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Investigating Trends in the Duration of the Regulatory Approval Phase for Biosimilars in the European Union and the United States of America

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Abstract

This thesis focused on investigating how the current commercialization landscape and, specifically, the regulatory landscape, affects the market entry of biosimilars. A biosimilar is a post-patent biologic medicinal product that delivers similar clinical outcomes to a reference originator biologic product that is currently marketed. Previous work has indicated that market entry of biosimilars has been slower than initially expected.

Thus, it remains an open question whether advantages accrue to the 1st mover biosimilar during the commercialization process, relative to the 2nd or 3rd or subsequent movers. These advantages could potentially accrue as a result from time gains made at any stage of the commercialization pathway. If the time efficiency is not sustained along the commercialization process, then a biosimilar that is first to apply for regulatory approval process might not necessarily be the first to enter a market and hence will not be able to capitalize its market position as the first mover. First mover disadvantages may deter companies from risking the development of biosimilars. The thesis investigates the duration of the pre-market regulatory phase for biosimilar drugs and the trends between first and subsequent generations of biosimilars in the current commercialization environment.

To investigate the trends in duration of regulatory approval of first and subsequent generations of biosimilars and identify whether there is an advantage or disadvantage to the first biosimilar applicant in terms of duration of the regulatory approval process, this study first identified the key regulatory milestones to define a measure for the duration of the regulatory approval process. Secondly, a quantitative method was utilized to assess first mover advantage or first mover disadvantage for the early generations of biosimilar applicants during the regulatory approval phase.

The data analysis demonstrated that there are no first mover advantages within the regulatory approval phase for biosimilars in Europe and the United States of America. Furthermore, a first mover disadvantage was evident for first generation of biosimilar applicants in Europe. It was also discovered that the duration of regulatory approval phase decreased with each subsequent

generation of biosimilars in Europe. In comparison, the duration of the regulatory approval phase remained fairly consistent for the different generations of biosimilars in the U.S.

In the latter stage, this thesis explored the reasons behind the findings of the study, with a particular focus on the presence of first mover disadvantage during the regulatory approval phase of biosimilar commercialization in the EU. The thesis also explored three potential policy interventions to improve market entry of biosimilars; providing incentives to early generations of biosimilar applicants, reimbursement, and promoting uptake.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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Publications included in this thesis

No publications included

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No manuscripts submitted for publication

Other publications during candidature

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Contributions by others to the thesis

No contributions by others.

Statement of parts of the thesis submitted to qualify for the award of another degree

No works submitted towards another degree have been included in this thesis

Research Involving Human or Animal Subjects

No animal or human subjects were involved in this research

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Keywords

biosimilars, biopharmaceuticals, biologics, regulatory approvals, first mover advantage

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List of Figures & Tables

List of Abbreviations used in the thesis

aBLA	Abbreviated Biologics License Application
aNDA	Abbreviated New Drug Application
ANOVA	Analysis of Variance analysis
BPCIA	Biologics Price Competition and Innovation Act of 2009
CDER	Center for Drug Evaluation and Research
cGMP	Current Good Manufacturing Practises
CHMP	Committee for Medicinal Products for Human Use
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	European Agency for Evaluation of Medicinal Products
EU	The European Union
FMA	First Mover Advantage
FDA	The Food and Drug Administration of the United States of America
FD&C	Food, Drug and Cosmetic Act of 1938
HCPCS	Healthcare Common Procedure Coding System
HWA	Hatch Waxman Act
ICH	International Conference on Harmonization
INN	International Nonproprietary Name
IP	Intellectual Property
PD	Pharmacodynamics
PF	Physician Fee Schedule
PIMS	Profit Impact of Market Strategies
PK	Pharmacokinetics
NDA	New Drug Application
U.S.	The United States of America
US$	The United States Dollar

CHAPTER 1: INTRODUCTION

Introduction of a new product to a market is associated with risks and uncertainties. From the viewpoint of the industrial firm, the actions leading to new product development and market entry include a long-term investment decision. This incorporates several stages of capital investment, research, development and commercialization. Companies often offset the risks of bringing new products to market, by factoring in the advantages of entering the market early. By entering the market early, these companies aim to capitalize on their investment and earn above average profits. This is evident in the case of the pharmaceutical industry.

