A Study on Performance of Biosimilars Across EU5 (Germany, UK, France, Spain and Italy) Nations

Internship Training
at
ZS associates, Gurgaon

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2012–14

Institute of Health Management Research
Jaipur
2014

May 12, 2014

EXPERIENCE CERTIFICATE

This is to certify that Mrs Kusha Korla (8431) has served in our organization from February 3, 2014 to May 8, 2014. At the time of leaving she was working in the capacity of Knowledge Management Associate - Intern and based at New Delhi office. .

This is to confirm that all information\Projects shared\worked in your Internship period is confidential and are not liable to be shared with anyone outside ZS network.

At last, wish you all success in future endeavors

For ZS Associates India Pvt Ltd

Stephen Redden
Office Managing Principal

ZS Associates India Private Limited
Gurgaon
HR

ACKNOWLEDGEMENT

"**Successful passage and outcome of every work comes with dedication, determination and team work. All these turn futile in the absence of visionary guidance."**

I acknowledge and express my heartily gratitude for the help, guidance, co-operation and assistance expanded to me by different individuals.

I shall always be indebted to Mr. **Nitin Aggarwal (Principal Knowledge management)** and **Dr. Mohit Saxena (Knowledge management consultant)** for giving this opportunity to undergo this project and also for their immense contribution towards execution and completion of this project.

I am especially thankful to **Dr. Santosh Kumar**, my project mentor who guided me through the whole course of the project and without his eloquent guidance this project would not have seen the light of this day. He helped me to bridge the gap between text book learning and real market environment.

I would like to thank ZS associates for providing me an opportunity to work with them.

Thanking you,

Kusha Korla

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Abbreviations:

IND	Investigational new drug
NDA	New drug application
CHMP	Committee for Medicinal Products for Human Use
USFDA	United states food and drug administration
EMA	European medicines agency
BPCI	Biologics price competition and innovation act
MHLW	Ministry of health labor and welfare
RBP	Reference biotherapeutic product
EPO	Epoetin alfa
HGH	Human growth hormone
G-CSF	Granulocyte colony stimulating factor
NICE	National Institute for Health and Care Excellence
NOB's	Non originator biologics
BLA	Biologics license application
CDER	Committee for drug evaluation and research
CBER	Committee for biologics evaluation and research

CHAPTER 1: INTRODUCTION

1.1 HISTORY

ZS associates is a global leader in sales and marketing consulting, outsourcing, technology and software. It has been rooted in an academic partnership that began in the early 1970s. In **1973**, **Andy Zoltners** completed a PhD in integer programming algorithms at Carnegie Mellon University, devoting a chapter in his dissertation to sales territory alignment problems. Andy subsequently accepted a teaching position at the University of Massachusetts (UMass).

The following year, Andy crossed paths with PhD student **Prabha Sinha**, who was exploring the use of higher math in meal planning for the military. The two collaborated on the Multiple Choice Knapsack problem and co-wrote a paper on the topic. Eventually they realized that this line of thinking was highly applicable to the problems of sales force sizing and resource allocation.

Over the next several years, the pair worked with a number of companies, gaining practical experience applying modeling techniques to sales force problems.

In **1982**, Andy presented his and Prabha's mathematical models for sales force sizing and territory alignment to the Pharmaceutical Management Science Association (PMSA), using an early Apple computer to display sales territories on-site. Executives from many of the attending companies were stunned by the model's ability to quickly solve sales force sizing, sales resource allocation, and territory alignment issues and see solutions visually in real time, with one exclaiming, "I've been waiting my whole life for this!"

By **1983**, both Andy and Prabha were teaching at Northwestern's Kellogg School of Management. They lectured by day, and by night they worked on the many client projects that came their way. Already having consulted to eight companies, the two professors concluded that there was an opportunity to help many clients address critical sales force effectiveness issues, and so they incorporated ZS Group, Inc., on September 21, soon renamed ZS Associates, Inc.

1.2 INSIGHT

ZS Associates is one of the world's largest business services firms specializing in transforming sales and marketing from an art to a science. They help clients gain market share at lower cost. They do so by creating data-driven strategies that they can implement rapidly and by taking on sales and marketing operations to make them more competitive.

With 20 offices around the world, they have worked with more than 700 companies in 70 countries across consumer products, energy, high-tech, insurance, medical products and services, pharmaceuticals and other industries.

ZS focuses exclusively on the two areas that create customer demand: sales and marketing. As a result, their expertise in this domain is both broad and deep. They provide a vast range of marketing- and sales-related services in the industry, from customer insight, product development, and sales and marketing strategies, to sales compensation planning and even plan

administration, to name just a few. They offer clients the unique advantage of understanding what will work best for their company as a whole.

Thirty years ago, they helped pioneer the shift in commercial strategy from being determined largely by intuition to being driven by data. The fundamental approach remains the same today. As a result, they possess deep expertise in what makes for successful sales and marketing, and have built a global team of more than 2,000 highly trained professionals who are committed to this pursuit.

Since 1983, ZS has been working shoulder to shoulder with leaders at hundreds of the world's top corporations. Their clients typically are large and mid-sized companies whose success depends on the effectiveness of their sales and marketing. They help them gather and analyze data to create the best strategies; orchestrate sales and marketing activities to increase demand efficiently; and change quickly to become more competitive.

1.3 MISSION

ZS associates, a global leader in sales and marketing has a mission to

"Help companies accelerate business performance by providing consulting, capability building and outsourcing services that drive sales and marketing excellence."

1.4 LIST OF SERVICES

ZS associates provide services in various sectors across different industries. There are four major service areas include:

1.41 CONSULTING: ZS's consulting services have helped hundreds of companies worldwide solve their most critical sales and marketing challenges. By bringing rigorous research and analysis, critical thinking, and thought leadership to decisions that are often otherwise based on intuition. They bring science to the art of demand generation.

1.42 OUTSOURCING: ZS associates break down processes to identify opportunities and challenges, using data, facts and rigorous analysis to drive our recommendations. The experts uniquely understand the interconnections in the entire sales and marketing system of each client. As a result, they develop solutions that improve their overall system, not just one piece of it, and not one piece at the expense of another.

1.43 TECHNOLOGY: ZS helps companies define and execute their technology strategy by designing, building and operating the business intelligence (BI), cloud, data management, dashboard and analytics capabilities that are at the core of sales and marketing operations.

1.44 SOFTWARE: To maximize the performance of the sales force ZS helps on sales planning, sales compensation, business intelligence and integration by giving their Javelin software solutions.

1.5 CLIENT INDUSTRIES: ZS offers cross-industry experience combined with deep expertise in sales and marketing strategy and operational issues. They have worked with clients in more than 70 countries around the world and across a vast array of industries.

1.5.1 Business Services

1.5.2 Financial services

1.5.3 Media

1.5.4 Private Equity

1.5.5 Consumer packaged goods

1.5.6 Industrial product and services

1.5.7 Medical products and services

1.5.8 Travel and transportation

1.5.9 Energy

1.5.10 High tech and telecommunications

1.5.11 Pharmaceutical and Biotech

1.6 GLOBAL LOCATIONS AND HEADQUARTERS

ZS Associates is one firm with multiple offices positioned to provide the highest quality and most attentive service to our clients. Each office can effectively serve local or regional clients while also contributing to project teams working around the world, assembling the optimal mix of capabilities, experience, geography, language and culture

TABLE 1: Global locations of ZS associates

AMERICA	EUROPE	ASIA
Boston	Barcelona	New Delhi
Chicago	Frankfurt	Pune
Evanston	London	Shanghai
Los Angeles	Milan	Tokyo
New York	Paris	
Philadelphia	Zurich	
Princeton		
San Diego		
San Francisco		
São Paulo		
Toronto		

CHAPTER 2: EXECUTIVE SUMMARY

INTRODUCTION AND BACKGROUND

Biosimilars are the emerging trends in pharmaceutical market across the globe. They are the biologic medical products whose active drug substance is made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene expression methods. The reference or biologic drugs are highly expensive and beyond the reach of a common man. Therefore biosimilars are gaining popularity in the market of medicine. They are similar to the reference products but cheaper due to less extensive approval pathway. They can be called "Biologics to biosimilars as "Branded to generics".

This report provides an analysis and evaluation of the current and emerging trends of biosimilars in European nation. It focuses on performance of biosimilars across five main geographies in Europe i.e. EU5 nations (Germany, France, UK, Spain and Italy), based on the uptake across geographies and also based on the therapeutic areas.

AIM OF STUDY

The aim of the study is to understand the trends and performance of biosimilars across EU5 (Germany, UK, France, Spain and Italy), the major five countries in Europe dealing with biosimilars.

OBJECTIVES OF THE STUDY

To identify the major biosimilars in market contributing to the economy of pharmaceutical industry in Europe and analyze the uptake of each across different geographies.

METHODOLOGY:

Method of analysis included studying the trends, horizontal and vertical analysis through secondary research using URL'S, websites, journals, databases from the organization etc.
The study also analyses the reasons for the increased or decreased uptake across geographies. It will also focus on the pricing pattern and the perception of the payers for the biosimilars. EMA (European Medicines Agency) is the main regulatory body for Europe still the differences in uptake are prominent.

Results of the data analyzed show the differences among the nations with variations across geographies and therapeutic areas. The highest uptake areas for respective biosimilars are

highlighted in the study for e.g. biosimilar Filgrastim shows highest uptake in UK; however it is not the overall best market in Europe for biosimilars.

The report focuses on the current trends of biosimilars in the market. It also talks about the drivers and barriers for the uptakes and how to overcome them so as to increase the sales of biosimilars in these geographies and make strategies or plan for the clients dealing with biosimilars. As mentioned above the biologic drugs are very expensive drugs, which are out of the reach of the common man, and they are used mainly for treatment of cancers, where the overall cost of treatment goes very high. Biosimilars are comparatively cheaper versions of the original or reference biotherapeutic product, but the cost reduction is not very high as the manufacturing and storage cost is very high. Maximum reduction in cost could be 20-30%. Therefore it also assesses the out of pocket expenditure and how much the population is insured making biosimilars accessible to them.

