Comparison of Different Bio-similar for the Treatment of Auto-Immune Disorders in Europe Market

Dissertation submitted in partial fulfillment of the requirement for the degree

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MASTERS OF TECHNOLOGY

(INTEGRATED 5- YEARS)

IN

BIOTECHNOLOGY AND BIOINFORMATICS ENGINEERING

By

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May 2019

DECLARATION BY THE SCHOLAR

We hereby declare that the work reported in the Integrated Match thesis entitled **"Comparison of Different Bio-similar for the Treatment of Auto-Immune Disorders in Europe Market"**, submitted by **Kumud Razdan** submitted at **Jaypee University of Information Technology, Waknaghat, India,** is an authentic record our work carried out under the supervision of **Shivani Hanjura.**

We have not submitted this work elsewhere for any other degree or diploma.

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SUPERVISOR'S CERTIFICATE

This is to certify that the work reported in the Integrated M. Tech. thesis entitled **"Comparison of Different Biosimilars for the Treatment of Auto-Immune Disorders in Europe Market"**, submitted by **Kumud Razdan** at **Jaypee University of Information Technology, Waknaghat**, **India,** is a bonafide record of their original work carried out under my supervision. This work has not been submitted elsewhere for any other degree or diploma.

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Kumud Razdan

Date:

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RESEARCH PROBLEM

In the last few decades, this era has witnessed a sharp significant progress in the area of drug development considering the fact about biologics. Many advances have been made in the subjects of genetics and biotechnology and this has immensely contributed to the development and the manufacture of biological drugs. These biological drugs, since then, have become a core part of the therapeutic industry in order to treat different autoimmune diseases.

Despite aware of the fact that these biologics have the ability to treat different diseases; the also well known fact is about the significant cost burden to their payer that these biologics come up with, for example, the healthcare system sector, insurance companies and patients.

Since this era has witnessed a significant increase in the use of biologics being utilized in clinics and also, in the cost of the treatment, there have been alternatively less possible low-cost drugs that can provide people with same benefits including efficacy and safety as the biologics present.

With a notion that a biologic with a great brand and with a maximum sales could result in huge revenue gain, there are many pharmaceutical manufacturing companies that have already begun to develop and manufacture biosimilars for some of the top-selling biologic drugs. Few of these biologic drugs include Humira, Remicade, Enbrel, Rituxan, Herceptin and Avastin these have their considerable share of biosimilars available in the market all over the globe. The growth of these biosimilar drugs have been greatly witnessed throughout the globe.

While the US biosimilar showcase displays huge potential as a speculation, few out of every odd conventional to a reference biologic will be a commendable venture. Since the improvement of a biosimilar requires huge capital, a medication organization inspired by the biosimilar adventure should have a procedure set up while choosing the biosimilar(s) it might want to create and progress to the US showcase.

While the pattern seems to support biosimilar contender for those reference biologics encountering high deals (Rader, 2013), this contextual investigation will investigate the biosimilars by assessing various biosimilar competitors with differentiating market profiles.

“BASICTERMINOLOGIES”

- "Biologics":

These biologics are often considered to be a fraction of medication which has been encapsulated from organisms which are living and are made up of biological substances.

- "Biologics Price Competition and Innovation (BPCI) Act":

This act was passed in order to allow the FDA to create a regulatory pathway for the approval of biosimilars.

- "Bioreactor":

Bioreactor can be defined as a vessel which can be used to cultivate cells to produce the drugs of interest.

- "Biosimilar":

It refers to a biologic that is strongly similar in comparison with the biological product.

CHAPTER1

ABSTRACT

There are many biologics which are somewhat same but are not exact copy of the reference product. These are often called the bio-similar.

Talking about this, these have higher atomic masses and are very complex and have been dictated in a completely different manner but global health management. These are produced from only the particulates present in the living cells.

The recent proposition given by the United States Food and Drug Administration (FDA) recently gave a fascinating proposition in order to praise appurtenant care drug developed by Sandoz , and also, particularly, the demoralization of biosimilars. Early biologics have given in a lot of effort to be insignificantly useful in the the treatment of serious illnesses.

So as to treat different immune system maladies, nowadays, increasingly complex biologics, for example, monoclonal antibodies (mAbs), cytokines and numerous other restorative immunizations are altering their treatment. For such illness zones requesting a greater expense of treatment, biosimilars ought to be instrumental in extending access to populaces which are in desperate need of these treatments yet have no entrance to them today.

1.1 AIM OF THE PROJECT

This project provides a strategic report on the comparison of biosimilars in different countries for its usage in the treatment of autoimmune disorders. This project gives an insight of the market availability and share of biosimilars across the globe and precisely, also, the challenges faced by the biosimilar industry in various countries.

CHAPTER 2

BACKGROUND

Autoimmune disorders, as we know are a mere result when our immune system loses its ability to demarcate amongst the two types of antigens which are the self- and non-self-antigens. The autoimmune disorders have an incidence of 5% in a worldwide population. Since these disorders could be referred to as chronic, these are the important reasons of any disability which often deriving a percussion in the virtue of life of the patients.

The pathogenesis of a few autoimmune disorders mighty relate to the deregulation of various inflammatory pathways. Amongst these, the one that tops are the explicitly resistant immune-mediated inflammatory diseases (IMID). Despite the fact that IMID can happen in various organs or tissues, they appear to have pathways that are normal, the ones, where the tumor necrosis factor (TNF) has its involvement. TNF has been related with may various kinds of immune system ailments like rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, and enclosing spondylitis.

The non-reacting patients which are regularly looked upon with calming specialists (non-steroidal anti-inflammatory agents (NSAIDS)) and basic illness altering antirheumatic drugs (DMARDs) are now prescribed with an all more up to date class of DMARDs. This more current class of DMARDS is totally centered on TNF adversaries that conceivably obstruct the connection among TNF and furthermore its receptors.

These were, infact, demonstrated to be effective in reducing the symptoms and also played a better role in the reduction of the symptoms and prevention of progression of diseases. These new set of DMARDs include adalimumab, infliximab, trastuzumab, golimumab and etanercept.

Reproduction of an exact human hereditary substance and advancement of in vitro organic generation system has permitted creation of many of the recombinant DNA based natural substance for inevitable improvement of a medication. Monoclonal antibody technology joined with recombinant DNA has given a unique way for customized and targeted medications for various auto-immune disorders. The new approaches that have emerged

significantly are the gene- and the cell- based therapies for the benefit of a vast section of population across the globe.

Recombinant restorative (therapeutic) proteins are of an intricate manner. These proteins are generated in the cells which are live, example, microscopic organisms, yeast, animals and human cell lines. Authoritative traits of a medication containing a therapeutic recombinant protein are to a huge portion dictated by the procedure in they are made or they are created which includes primarily, the decision of the cell type, advancement of the genetically modified cells for generation, the generation process, procedure for purification, and in conclusion, the plan of the helpful protein into a therapeutic medication.