The benefits associated with entering the market first are widely known as first mover advantages. Often, first mover advantage is analyzed in the literature in terms of post-market performance indicators such as market share and price. First mover advantages include the enjoyment of market monopoly through gaining intellectual property (IP) rights or market exclusivity periods, increased brand awareness or becoming the consumers' preference or standard in a product category. Furthermore, first movers can increase market entry barriers to later market entrants in a multitude of ways such as limiting the access to suppliers and raw materials, preempting assets, monopolizing distribution channels and by engendering brand loyalty.

1.1. An investigation of the duration of the pre-market regulatory phase for biosimilar drugs: trends between first and subsequent generations of biosimilars

Commercialization is the process by which a new service or product is introduced to the market. Commercialization, as a strategy often requires companies to anticipate market entry barriers and to develop plans to mitigate these challenges and to ensure successful market entry. Companies undertaking commercialization of products also focus on the identification of micro-economic and macroeconomic factors that might affect the commercialization process.

The pharmaceutical industry is highly regulated; pharmaceuticals undergo a unique commercialization process before market entry (refer to Figure 1-1). This process requires significant resources to prove to regulatory authorities that a product is effective and safe, *via* multi-step clinical

development and regulatory approval. This requires significant resources in multiple domains such as capital investment, technical know-how and regulatory expertise. The rate of passage of a pharmaceutical product through this multi-step process will determine the time taken to reach market entry.

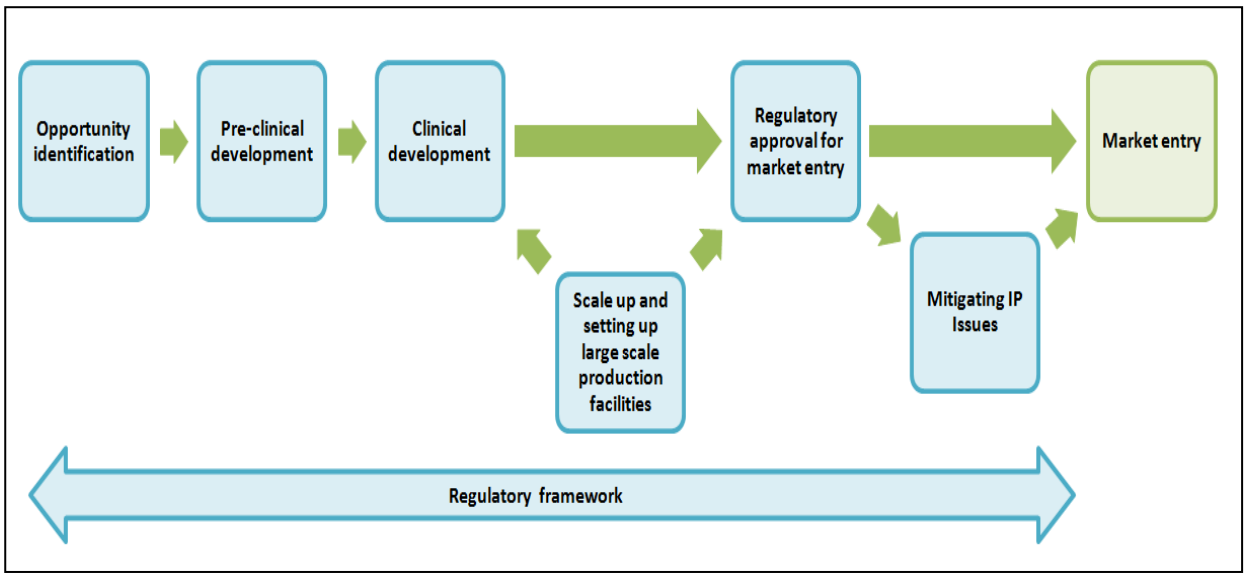


Figure 1-1: Summary of the commercialization pathway for pharmaceuticals

The United States Food and Drug Administration (FDA), the regulatory body for drug approvals in the United States of America (U.S.), estimates that, on average, only 250 drug compounds out of 5000 to 10,000 potential drug compounds in opportunity verification phase reach the stage of pre-clinical development[1]. Of the 250 drug compounds that reach pre-clinical development, only one compound will receive FDA approval; that is a success rate of 0.01% to 0.02%[1]. For these reasons a commercialization landscape that allows a new pharmaceutical product to retain and capitalize its market entry position is a sensitive and vital determinant in encouraging firms to take on the challenge of bringing new products to market. Absence or loss of the ability to retain and capitalize market entry position in the pathway to commercialization may deter companies from taking the risk of pharmaceuticals development.