The organization is a consultancy firm with expertise and focus on sales and marketing, so the recommendations were focused mainly on improving the sales of these drugs into the market with the study of existing competitors for the same. These could be like increasing the quota systems, tendering etc.

FINDINGS

- Germany was found to be the most favourable for biosimilars due to its reimbursement policies. The country has a biosimilar reference pricing policy, plus targets or quotas for biosimilars use for physicians and sickness funds

- The UK was also found to be favourable, with its buoyant generics market and cost-effectiveness analyses of biosimilars by the UK's National Institute for Health and Care Excellence (NICE)

- France was also found to be a potentially favourable market for biosimilars. Although the country also has a strict price regulation system and compulsory discounts for biosimilars, high volume sales of biologicals compared to other EU countries add to the attractiveness of the market for biosimilars

- Italy was found to be the least favourable country for biosimilars due to its strict price regulation system which requires a mandatory discount of 15–22% for biosimilars relative to that of the brand-name reference product

- Biosimilars are classified in Spain as HOM (hospital only medicine), meaning that they are only dispensed to outpatients attending hospitals, which could offer one explanation for the low uptake of biosimilars in Spain

RECOMMENDATIONS AND CONCLUSION

As per the findings Germany is the best market for biosimilars while Spain and Italy are the last. The study suggests that Germany holds the best market because of biosimilar reference pricing policy, plus targets or quotas for biosimilars use for physicians and sickness funds. Therefore to improve the market of biosimilars in Spain and Italy similar policies should be followed.

On the other hand for the biosimilars having safety concerns various education programs should be run for the physicians or payers to build trust. Not only this, the out of pocket expenditure should be reduced.

This can be done either by giving expected discounts on biosimilars, so that payers put them in their reimbursement panel for e.g. Italy expects discounts of 40% of the original brand price for some biosimilars (in hospitals) while Spain expects biosimilars with approximately 30-40% the price of the branded drug.

CHAPTER 3: INTRODUCTION TO BIOSIMILARS

3.1 BACKGROUND

Biosimilars also known as **follow-on biologics** are biologic medical products whose active drug substance is made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene expression methods.

Biosimilars (or follow-on biologics) are terms used to describe officially approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product. Biosimilars are also referred to as subsequent entry biologics (SEBs) in Canada. Reference to the innovator product is an integral component of the approval.

Unlike the more common small-molecule drugs, biologics generally exhibit high molecular complexity, and may be quite sensitive to changes in manufacturing processes. Follow-on manufacturers do not have access to the originator's molecular clone and original cell bank, nor to the exact fermentation and purification process, nor to the active drug substance. They do have access to the commercialized innovator product. Differences in impurities and/or breakdown products can have serious health implications. This has created a concern that copies of biologics might perform differently than the original branded version of the product.

Cloning of human genetic material and development of in vitro biological production systems have allowed the production of virtually any recombinant DNA based biological substance for eventual development of a drug. Monoclonal antibody technology combined with recombinant DNA technology has paved the way for tailor-made and targeted medicines. Gene and cell-based therapies are emerging as new approaches.

Recombinant therapeutic proteins are of a complex nature (composed of a long chain of amino acids, modified amino acids, derived by sugar moieties, folded by complex mechanisms). These proteins are made in living cells (bacteria, yeast, animal or human cell lines). The ultimate characteristics of a drug containing a recombinant therapeutic protein are to a large part determined by the process through which they are produced:

- Choice of the cell type
- Development of the genetically modified cell for production
- Production process
- Purification process
- Formulation of the therapeutic protein into a drug.

After the expiry of the patent of approved recombinant drugs (e.g. insulin, human growth hormone, interferon’s, erythropoietin, and more) any other biotech company can "copy" and market these biologics (thus called biosimilars)

However, because no two cell lines, developed independently, can be considered identical, biotech medicines cannot be fully copied. The European Medicines Agency, EMA, has

recognized this fact, which has resulted in the establishment of the term "biosimilar" in recognition that, whilst biosimilar products are similar to the original product, they are not exactly the same. Small distinctions in the cell line, in the manufacturing process or in the surrounding environment can make a major difference in side effects observed during treatment, i.e. two similar biologics can trigger very different immunogenic response. Therefore, and unlike chemical pharmaceuticals, substitution between biologics, including biosimilars, can have clinical consequences and does create putative health concerns. Biosimilars are subject to an approval process which requires substantial additional data to that required for chemical generics, although not as comprehensive as for the original biotech medicine. Originally the complexity of biological molecules led to requests for substantial efficacy and safety data for a biosimilar approval. This has been progressively replaced with a greater dependence on assays, from quality through to clinical, that show assay sensitivity sufficient to detect any significant difference in dose. However, the safe application of biologics depends on an informed and appropriate use by healthcare professionals and patients. Introduction of biosimilars also requires a specifically designed pharmacovigilance plan. It is difficult and costly to recreate biologics because the complex proteins are derived from living organisms that are genetically modified. In contrast, small molecule drugs made up of a chemically based compound can be easily replicated and are considerably less expensive to reproduce. In order to be released to the public, biosimilars must be shown to be as close to identical to the parent biological product based on data compiled through clinical, animal and analytical studies. The results must demonstrate that they produce the same clinical results. EMA and FDA regulations as well as scientific considerations indicate that biosimilarity does not imply interchangeability.

3.1.1 DEFINITION

Biosimilars are defined differently across different geographies by their respective regulatory bodies, with the ultimate meaning remaining the same, with highlighting some of the definitions here:

WHO (World Health Organization):

“A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. A biotherapeutic product, which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.”

EMA (European Medicines Agency):

“A biosimilar is a biological medicine that is similar to another biological medicine that has already been authorized for use

- Biological medicines are made by or derived from a biological source, such as a bacterium or yeast
- They consist of relatively small molecules such as human insulin or complex molecules such as monoclonal antibodies

US FDA (United States food and drug administration):

"A biosimilar is a biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference bio therapeutic production terms of the safety, purity, and potency of the product"

MHLW (Ministry of health labor and welfare, Japan):

"Biosimilars refer to a biotechnological product that is produced by a subsequent-entry manufacturer and claimed to be comparable to a biopharmaceutical product already approved in Japan".

3.1.2 BIOSIMILARS SAFETY AND EFFICACY CONCERNS

Biosimilars are designed to mimic biologic agents, but they are not precise duplicates of these drugs, leading to immunogenic reactions in some patients. Thus, immunogenicity represents significant patient safety concerns. Systemic approaches that employ public and private sector cooperation and partnerships for proactive warnings, education, and identification of immunogenicity are important to mitigate the potential for patient harm. Physicians are also reluctant to prescribe even if the cost difference is high, as they are not sure regarding the safety and efficacy of the drug.

3.1.3 BIOLOGICAL VERSUS CHEMICAL (SMALL MOLECULE) DRUGS

Table 2: Comparison between chemical and biologic drugs

	CHEMICAL DRUGS	**BIOLOGIC DRUGS**
Size	Small (single molecule) Low molecular weight	Large (mixture of related molecules) High molecular weight
Structure	Simple, well defined, independent of manufacturing process	Complex (heterogeneous), defined by the exact manufacturing process
Modification	Well defined	Many options
Manufacturing	Produced by chemical synthesis Predictable chemical process Identical copy can be made	Produced in living cell culture Difficult to control from starting material to final API Impossible to ensure identical copy
Characterization	Easy to characterize	Cannot be characterized

	completely	completely the molecular composition and heterogeneity
Stability	Stable	Unstable, sensitive to external conditions
Immunogenicity	Mostly non-immunogenic	Immunogenic

3.1.4 BIOLOGIC (REFERENCE) VERSUS BIOSIMILAR DRUGS

Table 3: Comparison between biologic and biosimilar drugs

PARAMETERS	BIOLOGICS	BIOSIMILARS
Definition	Biologic drugs are proteins produced by living cells, including monoclonal antibodies, soluble receptors, receptor antagonists, molecules derived by genetic engineering and other types of proteins that can be used to diagnose or treat human diseases	Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise
Manufacturing	Produced by biological process in host cell lines Sensitive to production process changes Expensive and specialized production facilities Reproducibility difficult to establish	Produced by biological process in host cell lines Sensitive to production process changes Expensive and specialized production facilities Reproducibility difficult to establish
Clinical Development	Extensive clinical studies, including phase I–III Pharmacovigilance and periodic safety updates needed	Extensive clinical studies, including phase I & III (phase II not required) Pharmacovigilance and periodic safety updates needed
Regulation	Needs to demonstrate “comparability”	Needs to demonstrate “similarity”
Cost	Manufacturing cost is very high as the pre-clinical and	Manufacturing cost is high as compared to generics but

	clinical development of biologics easily reaches 100-fold of those of small molecules	about 20-30% less than the originator drug