It is only after patent of approved recombinant drugs reach their time of expiration, that any other pharmaceutical organization could be able to formulate and commercialize all forms of biologics. And, hence, it gets its name- biosimilars. Each and every biological product shows a certain degree of variability and even a smallest batch of these displays a great variation. This is all due to the variability that is inherent of the elucidation system and that of the procedure of its manufacturing.

Any type of the reference item which has seen a number of changes in its procedures of manufacturing is provided with the appropriate amount of data and an approval by the EMA. Also, taking both non-clinical and clinical test is a mandate for biosimilars since it needs to show the contrasts between the two items regarding human pharmacokinetics and pharmacodynamics, proficiency, wellbeing and furthermore the immunogenicity .

Unlikely of how the small-molecule pharmaceuticals are manufactured with the help of the chemical process of synthesis, biologic produce are the ones that are developed using live entities. The necessary components present in them are derived from the contemporary sources, be it, humans, animals, fungus or even the microbes.

The history of these drugs goes back when these entered the market in 1980s. Since then, they have reached a global market share of 25% in terms of value.

The focus of this project report is mainly the distribution of various biologics present and their available biosimilars in the market throughout the globe. This project report would give an idea regarding the comparison of various biosimilars available and their usage in the treatment of various auto-immune disorders.

CHAPTER-3

INTRODUCTION

WHAT IS A BIOSIMILAR?

FDA Definition

Biosimilar is organic item that is exceedingly like authorized reference natural item not with keeping minute diversities in clinically sound fractions. Also, which is not important

Between the natural item and the reference item as far as the wellbeing, immaculateness and power of the item.

WHO Definition

Biosimilar is a bio-therapeutic item which is comparable regarding quality, security and viability to an officially authorized reference bio-therapeutic item.

EMA Definition

A biosimilar is a bio-therapeutic item which is comparable regarding quality, wellbeing and adequacy to an effectively authorized reference bio-therapeutic item.

Biosimilars

• Adventure of expiry of the one of the principal licenses on the initiation of biologics started in 2000s, which opened the totally different market to the biosimilars. These biosimilars were the new medications which could impersonate the first biologic prescriptions. This in the long run made a noteworthy surge in the improvement of biosimilars. Also, since where there are benefits, there are difficulties too. These biosimilars represented various difficulties in contrast with little particle generics, therefore making the medication advancement a way more and from this time forward, progressively exorbitant. Different difficulties waited and still keep on waiting in guaranteeing the steady quality in the generation procedure of biosimilars. More or less, this made high section obstructions for biosimilars in the worldwide market contrasted with the little atom generics in a manner as:

• Due to trouble of making a careful match to the reference drug, the development process is longer and costlier.

• Especially in quality control, the manufacturing process was challenging for the developers.

• The originator medicine had a pre-existing well-established process and market position.

Biologics

Biologics are exceptionally explicit and powerful medications made in living cells. They have a wide range of benefits in treating auto-immune disorders keeping in view their ability to improve wellbeing in numerous intricate conditions.

Many of the biologics available currently include “hormones, blood products, cytokines, growth factors, vaccines, gene and cellular therapies, fusion proteins, insulin, interferon, and monoclonal antibody (mAb) products”.

And this project report mainly emphasizes the use of monoclonal antibody products as biologics and also use as biosimilars.

Difference between biologics and biosimilars

In a way, it can be said that biosimilars are the produce which are somewhat same as a pre-existing brand name. But, unlike a generic drug, these biosimilars are no identical to the

reference biologic. The difference between biologic and other medicines could be better understood by:

CATTEGORY	Small-Molecule Drug	Biologic Drug
Mode of development	Chemical development	By a Living organism or cell
Structure	Fully known	Complex, usually partially unknown
Susceptibility to contamination during manufacturing	Low	High
Manufacturing methods	Simple, synthetic and continuous	Complex, recombinant, in batches
Distribution	Has a High distribution	Has a Low Distribution
Disposition	Often target-mediated	Rarely target-mediated
Half-life	Short	Long
Safety	Toxicity defined through differentiable mechanisms	Extravagant pharmacology

Small Molecule:

Most of the medicines present in the market are usually the little particle items, which implies that these have basic atomic structures. The simplicity of these structures makes the production of these medicines easier. And, once the patent for that particular small- molecule drug expires, the rest other pharmaceutical organizations can make duplicates of these small-molecule drugs by precisely imitating a similar dynamic fixing, which is ordinarily a synthetic as the first item. It is after an authoritative endorsement that the other companies can sell their developed version of drug as a generic version. The generic and the biologic drugs are considered to be bio-equivalents of each other since the active ingredient present in them has a similar behavioral mechanism in the body.

Biologics:

In contrast with others, biologics are enormous and complex sub-atomic structures created by living cells, that too from profoundly concentrated fixings including the use of a mind boggling biotechnology process. It is simply unimaginable for anybody to deliver a precise without utilizing precisely the same fixings, a similar living cell lines, and furthermore, the indistinguishable assembling conditions.

Just like the case with different medications, it is legitimate for different makers to recreate the medication just once the patent terminates for a biologic. Be that as it may, it isn't essential on the trend-setter organization's part to share the licensed assembling procedure of their biologic medication. This incorporates different factors, for example, the room temperature, the sort of cells delivering a biologic and furthermore, the sustenance utilized by the phones to develop. Since, there is a fluctuation even in a live organic framework; it is inconceivable for a biosimilar to be a careful indistinguishable duplicate of the biologic medication.

Since biosimilars are not indistinguishable to their originator sedate, they are not eluded as the conventional forms of the biologic they duplicate.

CURRENTCONCEPT

A straightforward guideline is followed in the present idea for the advancement of biosimilar mAbs. This rule depends on the way that a broad condition of physiochemical, systematic and practical examination of atoms is frequently supplemented by the information, be it be, clinical or the non-clinical information that centers around keeping up the foundation of comparable wellbeing and adequacy in a clinical model which is viewed as the most delicate to identify any current minor contrasts among biosimilar and its reference originator mAb at the clinical dimension.

Data Points to Consider about Biosimilars

Considering the facts about the biosimilars, some of the data points include-

- Biosimilars need not be proven for each and every disease indication.
- No requirements are needed for development/trials of biosimilars except the guidelines to follow (FDA, WHOand EMA).
- Biosimilarsmustmaintainastandardofcomparablequality, safetyandefficacy.

3.1.6 Barriers to entry and use of biosimilars

- Lack of incentives
- Lack of knowledge
- Innovator's reach IP rights
- No substitution
- Complex development.