The thesis reports the results of an investigation into whether there is first mover advantage or disadvantage for first mover biosimilars relative to subsequent generations of biosimilars, during the regulatory approval phase. It will also report any trends discovered in the regulatory time periods for these generations of biosimilars.

1.2. What are Biopharmaceuticals?

Biopharmaceuticals, also known as biologics, are medicinal drugs synthesized using living organisms including microorganisms and plants. Biopharmaceuticals were first introduced to the market in 1982, following the discovery and development of recombinant DNA technology. This technology made it viable for commercial large-scale production of biologic drugs[2]. The first biopharmaceutical approved for therapeutic usage was Humulin, a human insulin product developed by Genentech Inc. and manufactured by Eli Lily and Company[3]. Since then, biologics have had a profound impact on a variety of disciplines of medicine, especially in areas such as oncology, rheumatology and neurology. The continuous increase in demand for biologic drugs and the widespread acceptance of biologics as a therapeutic option are attributable to the number of unmet clinical needs for which biologic drugs provides a potential treatment option for and expanded innovative treatment choices for specialty diseases. Prior to the discovery of biologic drugs, such patients did not have any treatment options, or the treatment options available were inadequate[4]. The clinical benefits, including factors such as safety, effectiveness and immunogenicity, of biopharmaceuticals have also made them a care option in many indications[5]. Due to these advantages, and the rise in prevalence of diseases such as cancer and diabetes[5] the demand for biologic drugs continues to increase.

However, these advanced, targeted biologic therapies are expensive; on average biologics cost 20 times more per dose than simpler chemical drugs. Moreover, biopharmaceutical prices continue to rise at 10 to 15 percent *per annum*[6,7]. At present, biologics account for 20% of global pharmaceutical spending. Spending on biologic drugs was expected to reach US$ 21 billion by the end of 2017[8]. Biologic drugs also account for a large component of federal or government healthcare spending on prescription drugs across the developed world. In 2014, the United States (U.S.) government spent US$ 21.5 billion on Medicare Part B payments *for "drugs administered in doctor's setting and other outpatient settings"*[9], of which 53% (US$ 11.5 billion) was spent on the top 15 of the total 40 products[10]. Of these top 15 products, 11 were biologics, with each of the biologics in the top 6 contributing to over US$ 1 billion in Medicare Part B spending[10].

Biologic drugs are expected to constitute an expanding share of the entire pharmaceuticals market[11]. This is largely attributable to the increasing percentage of the aged population especially in the developed world, and a concomitant increase in the demand for targeted therapies[11]. Although the potential market size is increasing, the biopharmaceutical industry is at a critical juncture. The industry has experienced a "patent cliff", with many of the first in class, originator biologics (originators) that were brought to market in the last decade of the 20th century, are coming off patent protection. In 2015 alone, 32 biopharmaceuticals with combined sales of US$ 51 billion lost patent protection[12]. This has opened the biopharmaceutical market for potential competition from follow-on or "imitator" products. With a growing demand and rising prices, the current biopharmaceutical market appears to exhibit ideal characteristics for the emergence of a post-patent products industry. The open question is whether that potential for competition will be realized.

Biosimilars and biobetters are the key products of the post-patent biopharmaceutical industry and both variants of originator biopharmaceuticals (Refer to Figure 1-2). Biobetters are new molecular entities that are related to existing biologics by target or action, but they are deliberately altered to improve disposition, safety, efficacy, or manufacturing attributes via changes in the molecular structure such as recombinant fusions, antibody drug-conjugates, PEGylation, antibody engineering and affinity maturation[13]. Whilst biosimilars are required to have the same clinical outcome as the reference originator biopharmaceuticals, due to structural modifications biobetters provide a clinical outcome different to that of reference originator such as increased half-life, reduced immunogenicity, reduced toxicity or improved pharmacodynamic effects[13,14]. Unlike biosimilars, biobetters are not approved *via* abbreviated regulatory approval pathways, however, at present biobetters are eligible for patent protection and market exclusivity periods equivalent to that of originator biopharmaceuticals.