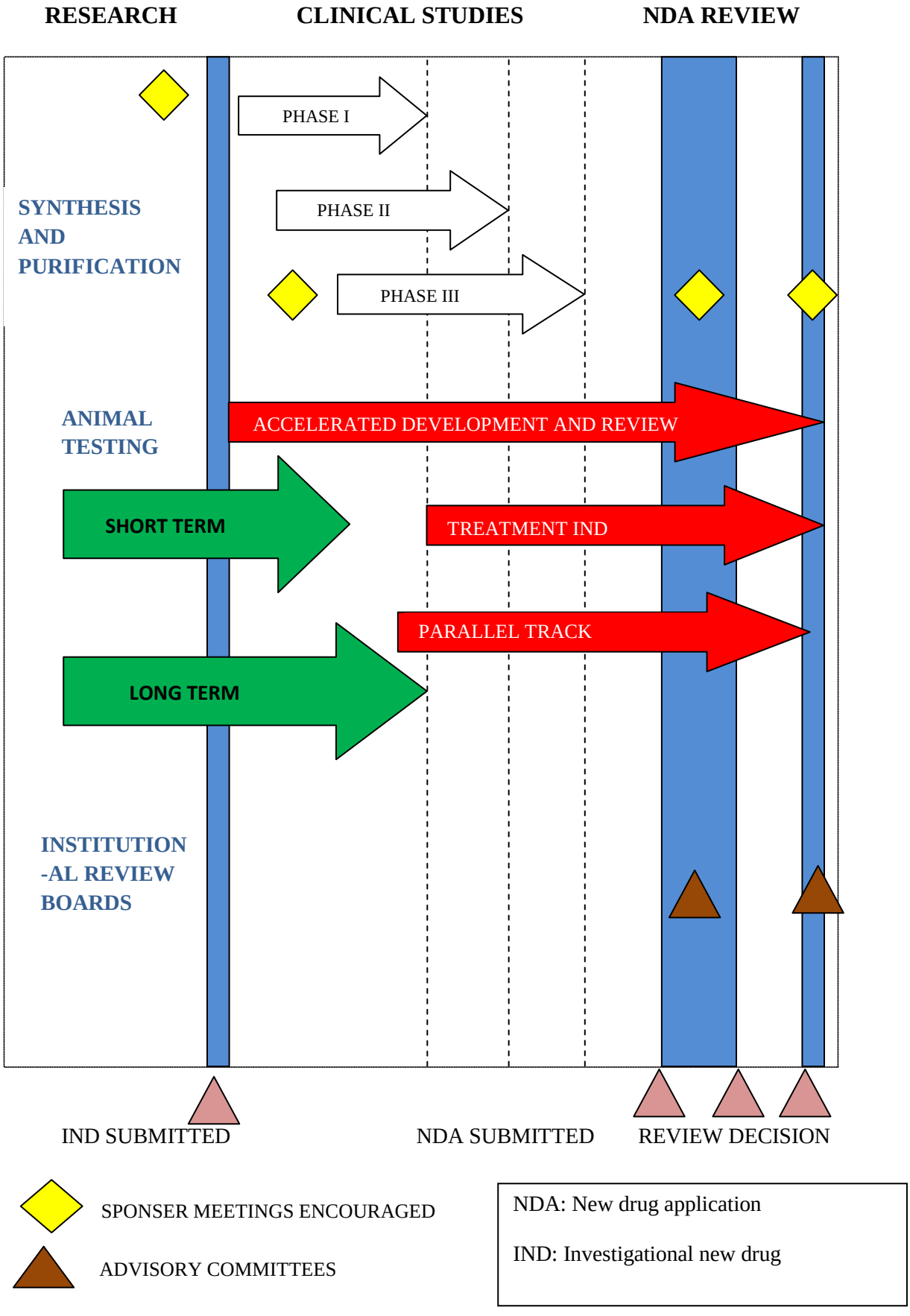
3.1.5 DRUG DEVELOPMENT PROCESS:

- **Drug development** is a blanket term used to define the process of bringing a new drug to the market once a lead compound has been identified through the process of drug discovery.

- It includes pre-clinical research (microorganisms/animals) and clinical trials (on humans) and may include the step of obtaining regulatory approval to market the drug.

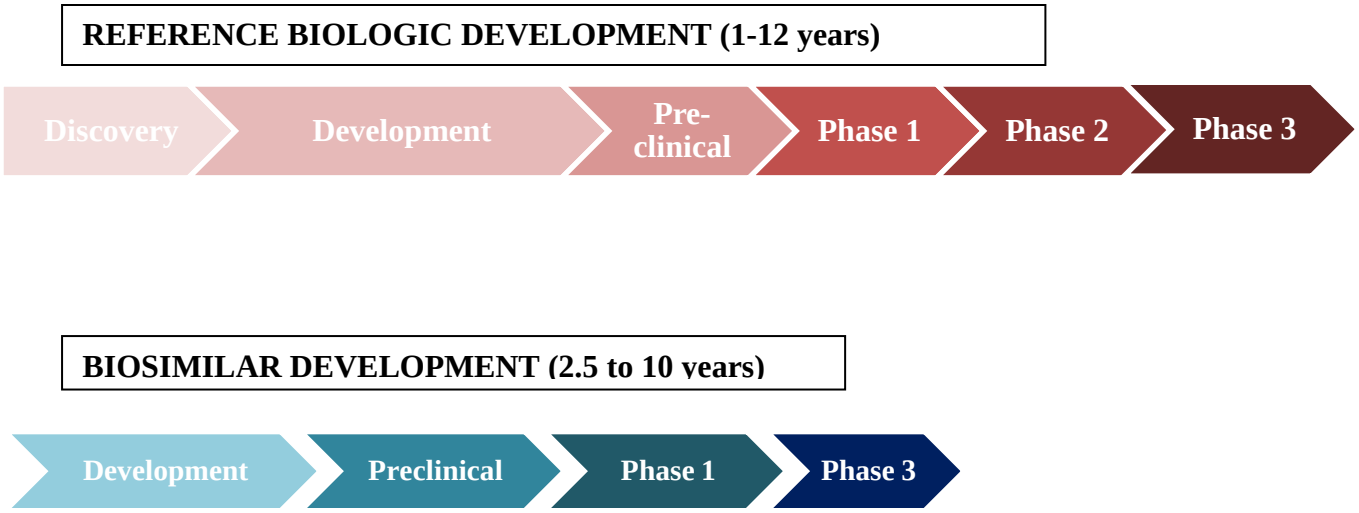
- Drug discovery is an iterative process. It goes back and forth between theoretical biology; the necessary, appropriate, and humane use of animal assays to determine a compound's biological activity in the body; and medicinal chemistry to optimize the compound. Then in human studies, clinical observations test hypotheses; determine its safety and effective doses.

Figure 1: Drug Development Process



This is the normal drugs development process, but there lies the difference between development of biologics and biosimilars as follows:

Figure 2: Drug Development of Biosimilars



- The biosimilars need not undergo discovery and phase 2 trials. The reason is the drug or active ingredient has already been discovered. Not only this the indications for the particular drug has also been same as the reference biologic
- The biosimilars comes into the market only when the patent for the originator has expired (loss of patent exclusivity), as it is for the generics and branded drugs
- Pharmacovigilance and periodic safety updates are needed for a biosimilar to be developed or launched into the market
- Manufacturing cost is very high as the pre-clinical and clinical development of biologics easily reaches 100-fold of those of small molecules
- Manufacturing cost is high as compared to generics for biosimilars but about 20-30% less than the originator drug

3.1.6 GENERICS TO BRANDED AS BIOSIMILARS TO BIOLOGICS

Generic drugs are essentially **"copycat"** versions of small molecule drugs – drugs that can be synthesized in the lab by following standardized, pre-defined procedures.

Using well-established analytic techniques, the generic version of a small molecule drug can be demonstrated to be chemically and structurally identical to the innovator drug.

Biologic drugs, however, are much more complex than small molecule drugs. These drugs are proteins that must be produced by a living cell – they cannot be chemically synthesized in the lab by following a standard set of procedures.

The cell makes these proteins by following a recipe provided by a short sequence of DNA – a gene – that is inserted into the cell. Here's the catch: **even if two different cells are provided the exact same recipe, the final product may be slightly different**. This may happen even if the two cells are of the same type – very slight environmental differences can have a profound effect on how a given cell follows a particular recipe. This makes intuitive sense – we know that we can follow the same recipe that the gourmet chef at our favorite restaurant follows, but somehow, the dish doesn't taste quite as good.

Slight difference such as the exact temperature of the frying pan, the brand of the heavy cream, and even the humidity level and elevation of the kitchen will influence the final outcome. The restaurant industry depends on these "trade secrets" to keep us coming back for more.

Complicating matters further for biosimilar products is the fact that because biologic drugs are structurally much more **complex** than their small molecule counterparts, it is not currently possible to demonstrate conclusively that a biosimilar drug is in fact identical to the original biologic drug.

Thus, since we know that there is a high likelihood that a biosimilar drug is not identical to the original biologic, and we have no way of precisely measuring whatever differences may exist, the term "biosimilar" is used rather than "generic", which implies identity.

The above phrases and examples make it very clear that as the generic is identical to branded or 100% replica of the branded drug, whereas biosimilars are similar to biologic or originator drugs but not identical making the approval and launch highly complex and needs to follow the stringent pathway for the same.