CHAPTER- 4

LITERATURE REVIEW

MAJORBIOSIMILARS

ADALIMUMAB

Adalimumab which is sold under the brand name of Humira is a medication which is used to treat many auto-immune diseases.

It is mainly given by injection under the skin. Being an exceptional immunosuppressant, it finds its use in the treatment of various auto-immune disorders. This drug can be used alone or with similar medicines for the treatment of rheumatoid arthritis. It shares its similarity in effectiveness withy methotrexate and plus, in combination with it, it nearly doubles the rate of response that methotrexate would have given alone. For Crohn's disease, adalimumab has been approved in UK since 2009. Also, this drug has been approved by the FDA for its use in treatment of ulcerative colitis.

INFLIXIMAB

Infliximab which is disposed off under the brand name of Remicade is basically an antibody which is administered intravenously to treat a few perpetual incendiary ailments. It works by blocking the effects of TNF alpha which has a crucial part in advancing irritation.
In particular, infliximab is utilized in the treatment of Crohn's disease, Rheumatoid arthritis, Psoriasis, Ankylosing spondylitis and Psoriatic arthritis. It is due to the blocking of the activity of TNF-alpha, infliximab diminishes the signs and manifestations of irritation. Likewise, it can possibly hinder the pulverization of joints by rheumatoid joint inflammation.

RITUXIMAB

Rituximab which is sold under the brand name of Rituxan is basically a chimeric monoclonal antibody against the CD20 protein, which is primarily found on the B cells' immune system surface. This results in the cell death as soon as it binds to the protein.

Rituximab was also approved for medical use in 1997. Not only this, it has a much greater potential as it finds it's name amongst the most effective and safe medication which finds its use in the health system.

It is well known for its use in the treatment of the auto-immune diseases.

GOLIMUMAB

Golimumab which is marketed under the brand name of Simponi is basically a human monoclonal antibody which has found its use as a great immunosuppressant drug. The mode of action of golimumab involves targeting the tumor necrosis factor alpha.

And not only this, the most fascinating fact is that golimumab makes an effective modulator of inflammatory markers and metabolism of bone.

Golimumab has received its approval from the EMA for its use in treating rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Also, it has been approved by the FDA and EMA to treat other auto-immune diseases like ulcerative colitis.

TRASTUZUMAB

Sold under the brand name ' Herceptin', this drug is a monoclonal antibody used in the treatment of HER2 + breast cancer. This drug can also find its use in the treatment either alone or in combination with other chemotherapy medication.

Considering its medical use, the approval date of trastuzumab for its use in treatment of auto-immune diseases goes back in the year 1998. It has its name listed among World Health Organization's List of Essential Medicines.

Talking about the mode of administration of the drug, trastuzumab is often given as a slow injection either into the vein or under the skin.

ETANERCEPT

Etanercept is widely being marketed under the trade names of Enbrel and Benepali which mainly focuses on the treatment of auto-immune disorders. It has its FDA approval under its name which treats rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis and ankylosing arthritis.

This drug in particular has immense potential in order to treat these various disorders via the inhibition of the TNF alpha.

TAKEAWAYS BYCOUNTRY

EU

The major driver of the adoption of biosimilars is European Union and also the European Medicines Agency (EMA). This has been achieved by the creation and development of a single approval pathway for the pharmaceutical drugs. The first approval pathway for similar biological medications was adopted in the year 2005. This regulatory pathway is valid in all EU5 countries (UK, Germany, France, Spain, and Italy) and also EEA member states which include UK, Germany, France, Sweden and Norway.

United Kingdom

United Kingdom, being a part of EU shares its marketing approval processes for biosimilars though the EMA regulatory authority. The most fascinating fact is that the biosimilars which get their market use approved by EMA are made available and reimbursed immediately. The process of procurement is carried out through tenders that are regional in England. Apart of England, Scotland, Wale and North Ireland generally have their own tenders. All of these tenders for biosimilars.

The local commissioners and Hospital Trusts jointly make decisions regarding which products toprescribe.

Also, the key driving force of the uptake of biiosimilars is the price competition between manufacturers, country level policies as dictated by NHS England as well as the local policies which are set by the CCGs.

Germany

Similar to UK, even Germany has a high rate of generic grasp already (81% by volume). The major driving force of the adoption of biosimilars is statutory health insurances which is formulated within the framework of healthcare and involves self-governance. The biosimilar market uptake is a bit different in Germany since the biosimilar manufacturers out there set their own pricing. The discount available on biosimilars there gives physicians an incentive as bait to use their limited prescription budgets on a better biosimilars. This in turn gives health incentive which allows pushing adoption rates to be even higher.

At the pharmacy level, in Germany, it is allowed to have limited substitution of biosimilars. But, this is only possible in the case of substances which are provided by the same supplier. Considering the industry side, Germany ensures a strong local presence taking in view both the innovators and the generic makers.

This in turn pushes both for better protection and also, an easier access to the market for the biosimilars.

France

The French government manages to set national healthcare policy goals with the help of de-facto single payer system. Since, France has a low volume share of generics, in order to increase the uptake of generics; it made the INN prescriptions a mandate in 2015.

The same is not the case with biologics as for them both INN and commercial name are required for prescription. In France, substitution is allowed at the pharmacy level for treatment naive patients under traumatic and severe conditions. And what is not allowed is the automatic substitution. For pricing, France has incorporated implementation of mandatory price cuttings for both the biosimilar as well as the originator on the entry of biosimilar in the market and also experiences a regularalization in price reevaluation every 1 or 2years.

Sweden

Of the boldest adopters of biosimilars in Europe is Sweden. All pharmaceutical products being used in the hospitals are purchased through a regional tender and after that these prescribed products are subjected to national negotiations with three parties for the sake of others, and also, it basically depends on the medicine/molecule.

Norway

Collaterally, Sweden, in order to procure medicines, Norway uses a tendering process. Each year there are numerous tenders which cover the entire country.

Biosimilar pricing and reimbursement

Depending on the national scheme for pharmaceutical pricing, rules on the price setting and reimbursement vary immensely and significantly.

Country	Biosimilar Pricing	Cost to Patient	Switching/Substitution
UK	Set by manufacturer; Procured by NHS / CCGs PPRS rules apply	Free at point of care (except prescription charge in England) Paid by NHS / taxes	Switching Yes; Substitution No
Germany	Free pricing in first year; Price group system; Rebate system to SHI	Co-payment limited to EUR 10 Surcharge if brand preferred	Substitution mandated if same manufacturing source; Regional prescription quotas
France	Originator price as limit; Mandatory price cuts; Hospital tenders; procurement at fixed price	Different co-payment levels based on needs / means	Switching allowed; Limited substitution; Excluded from mandatory INN prescriptions
Sweden	Country-level tender (hospital use)	In-patient cost covered by county councils	Preference for tender winner
Norway	National tender for hospital use in 6 areas	Patient cost covered by Regional Health Authorities	Preference for tender winner

Challenges for manufacturers

- Complexities in development
- Development requirements and costs
- Uncertain market
- Regulatory uncertainties

Challenges for policymakers

In regards to biosimilars, the legislators and policy makers have faced a number of challenges. These can be summarized:

- Market approval: Several patterns of approval include:

• Market approval as a new biologic despite having similariies

• Market approval under the same rules as a generic which is not being used.