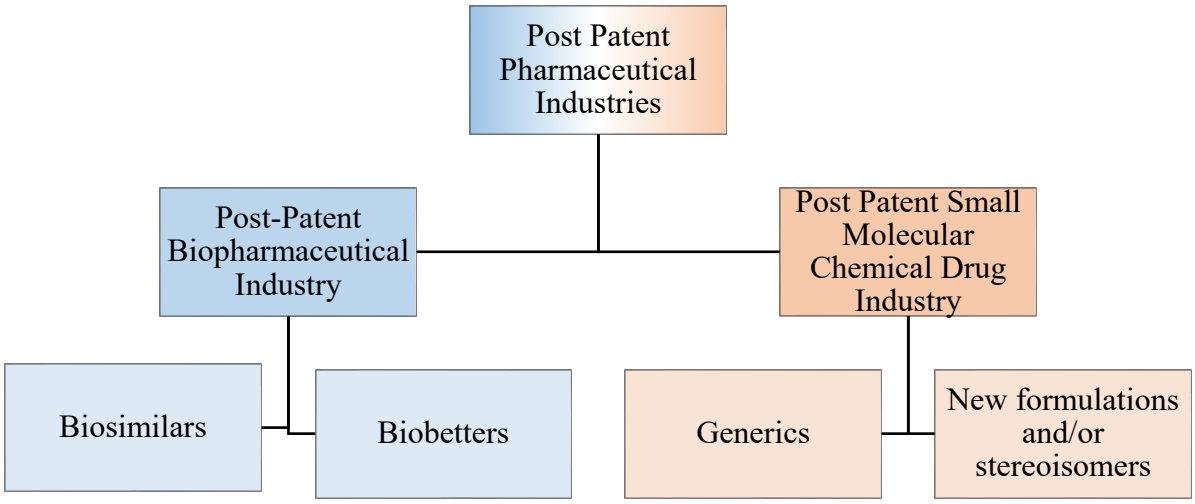


Figure 1-2: Overview of different post-patent pharmaceutical industries

1.3. Biosimilars

Biosimilars are a second (or subsequent) generation of follow-on products that imitate originator biologic drugs. As such they are often likened with generic drugs, which are second (or subsequent) generation products imitating the originator small molecule chemical drugs. Although, biosimilars and generics are comparable in many aspects (they are both follow-on products to a successful reference product) a key distinction lies in the definition. Generics drugs are required to have the same *Active Pharmaceutical Ingredient* (API) as their reference originator product and as a result the API in the generics has to possess the same chemical structure as the reference[15]. In contrast, biosimilars are similar but not necessarily chemically identical products[16]. Many regulatory authorities, including European Medicines Agency (EMA) and the FDA base biosimilar definitions on equivalence in clinical outcome rather than having the same molecular structure (refer to Table 1-1). The reasoning why biosimilars are not defined based on their structure lies in the inherent inability to have uniform APIs in products manufactured using living systems[2].

As biosimilars are produced using living cells, formulation, testing, trials and manufacturing are much more complex than traditional small molecule drugs. As a result, the commercialization process is significantly longer and more costly for biosimilars in compared to the process for generics[17].

Biosimilar Definition	
FDA	"A **biosimilar** is a biological product that is highly similar to a US-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 product in terms of the safety, purity, and potency of the product"[18]
EMA	"A **similar biological** or **'biosimilar'** medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies"[19]

Table 1-1: Comparison of biosimilar definitions by the EMA and FDA

1.3.1. Potential for Biosimilars

The biosimilar market is largely driven by the urgency to capture growing healthcare markets and the potential to provide much needed cost savings to patients[4]. In the years after global financial crisis in 2008 there has been a systemic effort by national governments in developed countries to reduce healthcare expenditure, however the emergence of expensive biologics has created significant economic pressures on national healthcare budgets[4].

The number of biosimilars entering the market will be dependent on potential market size, development cost and the barriers faced during the drug development pathway[20,21]. The numbers of biosimilar market entrants will affect competition and the price of biosimilars[22,23]. It is expected that greater competition among biosimilars will lead to decrease in price and increase in cost savings to payers [22,23]. In the case of the generics industry, price of generics has been observed to decrease with the increase in number of market entrants [20,21,24]. A report by the FDA that considered retail prices of generics and their corresponding brand name originators showed that emergence of a second generic reduces the average retail price of generics to nearly 50% of the originator brand name price [25]. The same report found that the average retail prices of generics continue to decrease as competition increases, leading to greater cost savings to the payers [25].