3.1.7 BIOSIMILARS TERMINOLOGIES USED ACROSS THE WORLD

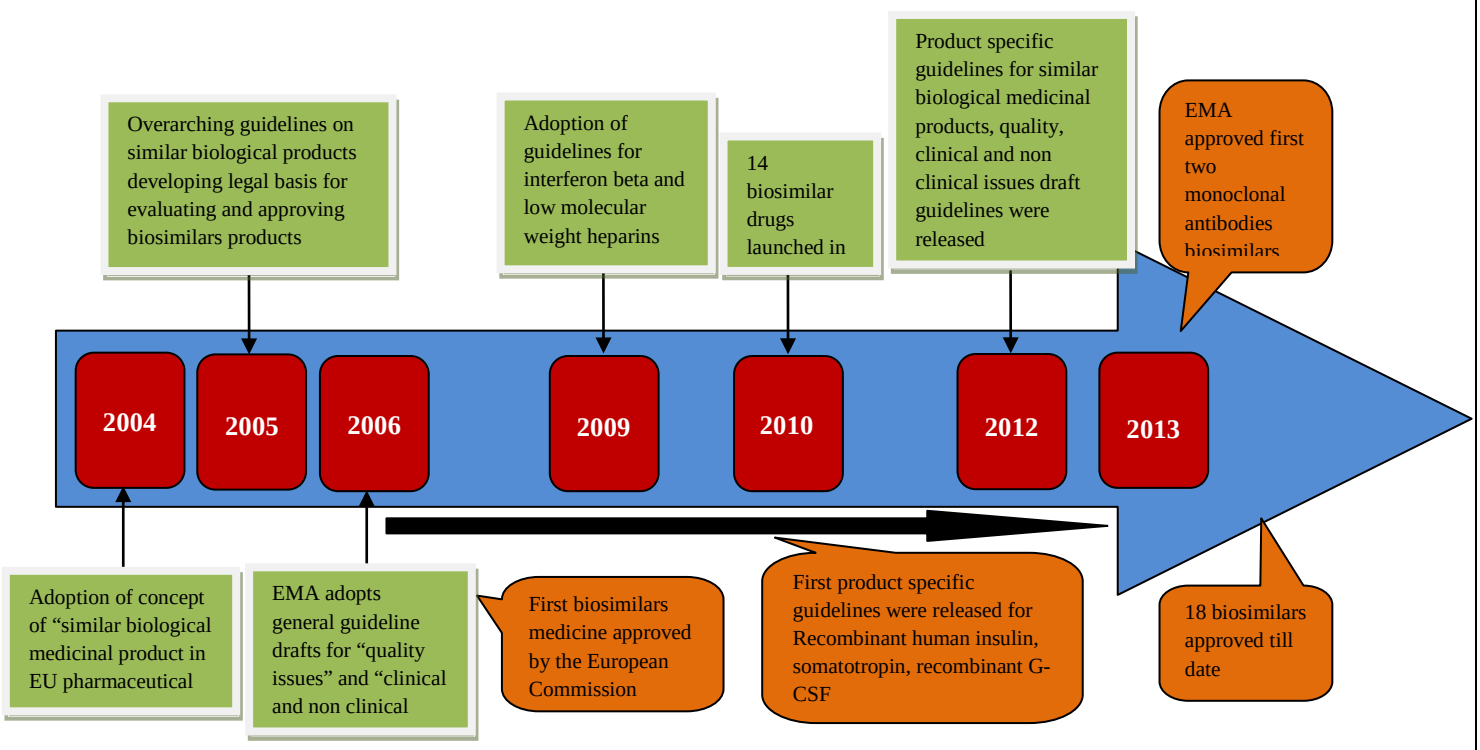
Although biosimilars carry the same meaning across different geographies, yet they are called out differently in different nations as per their norms and standards as follows:

Table 4: Biosimilar Terminologies

TERMINOLOGIES USED	GEOGRAPHIES
Biosimilars	Europe and Australia
Follow on proteins/ Biologics	US and Japan
Subsequent entry Biologics (SEB)	Canada
Similar Biologics	Asia excluding Japan

3.1.8 DEVELOPMENT OF BIOSIMILARS IN EUROPE

Figure 3: Evolution of Biosimilars in Europe



3.1.9 APPROVAL PROCESS OF BIOSIMILARS IN EUROPE

In the European Union, marketing authorization applications for biotechnology-derived medicinal products, including biosimilar medicinal products, are by law reviewed centrally by the European Medicines Agency (EMA). The European Commission issues the Decisions concerning the authorization of these medicinal products on the basis of the Scientific opinions from the EMA. The resulting marketing authorization is valid in all EU Member States.

The EU is the first region in the world to have set up a legal framework and a regulatory Pathway for “similar biological medicinal products”, more commonly called “biosimilars”. The EU regulatory framework inspired many countries around the world e.g. Australia, Canada, Japan, Turkey, Singapore, South Africa, Taiwan, USA etc. as well as the World Health Organization (WHO)

Every pharmaceutical company must have a pharmacovigilance system in place which is used by the marketing authorization holder to monitor the safety of authorized medicinal products and detect any change to their benefit-risk balance. This pharmacovigilance system is subject to inspections by the regulatory authorities.

Every pharmaceutical company must have a pharmacovigilance system in place which is used by the marketing authorization holder to monitor the safety of authorized medicinal products and detect any change to their benefit-risk balance. This pharmacovigilance system is subject to inspections by the regulatory authorities.

The EU-RMP for a biosimilar medicinal product is product-specific and has to be approved by the competent authorities before the medicine is marketed. Every biosimilar medicine on the market has an EU-RMP in place with information on the RMP included in the Assessment Report published on the EMA website.

3.1.10 MAJOR BIOSIMILARS IN EUROPEAN MARKET WITH RESPECTIVE THERAPEUTIC AREAS

Table 5: Three major biosimilars in Europe

NAME OF ACTIVE INGREDIENT	LAUNCH YEAR	TOTAL BIOSIMILARS LAUNCHED	INDICATIONS
Filgrastim (G-CSF)	2008	7	• Cancer • Hematopoietic stem cell transplantation • Neutropenia
Epoetin alfa (EPO)	2007	5	• Anemia • Cancer • Chronic kidney failure
Somatropin (HGH)	2006	2	• Growth hormone deficiency • Pituitary dwarfism • Prader-Willi syndrome • Turner syndrome

- These are the major biosimilars in the European market; they differ in their distribution and uptake across different geographies within Europe depending on the therapeutic areas.
- Europe has always taken the lead in case of biosimilars with other countries following the same
- Filgrastim, Epoetin alfa and Somatropin are the three main classes of biosimilars in European market

3.1.11 LIST OF BIOSIMILARS LAUNCHED TILL DATE IN EUROPE

Due to well established guidelines for approval of biosimilars 18 biosimilars are launched till date in Europe

Table 6: Total biosimilars launched till date in Europe

PRODUCT NAME	ACTIVE SUBSTANCE	AUTHORIZATION DATE
Omnitrope	Somatropin	Apr-06
Abseamed	Epoetin alfa	Aug-07
Binocrit		Aug-07
Epoetin alfa Hexal		Aug-07
Retacrit	Epoetin zeta	Dec-07
Silapo		Dec-07
Biograstim Filgrastim	Filgrastim	Sep-08
Ratiograstim		Sep-08
Tevagrastim		Sep-08
Filgrastim Hexal		Feb-09
Zarzio		Feb-09
Nivestim		Jun-10
Somatropin Biopartners	Somatropin	Aug-13
Remsima	Infliximab	Sep-13
Inflectra		Sep-13
Ovaleap	Follitropin alfa	Sep-13
Grastofil	Filgrastim	Oct-13
Bemfola	Follitropin alfa	Jan 2014

3.1.12 DRIVERS FOR THE BIOSIMILARS MARKET

Potential cost savings for healthcare providers and patent expiry of blockbuster biologics are key drivers for biosimilars

Table 7: Drivers in biosimilar market

Healthcare Cost Savings and Improved accessibility for patients

- Biosimilars serve as Cost-saving lever for mature economies experiencing increasing pressure on resource
- Price of biosimilar is 20% to 30% lower than original biologics so their substitution will offer compelling opportunity for third-party payers and the pharmacy benefit managers to reduce drug spending
- Broaden access to life saving drugs by increasing affordability e.g. biosimilar filgrastim (recombinant human G-CSF) exhibit a strong performance by boosting overall filgrastim market with a 40% increase in overall daily volume usage

Biologics patent expiry creating opportunity for biosimilar manufacturers

- Upcoming expiry of biologics patents
- The worldwide biosimilar landscape is becoming over-populated with various companies clearly entering this arena
  - Innovator companies: Amgen, Merck, Pfizer
  - Generic companies: Sandoz, Dr. Reddy's, Hospira, Teva
  - Unusual players: Fujifilm, Samsung, GE Healthcare

Collaboration:

- With generic companies bringing together development and marketing
- With different geographies with access to wider markets

3.1.13 BARRIERS FOR THE BIOSIMILARS MARKET

- Uncertainties in regulatory frameworks and greater manufacturing and clinical development complexities have limited the growth of biosimilar market

Table 8: Barriers in biosimilars market

Complex Regulatory framework

- Regulatory framework is complex, regulations bear greater burden on biosimilars in proving safety and efficacy to be interchangeable to RBP
- Currently long approval times in Japan (three years), US (just recently introduced legislative framework)
- Fragmented regulations in other geographies cause delay/block launch

High Cost of Manufacturing and Trials

- Manufacturing is complex, require significant time (6-9 years), technical capability, and clinical trial expertise
- Huge clinical development costs ranging from $40-$300 million as compared to $1-4 million for generics
- High cost of conducting pre-clinical and clinical studies

Physicians reluctance to prescribe

- Physicians oppose biosimilars on efficacy and safety grounds
- Biosimilars are deemed interchangeable or are granted automatic substitution on case by case review so physician remain skeptical

Storage

- Being less stable, need cold chain distribution and have a shorter shelf life increasing cost and complexity of distribution

3.2 AIM OF THE STUDY

The aim of the study is to understand the emerging trends of biosimilars in EU5 nations and analyze the performance of biosimilars in pharmaceutical market based on their respective uptakes across different geographies and also based on the therapeutic areas.

3.3 OBJECTIVES

The objectives of the study are:

- To identify the uptake of biosimilars across EU5 (Germany, UK, France, Italy and Spain).
- To identify the major biosimilars in the market based on their respective uptakes across EU5 nations
- To identify the drivers and barriers for the variations in the uptake

CHAPTER4: RESEARCH METHODOLOGY

The study of biosimilars was done to identify the trends of biosimilars across Europe for a consulting firm based in Gurgaon and having a substantial business interest to help their clients achieve success in sales and marketing of biosimilars in Europe. The data collection was done during 3rd February to 8th May.

It was a meta analysis research using systematic literature review. Both paper based and electronic resources were used in the study as given below:

- Paper based sources: Journals, periodicals, abstracts, research reports, annual records of organizations, market reports, annual reports etc.
- Electronic sources: Internet, On-line databases, URL's, websites, Pub med, company websites, broadcasts

TIME PERIOD

The time period for completion of study conducted was 3 months in the organization. The latest data was collected including data for last 0 to 5 years.

CATEGORIZATION

The countries studied in Europe were shortlisted based on:

- Clients of the firm
- Emerging trends of biosimilars across Europe

TOOLS OF DATA COLLECTION

The data collection was done through secondary research using various websites, URL's, articles and databases of the organization such as:

Biotrends.com, Gabi journals, Xcenda.com, Frostand Sullivan specialty physicians, Sandoz, assogenerici.org, pharmaletter.com etc.

Databases from the organization: Bloomberg, OneSource etc

KEYWORDS USED

Initially on searching biosimilars approximately 8.86 crore results were found. Further short listing of the sites was done using various keywords like "biosimilars trends in Europe", "biosimilars uptake", "major biosimilars in market", "biologics versus chemical drugs", "total biosimilars launched", "why Europe for biosimilars" etc.