• Customized approval process for biosimilars, which mainly focuses on–

(1) structural similarity within natural pre-existing variability and

(2) Precise absence of meaningful clinical diferences.

- Pricing
- Reimbursement:
- Switching and substitution
- Incentives and quotas
- Education towards physicians and patients
- IP, Patents, and Exclusivity
- Labeling
- Pharmacovigilance
- Import /Export

CHAPTER- 5

METHODOLOGY

The strategy embraced for the culmination of this task includes broad Market Research. The strategy for this can be clarified as –

MARKETRESEARCH

Essential research includes "direct correspondence or contact with vital individuals or as it was respondents so as to accumulate their suppositions as a piece of effective contribution to the task". This should be possible either by eye to eye interviews, telephonic meetings, online overviews or even board interviews. In this venture, use of CATI (Computer supported telephonic Interview) and IDI (In-Depth Interviews) was accomplished for social affair the significant and vital data and sentiments from target gathering of individuals. It is likewise alluded to as "field look into".

In this organization, Unimrkt Research, CATI type of essential research is basically engaged upon to accumulate data from individuals.

METHOD:

1. The database was curated according to our target respondent audience.
2. A database was set with the contacts of various doctors and pharmacists.

3. Telephonic interviews were conducted as a part of research survey to gather all the required data.
4. The data acquired from the doctors and the pharmacists is strictly kept confidential.
5. Later, numerous IDIS were conducted with the doctors and pharmacists in Europe to acquire the relevant data and the knowledge about the current market scenario of biosimilars in Europe and also the number of prescriptions of biosimilar drugs given in whole to the patients.
6. Then, the patient group was divided into 4categories-
    - the new patient prescriptions
    - the existing patient prescriptions
    - biosimilar switch to new patients
    - biosimilar switch to existing patients
7. Accordingly the data was accumulated for the completion of the project.

SECONDARYRESEARCH

Auxiliary research structure is tied in with social occasion information from optional sources, for instance, showcase reports, guidelines and rules, different statistical surveying papers dependent on the task, logical investigations, etc. It in different terms is eluded as the work area examine.

It moreover fuses aggressive insight concentrates to grasp the significant driving associations battling being developed and assembling of the ideal item and alongside different administrations gave. The CI examination appreciates the present market circumstance and looks at the critical pioneers in the market business and the up and coming new interests in the business.

METHOD:

1. Auxiliary information points were accumulated from the site of numerous significant organizations dealing with the manufacture and sale of biologics.
2. The, data was collected accordingly regarding the biosimilars present for those present biologics in the Europe market.
3. Later, a thorough investigative study was conducted about the case studies of the biosimilars provided online, their regulatory processes, regulatory authorities involved

For the approval along with the clinical validation of the data provided about the biosimilars.

4. Analysis of different biologic drugs offered by different leading companies along with their biosimilars developed was conducted.
5. Further, comparative analysis of the same was done for better results.

COMPETITIVEINTELLIGENCE

Competitive Intelligence can be referred to as near investigation of various organizations in a specific industry.

METHOD:

1. At first, a contrast was made among many driving contenders of the biosimilar market, which are the innovator of the biologics and the manufacturers of the biosimilars.
2. The market contenders include the innovators of Adalimumab, Infliximab, Rituximab, Trastuzumab, Golimumab and Etanercept in comparison with the one manufacturing the biosimilars of these biologic drugs.
3. A comparative analysis chart is then made to support and validate the provided also by the other two methods of research.

CHAPTER-6

RESULTS AND DISCUSSIONS

This fraction of the project report gives an insight of the data collected after extensive research for biosimilars market in major countries in Europe.

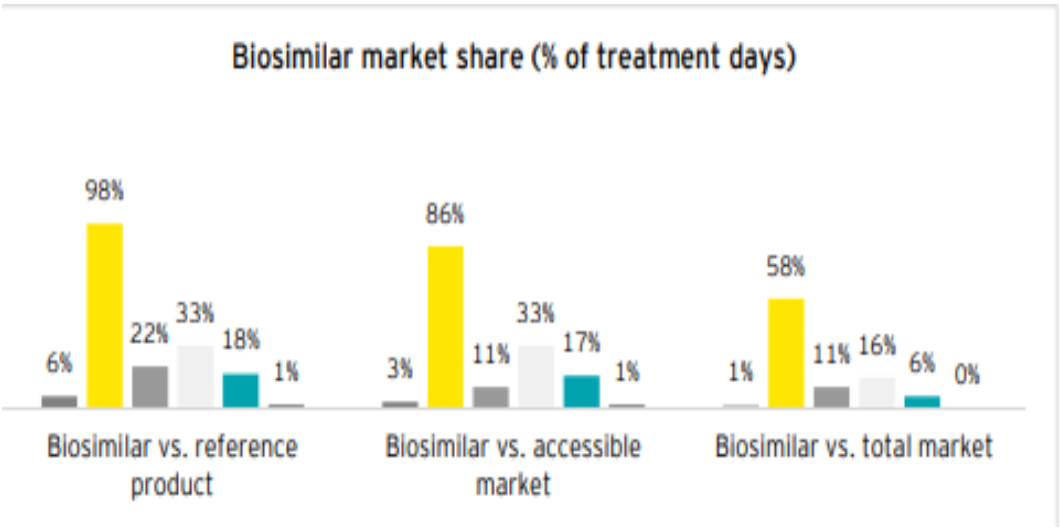
1. United Kingdom

The critical job as a discount cover for pharmaceuticals is authorized upon by the NHS in United Kingdom. So as to get financed, few of the originator pharmaceutical meds experience thorough evaluation by NICE, the National Institute for Health and Care Excellence. An esteem put together evaluation is led based with respect to the confirmations gave as far as clinical and monetary information. Likewise, NICE takes into view the QALY (the sum by which the medication sable to prolong or broaden the patient's life or improve patient's life quality). The medications which don't get affirmed by the NICE, those prescription medications are endorsed by the present 4 Regional Medicines Optimization Committees.