Initial market predictions of the biosimilar market size were in the range of US$ 24 billion in sales in 2014 and $30 billion in sales by 2020[26.] However, most of these figures have subsequently been revised by the industry and it is clear that there is a reduced momentum of product release into highly regulated markets in Europe and the U.S.[26]. Roche, one of the leading biopharmaceutical companies, in an announcement stressed the importance of constant evaluation and revision of market entry timing of competitor biosimilars targeting Roche's originator biologics. Roche initially anticipated that by year 2016, there would be competition from biosimilars to their originator biologics. Roche has since revised this position and now expects competition from biosimilars by year 2020[27]. Hence, despite the anticipated market potential for biosimilars, regulatory approval and subsequent market entry of biosimilars in the European Union (EU) and the U.S. has been slower than what was initially anticipated[28].

The countries in the EU leads the biosimilars market in terms of revenue, making up 80% of global purchases of biosimilars by 2012 [21]. Within the EU, Germany accounted for the largest percentage of biosimilar sales, with 34% of the overall European sales[21]. France accounted for the second largest percentage of sales, with 17% share of the European market[21]. The U.S. is expected to become the largest market for biosimilars in terms of revenue [29]. To date, sales of most biopharmaceuticals are markedly higher in the U.S. in comparison to the rest of the world, this is likely due to combination of higher volumes and price. Furthermore, the biologics market in the U.S. continues to show high growth rates. For example from years 2012 to 2013 the biopharmaceutical market in the U.S. grew by 18.2% from US$ 53.8 billion to US$ 63.6 billion [30].

When there is large market potential and anticipated demand, lack of market entry of a product has been attributed to the complex challenges associated with the commercialization process [24,31-33]. However, this is not the first time the post-patent pharmaceutical industry in developed pharmaceutical markets has shown slow market growth, despite the market needs. Before the enactment of Hatch-Waxman Act in 1984, the small molecular generics industry in the U.S. was facing long development timelines and high barriers to market entry [34]. The Hatch-Waxman

Act (1984) created an abbreviated, streamlined and less costly approval process by for generic drugs in the U.S, drastically reducing the development costs, so that in recent years the generic drug industry has shown some of the fastest growth rates seen in the pharmaceutical sector[35]. Previous studies have shown that first mover generics have benefitted from first mover advantage[35-37]. First mover generics have been sold at a higher price[35-37] and gained higher market share than later entrants[35-37.] Furthermore, first to market generics also benefit from brand loyalty, both from end product consumers as well as from channel managers such as hospitals and pharmacy chains[36-38]

1.4. Chapter Conclusion

From patient and public policy standpoints, biosimilars could offer significant cost savings. Biosimilars have shown slower than anticipated market entry and traction in developed pharmaceutical markets, specifically in the EU and the U.S. There are also differences in these two markets with much greater ground being gained in the EU[32]. This study investigates the duration of the regulatory approval phase for biosimilars and the trends in the duration of the regulatory process of first and subsequent generations of biosimilars. This investigation is conducted with the aim of identifying whether there is an advantage or disadvantage to first movers during the regulatory phase.

The thesis is divided into five chapters (refer to Figure 1-4). The first chapter introduces the topic (Introduction). The second chapter reviews the literature and introduces schools of thought on first mover advantage. This chapter also examines literature on the biosimilar industry and orientates the research question (Chapter 2: Literature Review). The third chapter details research methodology with the relevant contextual issues (Chapter 3: Research Methods) and data collection (Chapter 3: Research Methods). The last section of the thesis discusses the findings (Chapter 4: Findings) and the contributions (Chapter 5: Discussion) of this research. Chapter 5 also provides suggestions on directions for further research possibilities based on the findings of this thesis.

Figure 1-4: Overview of the thesis

Chapter 2, the literature review, considers the current body of literature on first mover advantage and disadvantage, and some of the unique challenges faced by the biosimilar industry.

CHAPTER 2: LITERATURE REVIEW

2.1. Introduction

The findings from this thesis will contribute to the theory of first mover advantage by analyzing the first mover biosimilar during a crucial stage of the commercialization process. Secondly, the thesis will add to the current body of first mover literature, by investigating the presence or absence of first mover advantage or disadvantage during the regulatory approval phase of a biosimilar product, prior to market entry. The advantage or disadvantage will be measured relative to subsequent generations of biosimilar, or relative to the originator product. The findings could potentially be extended to other complex pharmaceutical products. This study aims to bring clarity to the understanding of the segmentation of first mover advantage in the biopharmaceutical industry. Lastly, it will identify whether there is a first mover advantage or disadvantage for biosimilars at the regulatory stage of commercialization in the two key markets, the EU and the U.S. and discuss potential policy or regulatory interventions based on the findings.