SHORTLISTING OF DATA/STRATEGY

Since the initial inflow of data was very high; therefore the data was shortlisted based on the relevance of data, need of information for the organization, source of data (valid and reliable). The data was collected with assurance that the source is either from the known journals or articles for pharmaceutical industry or from the other competitor organization's data from reports or articles for comparison or reference purposes for e.g. IMS health consulting, WNS global, PWC, BGC consultancy, McKinsey etc

The data was analyzed and compared across results of different studies and certain calculations were made based on the data and trends collected from databases of organization, showing the growth rates and economic impact of biosimilars across European nations.

Sensitivity and specificity of data was analyzed based on the repetition of information in different sources or vice versa.

Chapter 5: LIMITATION OF THE STUDY

The report also investigates the fact that the analysis conducted has limitations. Some of the limitations include:

- Being an intern, access to all the databases was not allowed in the organization
- The area of research was very vast and time period was less to cover all the parameters
- The study was based completely on secondary research, therefore limitation of data was a concern

CHAPTER 6: FINDINGS

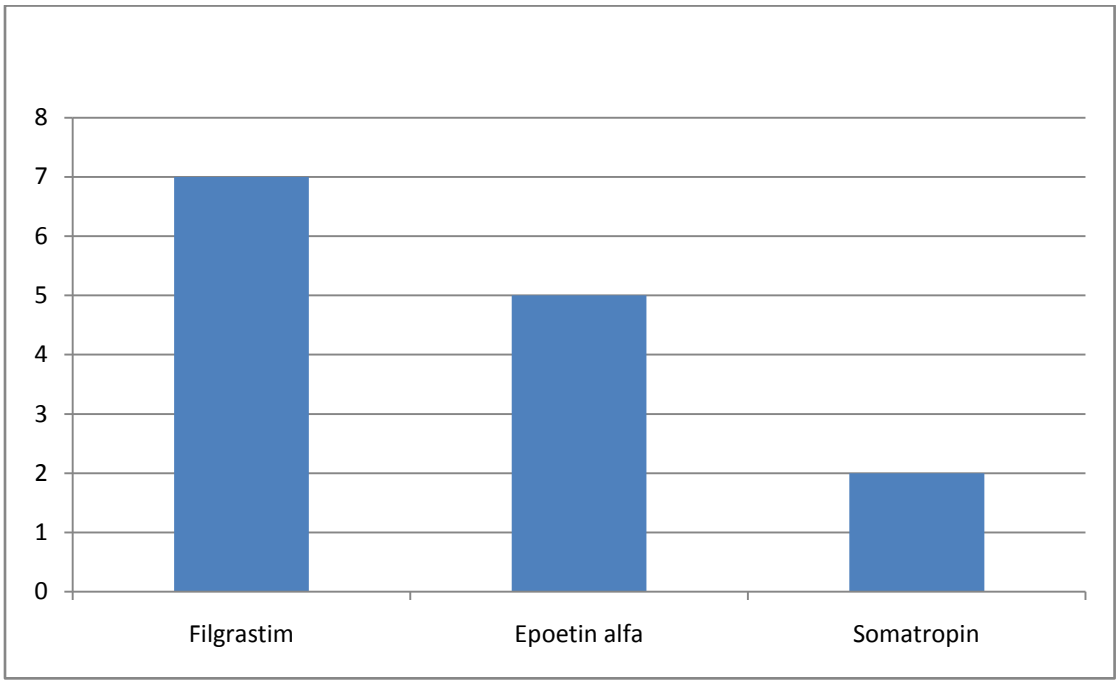
Across the globe Europe was the first to develop a regulatory model for biosimilars and has the maximum number of biosimilars launched till date

The uptake of biosimilars is variable in Europe. The uptake varies across geographies as well as different therapeutic areas, showing some markets as mature biosimilar players while some still upcoming with their new launches in biosimilars

6.1. THE MAJOR BIOSIMILARS IN EUROPEAN MARKET

Out of the total biosimilars launched three are the major market players with variations in uptake as follows:

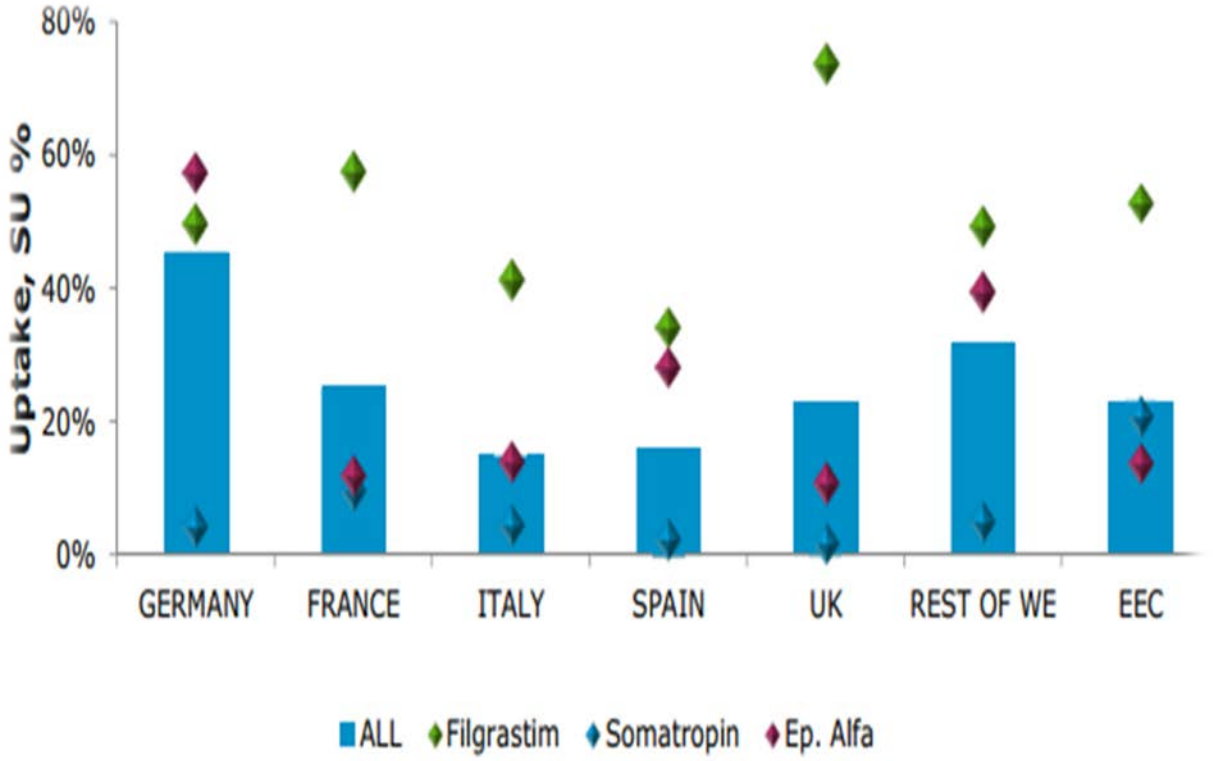
Figure 4: Key Biosimilars in the Market



6.2 DIFFERENCE IN UPTAKE OF BIOSIMILARS ACROSS EUROPE

- Variations in uptake of biosimilars in EU5 is mostly attributed to differences in the healthcare systems between different countries and also the differing attitudes in the different countries

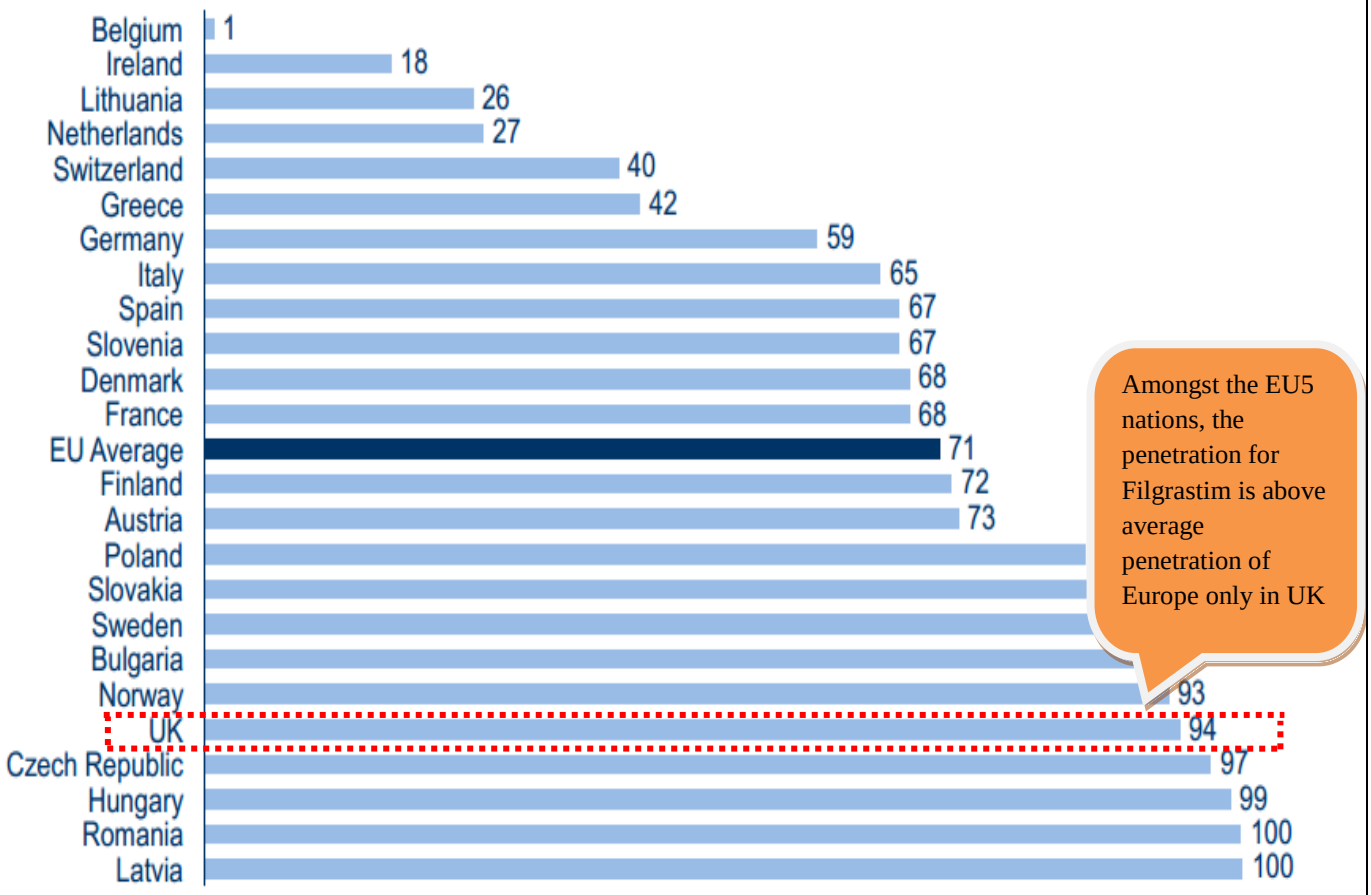
Figure 5: Variations in Uptake of Biosimilars across Europe



The vast majority of EMA markets accept the Filgrastim biosimilar concept but several lag behind.