Reimbursement	UK / England	UK / Scotland
Involved Institution for decision	NHS England (CCG at local level or CMU at national level)	NHS Scotland (Area Drugs and Therapeutic Committee formulary)
Involved Institution for evidence assessment, appraisal and recommendation	Appraisal Committee at NICE / external HTA institutes	Scottish Medicines Committee / New Drugs Committee
Interactions	AC advises NHS	NDC advises NHS
Pricing	Free pricing, PPRS scheme	Free pricing, PPRS
Type of reimbursement list	National negative list + positive list per payer ("CCG formulary")	National negative list + positive list per payer ("area drug list")
Reimbursement restrictions	Indication, patient group, prescriber group / context of prescription	Indication, patient group, prescriber group / context of prescription
Revision of decision	Regular revision (1-3 years)	Revision on initiative of NHSS / AD&TC due to change of evidence

Biosimilars would have a free access to be freely marketed just after the approval from EMA, if the originator drug is positively assessed by NICE. This figure below provides a compilation of biosimilars available in the UK market approved by the EMA.

Biosimilar brand name	Active substance	Company	EMA authorization date	Net price[7]
Benepali [35]	etanercept	Biogen	14/01/2016	1-mL prefilled pen =GBP164
Abasaglar (prev. Abasria) [36]	insulin glargine	Eli Lilly / Boehringer Ingelheim	09/09/2014	-
Bemfola [37]	follitropin alfa	Finox Biotech AG	27/03/2014	0.125 mL (75 units) = GBP23.50
Inflectra [38]	infliximab	Hospira	10/09/2013	100-mg vial = GBP377.66
Remsima [39]	infliximab	Napp	10/09/2013	100-mg vial = GBP377.66
Nivestim [40]	filgrastim	Hospira	08/06/2010	12 million-units (120 micrograms)/0.2 mL = GBP36.00
Zarzio [41]	filgrastim	Sandoz	06/02/2009	30 million-units (300 micrograms)/0.5 mL = GBP50.15
Ratiograstim [42]	filgrastim	Ratiopharm	15/09/2008	30 million-units (300 micrograms)/0.5 mL = GBP62.25
Retacrit [43]	epoetin zeta	Hospira	18/12/2007	1000 units = GBP5.66
Binocrit [44]	epoetin alfa	Sandoz	28/08/2007	1000 units = GBP4.33
Omnitrope [45]	somatropin	Sandoz	12/04/2006	1.5 mL (5-mg, 15-unit) cartridge = GBP73.75



SWITCHING AND SUBSTITUTION INUK

Switching in UK: Patient's medicines can be switched by the physicians only on case-to case basis.

INDUSTRY POSITION:

Following are the recommendations given by the Association of the British Pharmaceutical Industry which was made by authoritative body on biosimilars:

- The prescriptions of the biosimilars should be under their brand names and not by their INN.
- Automatic substitution is not considered appropriate for the biologics, also including the biosimilars. It is only under the supervision and with the consent of the physicians that a biologic or a similar can be substituted.
- Precise and complete information about the medication should be given to the patients and also, the patients need to be consulted if in case there is a change in the medication.
- Appropriate health technology assessment processes need to be done for the bio-similars.

2. GERMANY

It is just on the grounds of German Medicines Act, the completed restorative items are approved by BfArM. Over the range of these approving and permitting procedural techniques, it reviews the proof of reasonability, security, and palatable pharmaceutical nature of the completed restorative items. Licenses are limited to five years and furthermore revival is permitted upon the accommodation of an application and after new appraisal. BfArM must be educated regarding variance changes to formally approved aesculapian items.

It is simply after the endorsement by the BfArM that the noteworthy varieties must be executed.

Additionally, with respect to the estimating of the biosimilars, it was distinctly until 2011 that the pharmaceutical organizations in Germany were permitted to uninhibitedly set their very own discount costs for the drugs given through just the remedies. In Germany, the AVWG enabled the pharmaceutical firms to consult with clinics and the medical coverages in regards to the value limits for explicit medications.

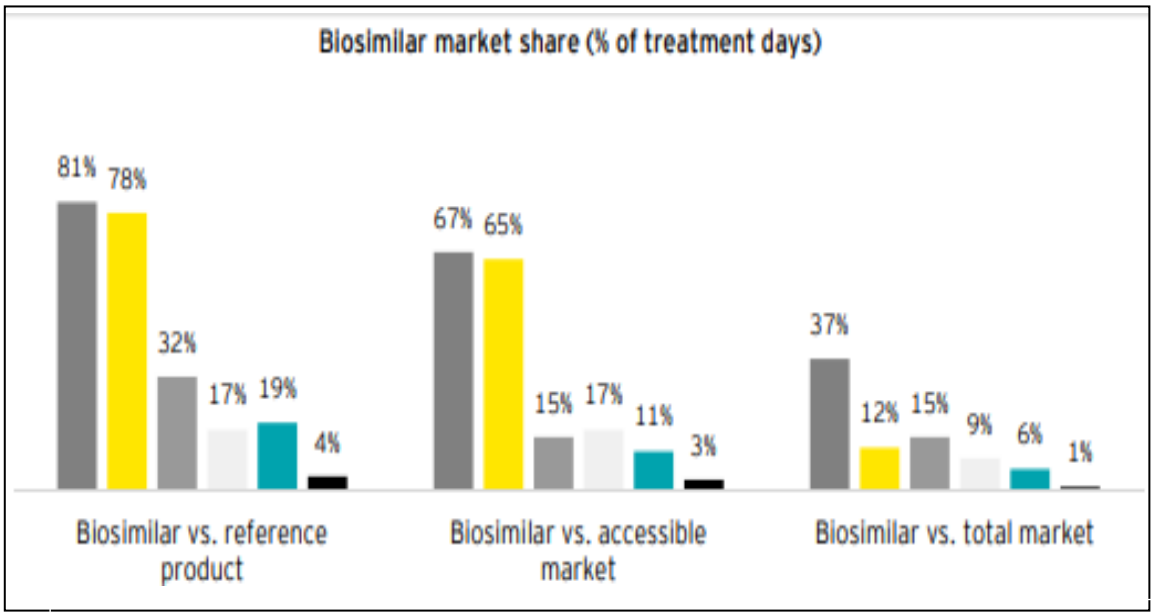
Reimbursement	
Involved Institution for decision, appraisal and recommendation	Federal Joint Committee (G-BA)
Involved Institution for evidence assessment	Institute for Quality and Efficiency in Healthcare (IQWiG)
Interactions	G-BA commissions IQWiG or a third party
Pricing	▸ Free Pricing for first year after market entry (originators) ▸ Internal reference pricing "Festbeträge" ▸ Value-based pricing (AMNOG process) ▸ External reference pricing for outpatient medicines as secondary criterion, references 15 EU countries, weighted based on market size and PPP
Type of reimbursement list	De-facto negative list
Reimbursement restrictions	Restriction of prescription due to inappropriateness / inefficiency
Revision of decision	Benefit assessment on application by manufacturer or investigation by G-BA due to new evidence

Talking about the switching and substitution in Germany for the biosimilars, it has been reported that while giving out prescriptions, physicians need to inform the patients the co-payment basis as they select amongst a biosimilar and its originator product. The bio-products which are considered to be identical can be added to the list of products allowed for the substitution process. These bio-identical products are referred to as the products which are developed by a similar supplier with a similar production line and however, are sold under different trade names in the market. Also, these biosimilar could be interchanged even at the pharmacy level done by the pharmacists alone without any prior permission by the prescribing doctors in the country.