The current chapter builds on Chapter 1, specifically exploring the concepts of:

- first mover,
- first mover advantages and disadvantages,
- defining the first mover in pharmaceutical markets,
- first mover advantages in post-patent pharmaceutical markets, and
- biosimilar commercialization challenges.

Figure 2-1 summarizes Chapter 2.

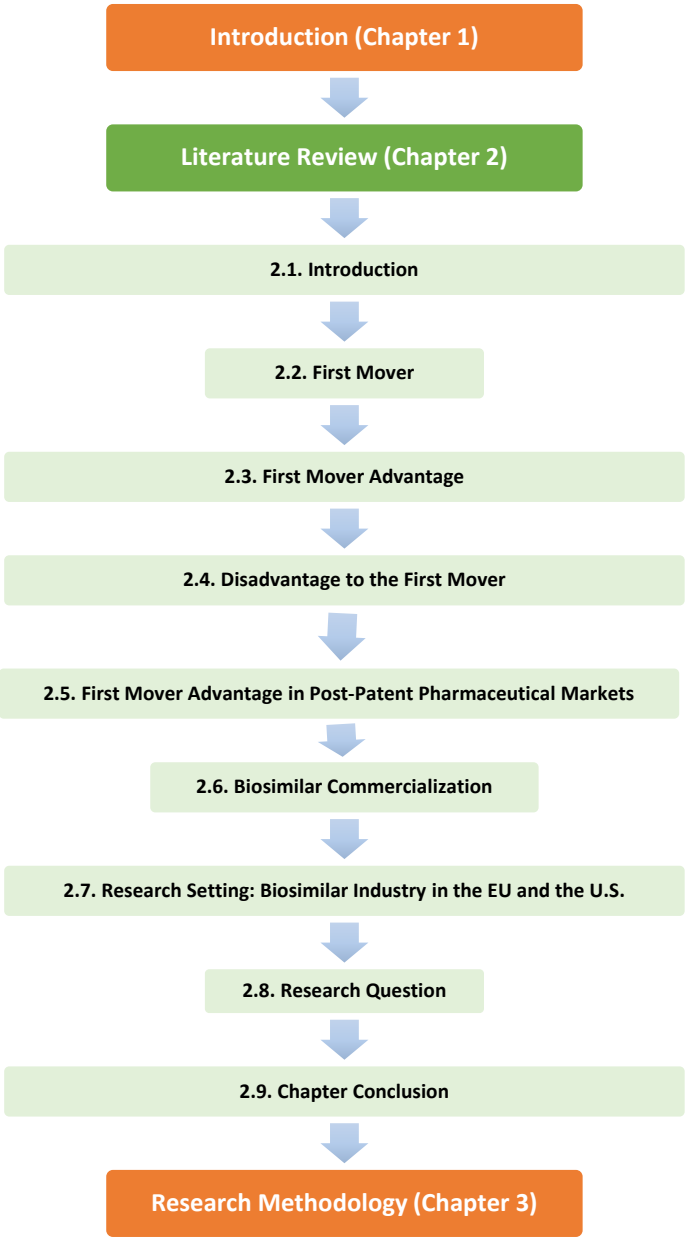


Figure 2-1: Chapter 2 summary

2.2. First Mover

The timing of market entry of a new product is one of the most important decisions a firm has to cope with[39]. Optimal timing for market entry is dependent on market dynamics, managerial decision-making, and organizational resources and capabilities[40]. Resources can be used to describe a firm's stock of intangible and tangible assets. Resources can be quantified or valued and traded when necessary[41]. Capabilities of an organization consist of a firm's ability to deploy resources utilizing organizational procedures and processes to reach a desired target, and the abilities of a company to manage its resources [41,42]. Pioneering is found to be a preferred strategy for firms who possess relatively higher skills in new product development. In contrast, firms with relative strengths

in manufacturing and marketing prefer to enter after the pioneers, once the initial technological and market uncertainties are settled[42].