- Although he overall biosimilars market remains small in the UK, yet the market share of Filgrastim is highest(above 90%) among all EU5 nations
- Biosimilar penetration of Filgrastim across Europe in % standard units (Feb 2013)

Figure 6: Filgrastim Uptake across Europe showing above 90% in UK



UK is the largest market for biosimilar Filgrastim followed by France and Germany

- Biosimilar Filgrastim has a 90% volume share (January 2013) of the Filgrastim market in the UK with a dramatic increase in patient access
- In UK G-CSF market, shows a 44% increase in daily volume usage of G-CSF since biosimilars were launched
- Reasons for high uptake
  - Biosimilar G-CSF and EPO are hospital prescribed in UK
  - Transparent multi factor tenders operate to select single preferred agent
  - Hospital protocols are changed to reflect the winning bid with exception criteria for defined patient groups
  - Hospitals publish success of uptake in achieving real savings
  - Low safety concerns associated with this product class

Figure 7: Filgrastim Uptake across EU5 (Commodity Market)

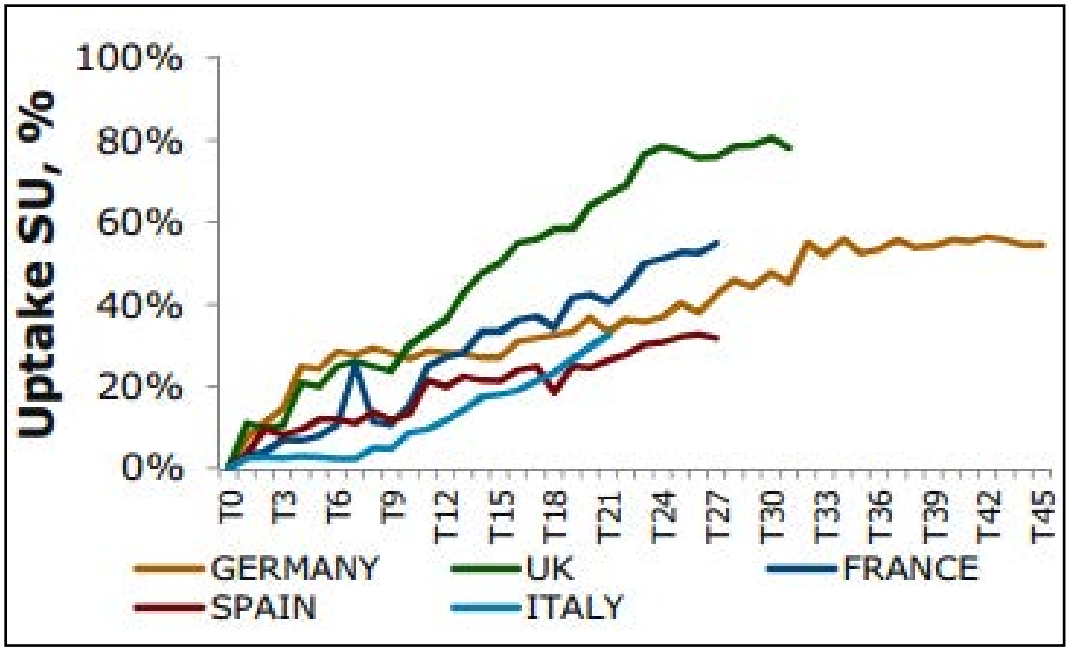


Figure 8: Originator Daily Uptake Goes Down While Biosimilar Filgrastim Rises Steeply

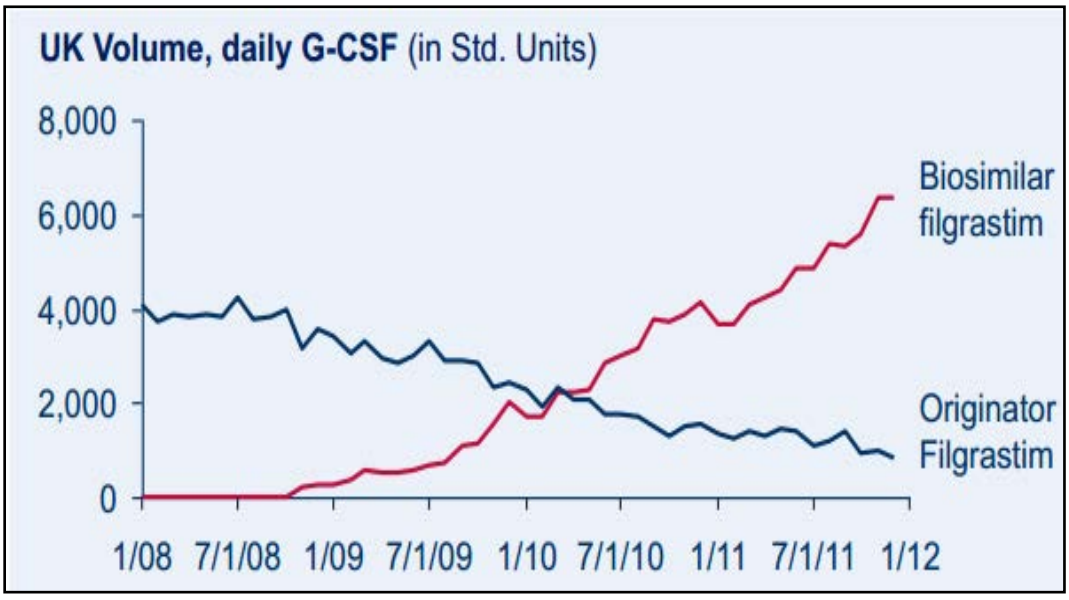
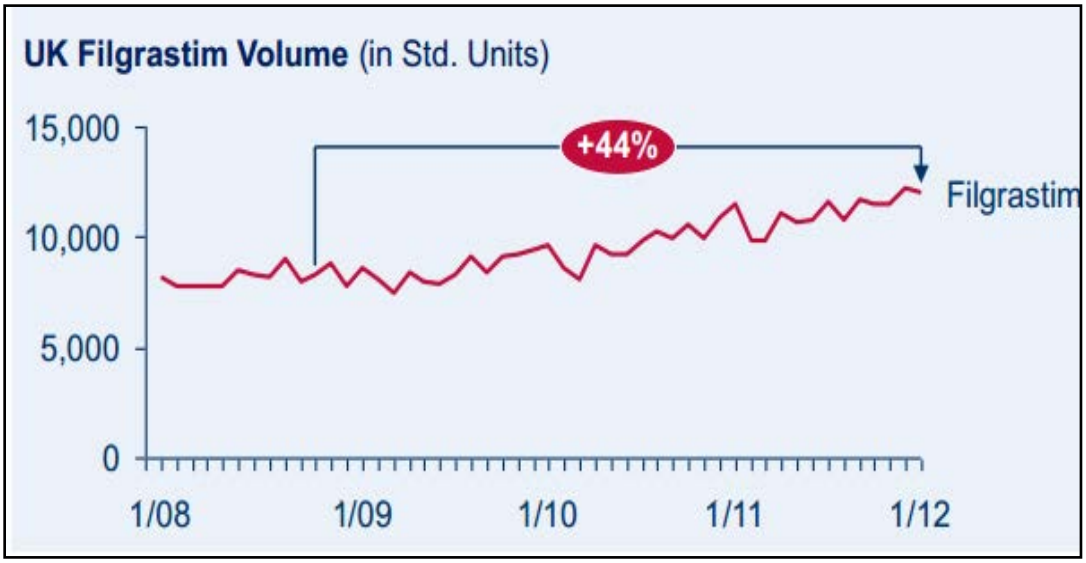
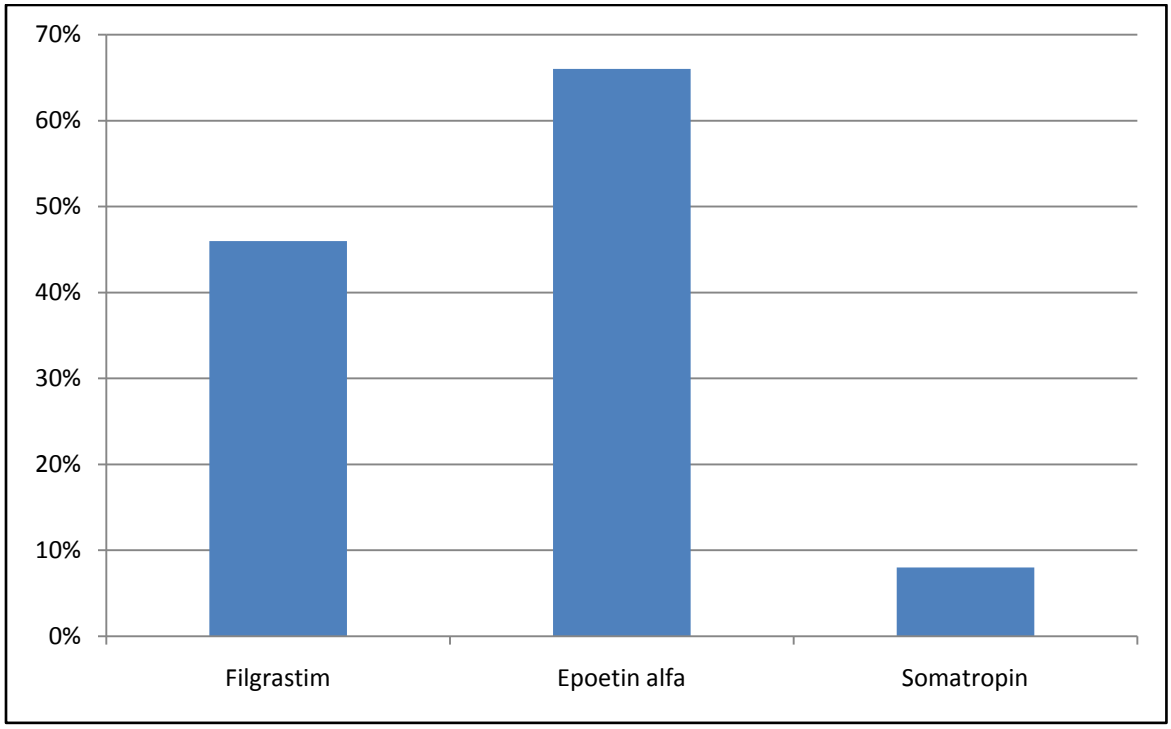