According to the framework agreement, the biosimilars which can be substituted automatically alone at the pharmacy level are listed below in the figure provided-

Active substance	Biosimilar brand name	Company	Automatic substitution start date
epoetin alfa	Abseamed	Medice Arzneimittel Pütter GmbH & Co. KG	01/10/2011
	Binocrit	Sandoz GmbH	
	Epoetin alfa Hexal	Hexal AG	
epoetin zeta	Retacrit	Hospira UK Limited	01/10/2011
	Silapo	Stada Arzneimittel AG	
epoetin theta	Biopoin	Teva GmbH	01/06/2015
	Eporatio	ratiopharm GmbH	
filgrastim (1)	Biograstim	AbZ-Pharma GmbH	01/06/2015
	Ratiograstim	Ratiopharm GmbH	
	Tevagrastim	Teva GmbH	
filgrastim (2)	Filgrastim Hexal	Hexal AG	01/06/2015
	Zarzio	Sandoz GmbH	
filgrastim (3)	Accofil	Accord Healthcare Ltd	01/06/2015
	Grastofil	Apotex Europe BV	
infliximab	Inflectra	Hospira UK Limited	01/06/2015
	Remsima	Celltrion Healthcare Hungary Kft.	
interferon beta-1b	Betaferon	Bayer Pharma AG	01/10/2011
	Extavia	Novartis	

This figure below shows the market share of the currently available biosimilars in Germany-



In reference to Germany's industry position, it could be analyzed that-

• For before and hindmost market entry of a biosimilar, pharmacovigilance studies are highly required.

• In case of side effects, INN prescribing could not be done and also, the tracking of the batches could also not be done.

• Pharmacy-level substitution could not be done without the patient's consent.

• Physician has the freedom to prescribe any drug, be it biologic or biosimilar at any price set by them only.

3. FRANCE

A price setting process is mandatory to be undergone in France to get a new prescription medication available to the masses. .

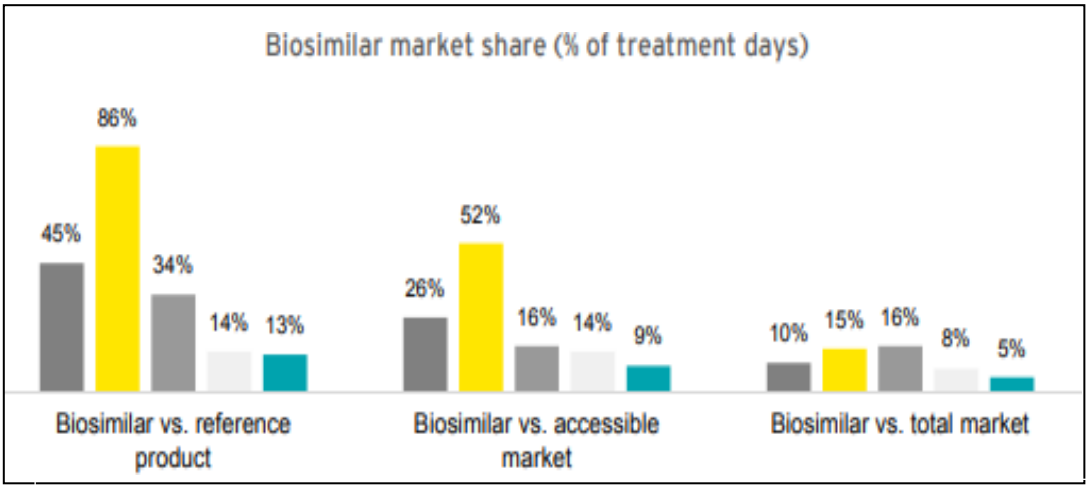
Reimbursement	
Involved Institution for decision	Ministry of Social Affairs and Health
Involved Institution for evidence assessment, appraisal and recommendation	French National Authority for Health (HAS)
Interactions	Committee at HAS performs assessment and advises the minister; for highly innovative and expensive medicines, the Economic and Public Health committee (CEESP) performs an economic assessment
Pricing	▸ External reference pricing for ASMR I, II, or III (Outpatient medicines and some inpatient medicines (not financed through DRG system)); References DE, ES, IT, UK; No specified calculation method ▸ Internal reference pricing ▸ Value-based pricing ▸ Negotiation
Type of reimbursement list	Positive list
Reimbursement restrictions	Therapeutic benefit, patient group
Revision of decision	Every 5 years or ad-hoc due to new evidence, change of indication, or ministerial request

The price setting process begins with the evaluation of the clinical benefits and the amendments in the clinical benefits over the existing products. Based on this, five benefit levels are allotted to the product.

In regards with the market of biosimilars, it was analyzed that 19 biosimilars have been received approval by ANSM in France and out of these 19, 15 bioimilars are being marketed:

Biosimilar brand name	Active substance	Company	EMA authorization date	ANSM authorization date	Commercialization status
Truxima	rituximab	Celltrion Healthcare Hungary Kft.	17/02/2017	17/02/2017	Marketed
Lusduna	insulin glargine	Merck Sharp & Dohme Limited	04/01/2017	04/01/2017	Not marketed
Flixabi	infliximab	Samsung Bioepis UK Limited (SBUK)	26/05/2016	26/05/2016	Marketed
Benepali	etanercept	Samsung Bioepis UK Limited (SBUK)	14/01/2016	14/01/2016	Marketed
Accofil	filgrastim	Accord Healthcare Ltd	18/09/2014	18/09/2014	Marketed
Abasaglar	insulin glargine	Eli Lilly Regional Operations GmbH	09/09/2014	09/09/2014	Marketed
Bemfola	follitropin alfa	Gedeon Richter Plc.	27/03/2014	27/03/2014	Marketed
Grastofil	filgrastim	Apotex Europe BV	18/10/2013	18/10/2013	Not marketed
Ovaleap	follitropin alfa	Teva Pharma B.V.	27/09/2013	16/09/2014	Marketed
Inflectra	infliximab	Hospira UK Limited	10/09/2013	10/09/2013	Marketed
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	10/09/2013	10/09/2013	Marketed
Nivestim	filgrastim	Hospira UK Ltd	08/06/2010	08/06/2010	Marketed
Zarzio	filgrastim	Sandoz GmbH	06/02/2009	06/02/2009	Marketed
Ratiograstim	filgrastim	Ratiopharm GmbH	15/09/2008	15/09/2008	Not marketed
Tevagrastim	filgrastim	Teva GmbH	15/09/2008	06/02/2012	Marketed
Retacrit	epoetin zeta	Hospira UK Limited	18/12/2007	11/10/2010	Marketed
Abseamed	epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	28/08/2007	28/08/2007	Not marketed
Binocrit	epoetin alfa	Sandoz GmbH	28/08/2007	28/08/2007	Marketed
Omnitrope	somatropin	Sandoz GmbH	12/04/2006	12/04/2006	Marketed

