penetration of Biosimilars in Europe. J Mark Access Health Policy; 2017; 5(1):1272308.

22. Medicines for Europe: Biosimilars. Biosimilar Medicines Handbook; 3rd edition; 2016.

23. European Commission. What you need to know about Biosimilar Medicinal Products; 2013.

24. Parexel. Accelerating the Biosimilar Journey; March 2016.

25. What Biosimilars Need to Succeed in Clinical Practice: Biosimilar Development; December 27, 2016. [Accessed March 12, 2017]
Available from:
https://www.biosimilardevelopment.com/doc/whatbiosimilarsneedtosucceedinclinicalpractice0001?vm_tId=1983039&user=971a430c7c0849a0a8aea…

26. Long D. Impact of Biosimilars on the Pharmaceutical Industry. Magellan Rx Specialty Summit, New York; September 1-3, 2015.

27. Neiderwieser D, Schmitz S. Biosimilar agents in Oncology/Hematology: From Approval to Practice. European Journal Hematology; 2010; 277-288.

28. EuropaBio. EuropaBio's Statement on French Substitution Policy; January 24, 2014. [Accessed March 15, 2017]
Available from:
http://www.europabio.org/news/europabiosstatement-frenchsubstitution-policy.

29. QuantiaMD. Reading the Signs: A Roadmap for Engaging Physicians in the Biosimilars Discussion. Web-based survey; March 2016.

30. Deirdre Coleman. The Challenges of Commercializing Biosimilars. Thought Leadership and Innovation for the Pharmaceutical Industry. EyeforPharma; January 2014. [Accessed March 12, 2017]
Available from:
http://social.eyeforpharma.com/evidence/challengescommercializingbiosimilars

31. Jacob F. Siegel and Aron Fischer. Ten Years of Biosimilars in Europe; December 8, 2015. [Accesses February 21, 2017]
Available from: https://www.biologicsblog.com/tenyearsofbiosimilarsineurope/

32. Francis Megerlin et.al. Biosimilars and the European Experience: Implications for the United States. Health Affairs; October, 2013; 32(10); 1803-1810; doi: 10.1377/hlthaff.2009.0196.

33. Evelien Moorkens et.al. Overcoming Barriers to the Market Access of Biosimilars in the European Union: The Case of Biosimilar Monoclonal Antibodies. Frontiers in Pharmacology; June 2016; 7:193; PMCID: PMC4925708. [Accessed March 21, 2017]
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4925708/

34. Erwin a Blackstone et.al. The Economics of Biosimilars. Am Health Drug Benefits; 2013; 6(8); 469–478; PMCID: PMC4031732. [Accessed February 22, 2017]
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/

35. EMA [Accessed February 8, 2017]
Available from: www.ema.europe.eu/ema/

36. International Society for Pharmacoeconomics Outcomes and Research (ISPOR). [Accessed February 18, 2017]
Available from: https://www.ispor.org/HTA-RoadMaps

37. Simon-Kucher & Partners. Payers' Price & Market Access Policies Supporting a Sustainable Biosimilar Medicines Market. Medicines for Europe; September 2016. [Accessed March 10, 2017]
Available from: www.simon-kucher.com

38. Murray Aitken. Delivering on the Potential of Biosimilar Medicines: The Role of Functioning Competitive Markets. IMS Institute for Healthcare Informatics; March 2016.

39. Monitor Deloitte. Biosimilar EU Market Expansion Strategy; December 2016.

Annexure

i) Discussion Framework approach

The study deployed the Dual approach system to establish the Objective sphere. Discussion Framework is one of the approach implied in the study.

Discussion Framework approach implies the systematic interactions with the team of experts in Biologics, as to have the insights from the companies' prospective towards the Regulatory and Go-to-Market considerations for substantiating the Commercialization approach by countering the Gray areas in European Union and also the Stakeholder alignment prospects across EU.

Overview of the subject matter (Biosimilars) entails;

- Streamlining of Clinical Development process
- Real World Evidence (RWE) as a base for Totality-of-Evidence approach
- Commercialization considerations/strategies
- Stakeholders' Prospects across the EU
- Sustainability factors
- Gray areas to counter for EU market space
- Commercial Success framework.

The information incurred is transcribed and formulated in to the study theme.

ii) Glossary

- **EMA -** The European Medicines Agency (EMA) is a Centralized agency of the EU that is responsible for the scientific evaluation of medicines developed by Pharmaceutical companies for use in the European Nations.
- **Extrapolation -** It the process by which a proposed biosimilar product may be licensed in one or more additional indications of use for which the reference biologic is licensed, if appropriate scientific justification is provided and the patent landscape allows for it. In practical terms, this means that the biosimilar can receive approval for multiple indications with no additional clinical studies.
- **Immunogenicity** – It is the capability of a specific product to elicit an unwanted or notorious immune response triggered by more than a single factor.
- **INN -** Allocated by the World Health Organization (WHO), an International Nonproprietary Name (INN) identifies Pharmaceutical substances/Active Pharmaceutical ingredients. Each INN is a unique name that is globally recognized for the product.
- **Interchangeability -** An interchangeable biological product is a biosimilar which is expected to produce the same clinical result in terms of safety and efficacy as the reference biologic in any given patient. A biosimilar should only be considered as interchangeable with the reference biologic if the EMA has approved the criteria and designated it as an interchangeable.
- **Pharmacovigilance -** Procedure that monitors the safety to detect, assesses, understand and prevent the adverse effects/events or any other safety-related issues in the patients with regards to the medicines.
- **Reference Biologic -** A reference biologic (Innovator/Originator biologic) is a previously licensed product used as the comparator for head to head comparability studies with the similar biotherapeutic product (Biosimilar) in order to establish similarity in terms of quality, safety and efficacy.
- **Substitution -** A practice allowed by law wherein a pharmacist may dispense a biosimilar for a prescribed biologic medicine with/without the approval of the prescriber.
- **Switching -** A practice wherein a prescriber may change the prescription from the reference biologic to a biosimilar version of it.