Figure 9: 44% Increase in Daily Volume Usage of biosimilar Filgrastim



- Germany is the largest market for biosimilar EPO followed by Spain and Italy
- It is the most favorable market for biosimilars and it already has an account for over 50% of the EPO market by value.
- Biosimilars G-CSF and Epoetin are used predominantly in retail setting
- Reasons for high uptake:
  - Germany has provided the most favorable incentives for biosimilars
  - In addition to a **reference pricing system** in place for biosimilars, it also has specific targets or **quotas** for physician and sickness funds for biosimilars that vary by region
  - Education sessions with clinicians to reinforce biosimilar concept
  - Publish real world utilization data to counter originator myths

Figure 10: Variations in Uptake of Biosimilars Across Products In Germany



- German companies lowered ex-factory prices in retail market for biosimilars due to sensitivity of payers & prescribers and also the enhanced competition were the key to Germany attaining it's cumulative savings

Figure 11: Biosimilar Share of Epoetin Market Segment

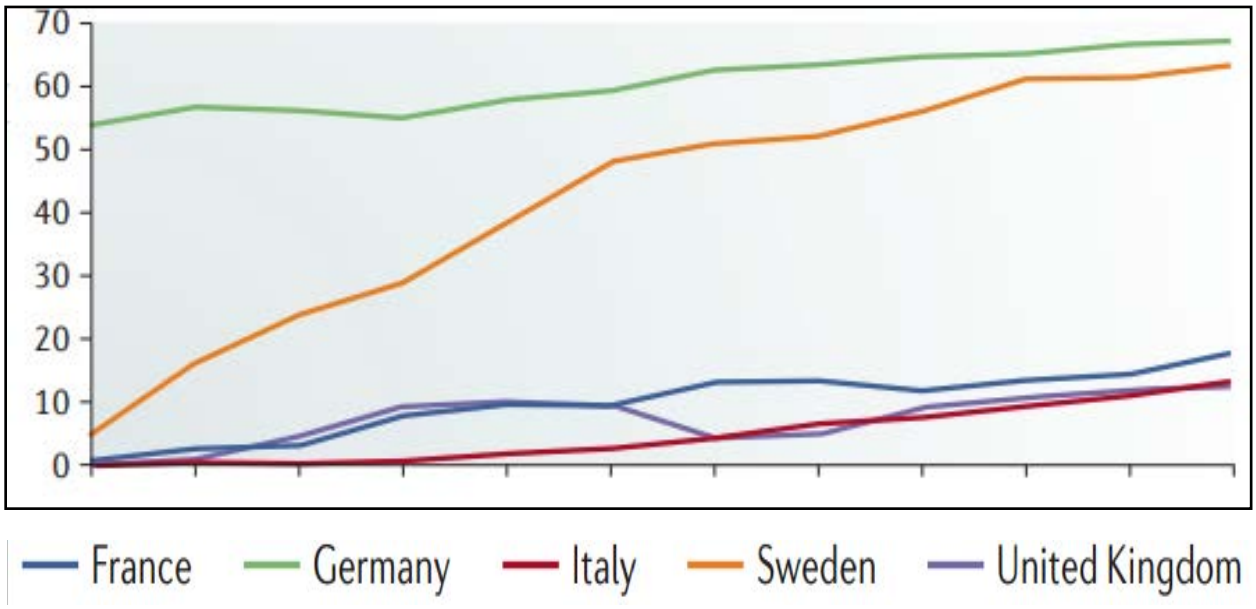
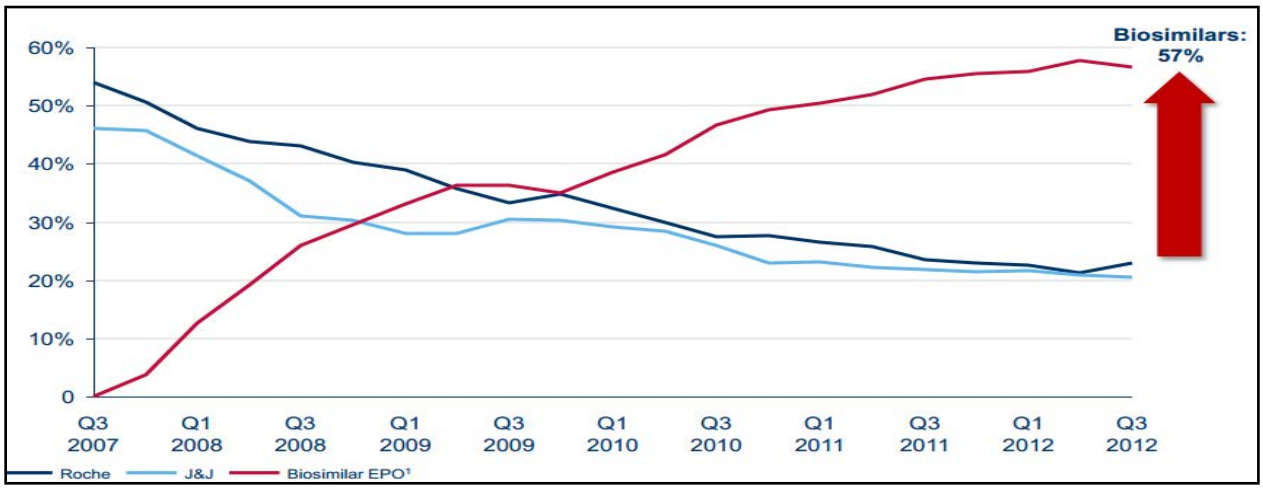


Figure 12: Value Market Share for Originator Goes Down, While Increases By 57% For EPO In Germany



- Germany has provided the strongest incentives with a quota system and reference pricing for biosimilars

Table 9: Trends and policies for biosimilars in European nations

PARAMETER	GERMANY	FRANCE	ITALY	UK
High generic usage	Yes	No	No	Yes
Quotas	Yes	No	Yes	No
Reference price system for biosimilars	Yes	No	No	No
Price relative to reference brand	Variable	Fixed	Fixed	Variable
Patient co-pays	Capped	Mixed	Mixed	No

- Germany worried about the use of tendering in biologics market
  - Tendering has been blamed for drug shortages
  - Reference pricing for biosimilars has been criticized, as it has resulted in biosimilars competing at a price that is similar to the originator

- Expected solution is to use quotas
  - Solutions to the biosimilars issue could come in the form of quotas
  - By allowing biosimilars to reach a certain penetration level (say 50%) before any reference pricing is introduced.(*Quotas have already proven successful in Bremen where prescribing quotas have been agreed and where biosimilars now account for 70% of the market)*

- France prove out to be a better market for biosimilar Somatropin due to support of both government policies and reimbursement schemes whereas U.K. seems more skeptical
- Somatropin uptake highest across France and Italy with UK being the smallest

Figure 13: Variation in Percentage of Sales DDD (Differential Daily Dosage) For Somatropin across Eu5