The figure given below provides an insight of the contrast in the market share of biosimilars available in France:



Source: TheImpactofBiosimilarCompetitioninEurope, IMS (sourcedfromapubliclyavailablereport)

4. SWEDEN

On analysis of the market of biosimilars in Sweden, it was found that the cost of the out-patient drugs in Sweden is financed by the central government while the out-patient drugs are financed by the county councils directly.

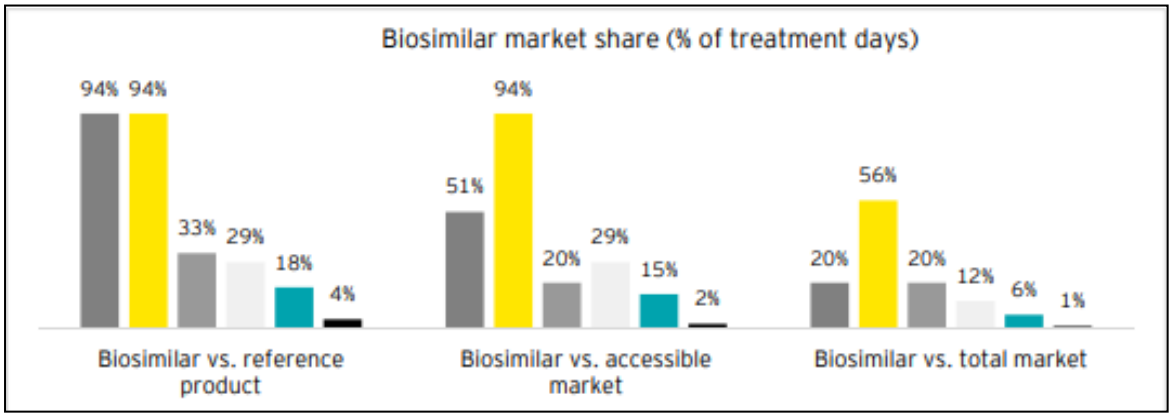
Reimbursement	Out-Patient	In-Patient
Involved institution for decision, evidence assessment, appraisal and recommendation	Dental and Pharmaceutical Benefits Agency (TLV)	County councils
Interactions	TLV determines prices, assesses drugs and decides on reimbursement status	
Pricing mechanism	Internal reference pricing, value-based pricing	Tendering process (joint or single council)
Type of reimbursement list	Positive list	Positive list (usually only one product per indication)
Reimbursement restrictions	Product specification, patient group	
Revision of decision	Due to change of indication, linked to assessment of other medicine	1-2 years

List of available biosimilars in Sweden include-

Biosimilar brand name	Active substance	Company	EMA authorization date
Benepali	etanercept	Samsung Bioepis UK Limited (SBUK)	14/01/2016
Accofil	filgrastim	Accord Healthcare Ltd	18/09/2014
Abasaglar (previously Abasria)	insulin glargine	Eli Lilly Regional Operations GmbH	09/09/2014
Bemfola	follitropin alfa	Gedeon Richter Plc.	27/03/2014
Inflectra	infliximab	Hospira UK Limited	10/09/2013
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	10/09/2013
Nivestim	filgrastim	Hospira UK Ltd	08/06/2010
Zarzio	filgrastim	Sandoz GmbH	06/02/2009
Ratiograstim	filgrastim	Ratiopharm GmbH	15/09/2008
Tevagrastim	filgrastim	Teva GmbH	15/09/2008
Retacrit	epoetin zeta	Hospira UK Limited	18/12/2007
Binocrit	epoetin alfa	Sandoz GmbH	28/08/2007
Omnitrope	somatropin	Sandoz GmbH	12/04/2006

Source: European Observatory on Health Systems and Policies

Comparison of “marketable biosimilars” :-



Source: The Impact of Biosimilar Competition in Europe, IMS (sourced from a publicly available report)

5. NORWAY

Analysis of Norway market of bioimilars shows that here all the medicines undergo a HTA process for taking into account the consideration whether reimbursement on medicines is to be granted or not. These can be approved EU-wide by the EMA.

Reimbursement	Outpatient	Inpatient[15]
Involved Institution for decision, evidence assessment, appraisal and recommendation	Norwegian Medicines Agency (NoMA)	NoMA, Regional Health Authority, Sykehusinnkjøp HF
Interactions	-	Sykehusinnkjøp HF is tasked with procurement
Pricing	Free Pricing, External Reference Pricing	Tendering
Type of reimbursement list	-	Tender winner only
Reimbursement restrictions	-	-
Revision of decision	-	1-2 years

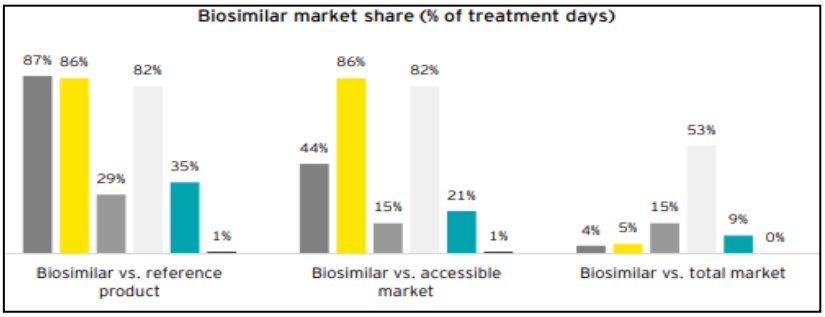
As of June 2017, the following biosimilars are actively marketed in the country:

Biosimilar brand name	Active substance	Company	Authorization date	Status
Rixathon	Rituximab	Sandoz GmbH	15/06/2017	Marketed
Benepali	Etanercept	Samsung Bioepis UK Limited (SBUK)	14/01/2016	Marketed
Abasaglar (previously Abasria)	insulin glargine	Eli Lilly Regional Operations GmbH	09/09/2014	Marketed
Bemfola	follitropin alfa	Gedeon Richter Plc.	27/03/2014	Marketed
Ovaleap	follitropin alfa	Teva Pharma B.V.	27/09/2013	Marketed
Inflectra	infliximab	Hospira UK Limited	10/09/2013	Marketed
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	10/09/2013	Marketed
Nivestim	filgrastim	Hospira UK Ltd	08/06/2010	Marketed
Zarzio	filgrastim	Sandoz GmbH	06/02/2009	Marketed
Tevagrastim	filgrastim	Teva GmbH	15/09/2008	Marketed
Retacrit	epoetin zeta	Hospira UK Limited	18/12/2007	Marketed
Omnitrope	somatropin	Sandoz GmbH	12/04/2006	Marketed

- Thefollowingmedicineshavebeenapproved,buttheyarenotcurrentlymarketed-

Biosimilar brand name	Active substance	Status
Abseamed	epoetin alfa	Approved
Binocrit	epoetin alfa	Approved
Epoetin alfa Hexal	epoetin alfa	Approved
Silapo	epoetin zeta	Approved
Accofil	filgrastim	Approved
Filgrastim Hexal	filgrastim	Approved
Grastofil	filgrastim	Approved
Ratiograstim	filgrastim	Approved
Flixabi	infliximab	Approved

The figure given below provides an insight of the contrast in the market share of biosimilars available in Norway:

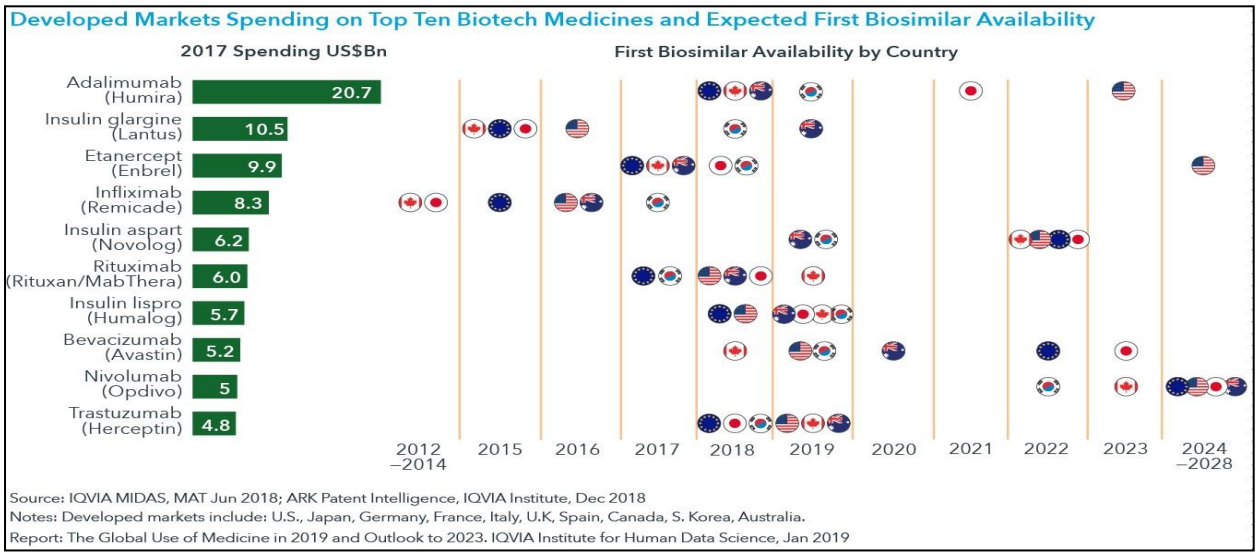


CHAPTER-7

CONCLUSION

When it comes to the adoption of the biosimilars, it could be rightfully said that Europe is ahead of the other countries. The EMA got its first biosimilar approved in 2006. In regards with the biologics and chemical drugs, Europe holds an exclusivity period of 10 years for both. The companies with generic products and those with biosimilar associations have come together to counter the misconceptions regarding their pharmaceutical drugs and also, ease off the challenges yet faced by the biosimilar industry. The global market of biosimilars has been putting in continuous efforts to favor manufacture of generic or the biosimilar drugs which in turn benefit the vast patient population with the low-cost alternatives.

The public has always looked towards the biosimilar companies in order to lower the costs of the older drugs and also in parallel, look up to the innovator drug companies for more efficient and new therapeutics. It has always been a war between the "innovator" and the "biosimilar" sponsors. It has always been of importance to rightly ensure the efficiency and the safety of biosimilars while also ensuring that the patients have adequate access to the available biosimilars.



The usage of these biosimilars for different auto-immune disorders has been summed up in the form of the figure given below which gives an insight of which of the biosimilars are used for the treatment of which auto-immune disorders.

	Rheumatoid Arthritis	Crohn's Disease	Ankylosing Spondylitis	Psoriasis	Ulcerative Colitis
Orencia (abatacept)	X				
Humira (adalimumab)	X	X	X	X	X
Cimzia (certolizumab)	X	X	X		
Enbrel (etanercept)	X		X	X	
Simponi (golimumab)	X		X		X
Remicade (infliximab)	X	X	X	X	X
Rituxan (rituximab)	X				
Actemra/RoActembra (toclizumab)	X				
Stelara (ustekinumab)		X		X	
Entyvio (vedolizumab)		X			X
Tysabri (natalizumab)		X			
Xeljanz (tofacitnib)	X				
Biosimilars	X	X	X	X	X

After doing the extensive primary and secondary research needed, it has been concluded that Humira is a highly differentiated drug as compared to the other available drugs. As it could be seen from the figure that Humira widely treats a number of disease indications. Apart from this, Humira has proven to be effective in bringing and maintaining remission in people who are suffering from Crohn's disease. It helps in the reduction in the need for hospitalization and surgery.In some parts of UK, the use of Inflectra, the biosimilar has been in practice for the new starter patients since 2005. It was also reported from the research that the biosimilar of Etanercept, that is, Benepali is being used in UK apart from its other biosimilar Enbrel. This Benepali is available in the market as auto-injector devices.

While having my research done, in one of the articles it was mentioned that even prior to the development and commercialization of the adalimumab biosimilar, the NHS had released its framework of commissioning for the biologics which seek to mandatorily ensure that the best-value adalimumab must be prescribed to at least 90% of the new patients.

Apart from this, it was stated that Germany in contrast to other companies has one of the strongest uptake of biosimilars across the globe. The regulatory body in Germany

Incentivizes its doctors to prescribe biosimilar drugs through various modes, which include through either quotas, budgeting or programs for checking and monitoring the market penetration.

So, last but not the least this project provided an overview of the healthcare system and pharmaceutical market in different countries in Europe and gave a possible insight of the contrast between all the biosimilars available in the market.

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