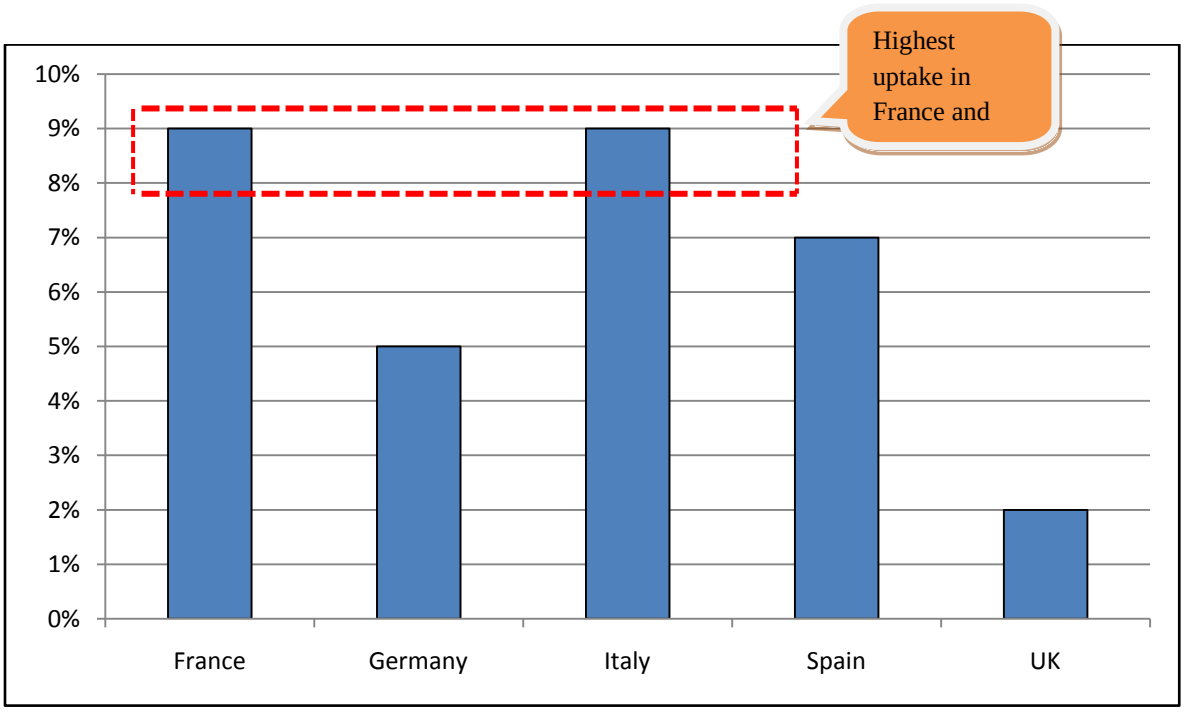
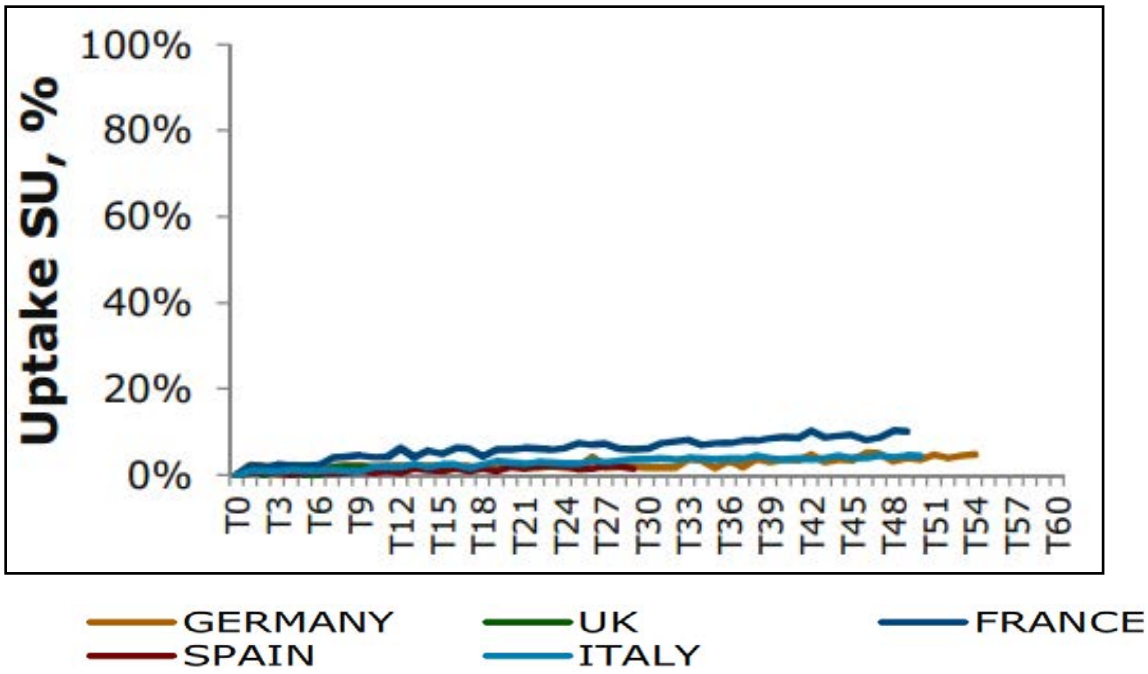


Figure14: Somatropin Uptake across Eu5 (Differentiated Market



- Somatropin shows overall least uptake, with UK being the worst market
- Biosimilar Somatropin (recombinant human growth hormone) has fared significantly well in terms of uptake in the France and Italy
- Somatropin uptake forms a differentiated market
- Reasons for high uptake in France:
  - Biosimilar Somatropin are hospital prescribed in France
  - Prescription quotas, their more widespread use by sickness funds
  - Prescribing encouraged by the health insurance funds
  - Transparent multi factor tenders operate to select single preferred agent

- Reasons for low uptake:
  - Concerns about its suitability for children
  - Existence of several well known branded products in various formulations and delivery devices
  - The length of time it takes to see the benefit of growth hormone therapy is very long

5.1 REASONS FOR VARIABLE UPTAKES

Table 10: Reasons for variable uptakes

VARIABLE UPTAKES FOR THE THREE BIOSIMILARS ACROSS DIFFERENT GEOGRAPHIES		
FILGRASTIM - Highest uptake in UK - REASON: Biosimilar G-CSF and EPO are hospital prescribed in UK Transparent multi factor tenders operate to select single preferred agent Hospital protocols are changed to reflect the winning bid with exception criteria for defined patient groups Hospitals publish success of uptake in achieving real savings Low safety concerns associated with this product class	**EPOETIN ALFA** - Highest uptake in Germany - REASON: Germany has provided the most favorable incentives for biosimilars In addition to a **reference pricing system** in place for biosimilars, it also has specific targets or **quotas** for physician and sickness funds for biosimilars that vary by region Education sessions with clinicians to reinforce biosimilar concept Publish real world utilization data to counter originator myths	**SOMATROPIN** - Highest uptake in France and Italy -REASON: Biosimilar Somatropin are hospital prescribed in France Prescription quotas, their more widespread use by sickness funds Prescribing encouraged by the health insurance funds Transparent multi factor tenders operate to select single preferred agent

OVERALL SOMATROPIN SHOWS LEAST UPTAKE ACROSS EUROPE:

- Reasons:
- Concerns about its suitability for children
- Existence of several well known branded products in various formulations and delivery devices
- The length of time it takes to see the benefit of growth hormone therapy is very long

CHAPTER 7: CONCLUSION AND RECOMMENDATIONS:

The study is of international level; therefore recommendations are for the organization to put forth in front of their clients.

Firstly as we could see that Germany is an outstanding market for biosimilars, other countries like France, Spain and Italy can follow the systems already approved in Germany like tender system, quota system for physicians and healthcare organizations especially where the biosimilars are hospital prescribed. This could increase the overall sales of biosimilars.

Secondly, as the physicians are apprehensive to prescribe biosimilars due to the safety and efficacy concerns, therefore special education programs should be run for the healthcare providers to give the overall understanding of biosimilars

Thirdly, the biosimilars are launched to reduce the cost of biological drugs, therefore the overall cost reduction should be increased to make them accessible to the overall population. They should be put into insurance coverage for the benefit to people.

All the five countries demand different discounts for biosimilars as follows:

France - "I'd like to see a 30% discount and maybe we have like a 15% at the moment"

Germany - "On average, I think biosimilars are priced 20% less"

Italy - "We have reached discounts of 40% of the original brand price for some biosimilars [in hospitals]"

Spain - "Biosimilars are approximately 30-40% the price of the brand drug"

United Kingdom - "For the biosimilars that are already available in Europe the level of discount is running about 20, 25%

If all these requirements are fulfilled the overall sales will definitely be increased.

CHAPTER 8: ANNEXURE

IMPORTANT TERMS USED IN THE STUDY

- **A Reference Bio therapeutic Product (RBP)** is used as the reference product for head-to-head comparability studies with the similar bio therapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP

- **Biosimilars (also known as follow on biologics in the US)** are biologic products that are highly similar to reference bio therapeutic product (originator biologic) without clinically meaningful differences in safety, purity and potency, approved in a country which has an abbreviated approval process for biologic products

- **Non-original biologics (NOBs)** are those copies of innovative brands that have not been approved through such a dedicated pathway, undergo less stringent comparability
  - ✓ Typically, they are introduced in pharmerging markets as NOB's generate more than twice the sales of biosimilars in mature markets
  - ✓ Hold 11 percent of the biologics market value in pharmerging markets
  - ✓ Physicians in emerging markets often turn to non-original biologics, rather than originator products, as the first line of therapy due to their price and accessibility

- **Biobetter (functionally enhanced biologics) or Biosuperiors** contain **s**imilar active agent in either a different physical form(long-acting formulations) or chemical substructure (pegylated) intended to be better or superior to the innovator product with measurable superiority features such as extended therapeutic effect time, reduced adverse event profile, improved dosing regimen thereby reducing treatment cost

- **Biosimilarity** means that the biosimilar product is highly similar to the reference bio therapeutic product not withstanding minor differences in clinically inactive components, with no clinically meaningful differences in terms of the safety, purity, and potency of product

- **Interchangeability** is where a biosimilar deemed interchangeable with reference product, that are judged to be similar in terms of clinical result in any given patient, show no increased risk in terms of safety or diminished efficacy and can be exchanged one with another without a significant risk of an adverse health outcome

- **Substitution (Automatic substitution)** : The practice by which a product other than the one specified on the prescription is dispensed to the patient by the pharmacist, without prior informed consent of treating physician
  - ✓ A variation of substitution is practiced in some countries where, if the physician prescribes by international non-proprietary name (INN), the pharmacist may dispense any product with the same active ingredient.

- In all cases, however, the essential features of substitution are that:
  - ✓ It is the pharmacist (and not the doctor) who decides which brand the patient receives
  - ✓ The doctor is not routinely informed of the brand the patient has received
  - ✓ The patient may potentially receive a different brand every time their medicine is dispensed

- **Extrapolation of indications:** The decision whether to extend the efficacy and safety data from an indication (a medical condition, disorder or disease) for which the biosimilar has been clinically tested to other indications for which the reference bio therapeutic product being used is approved, is known as " Indication Extrapolation"

CHAPTER 9: REFERENCES

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14. Databases from the organization:

- ✓ Bloomberg
- ✓ Onesource