One of the fundamental debates in first mover literature is related to the broad and varied definitions associated with the term “first mover”. Typically, the first mover is widely understood as the first market entrant[43, 44,45]. Many of the widely used definitions for first mover are broadly based on the order of product development or market entry (Refer to Appendix 2-1). Importance of being the first mover is linked to whether there are any advantages associated with being first. First mover related literature first developed in the late 1950s with the studies carried out by Bain in 1956 related to market entry barriers[46]. The concept of first mover advantage was further developed by multiple studies carried out in the late 1980s[42-44].

2.2.1. Defining the First Mover in the Pharmaceutical Industry

In the literature, definition of the first mover often entails the following questions. Firstly, if a firm accesses an established market, but capitalizes on some technological discontinuity or appeals to a novel demand segment, should this firm be considered as first movers? What extent of discontinuity or segment novelty is sufficient for a firm to be considered a pioneer?[42] These questions are especially important when defining a first mover in the pharmaceutical industry.

From an industry vantage point, originator pharmaceutical products would be considered as the first mover and post-patent pharmaceutical products would be considered as the late entrants. However, due to the lengthy exclusivity periods enjoyed by originators, market entry conditions and market dynamics for the originators are significantly different from the post-patent pharmaceutical products. These differences are further enhanced due to the presence of unique regulatory approval pathways for post-patent pharmaceutical markets. For example in the United States, the originator biologics are approved *via* the 351(a) pathway, whereas the biosimilar drugs are approved via 351(k) pathway (refer to Table 2-1)[47].

Type of Drug	Act	Type of Application	Approval Pathway	Requirement for clinical data
Originator Biologic	Public Health Service Act	Biologic License Application (BLA)	351 (a)	Yes
Biosimilar		351 (k) abbreviated Biologics License Application (aBLA) – created by the Patient Protection and Affordable Care Act (Year 2010)	351 (k)	Yes, requiring assessment of immunogenicity & pharmacokinetics (PK) or pharmacodynamics (PD) sufficient to demonstrate safety, purity & potency to an approved reference product
Originator small molecule chemical drug	Food, Drug and Cosmetic Act (FD&C Act)	New Drug Application (NDA)	505(b)1	Yes
Generic		Abbreviated New Drug Application (ANDA) – created by Hatch Waxman changes (Year 1984) to FD&C Act (Year 1938)	505(b)2	Yes, require safety and effectiveness data. Certain studies do not need to be carried out by the sponsor
Generic			505(j)	No, approval based on bioequivalence

Table 2-1: Summary of FDA approval pathways for branded, generic, originator biologic and biosimilar drugs

In addition, post-patent pharmaceutical markets are unique as the first movers in a new post-patent pharmaceutical market enter into a proven and established market where the reference product has enjoyed a significant time period of monopolistic market conditions particularly in developed countries. For example, a reference originator product in the U.S. enjoys an exclusivity period of 12.9 years on average because of intellectual property protection and marketing exclusivity provisions[48.] Furthermore, in post-patent pharmaceutical markets, the competing products are essentially undifferentiated to one another or to their reference originator product in terms of the target clinical outcome. Whilst the market need and acceptance for the product has already been proven by the reference originator, post-patent pharmaceutical product companies do not have much control of positioning their products as there can be no differences in safety, efficacy and quality in comparison to their predicate or competitors[35].

As such, in the literature post-patent pharmaceutical product and originator pharmaceutical product markets are differentiated, and the first mover in a post-patent pharmaceutical market is considered to be the first imitator product to enter the market after the market exclusivity expiration

of the originator[32,35,36,49]. As such the post-patent pharmaceutical industry is an interesting and unique context within which to study first mover advantages.

2.3. First Mover Advantages

Most researchers have approached first mover advantage (FMA) from either an economic-analytical viewpoint or consumer behavior based analysis[35]. The key question with respect to first mover theory is whether there are any advantages or disadvantages of being the first mover. FMA can be defined as an organization's ability to earn more economic profits than its competitors as a result of being the first to market in a novel product category[50]. FMA is considered to occur endogenously through a multi-stage process, in the early stages asymmetry is created, allowing one firm to gain an edge over other competing firms[42]. This head start may be related to the foresight of the firm's decision makers, unique resources or luck. This asymmetry created allows one of the competing firms to exploit its position. FMA can arise from a variety of reasons; the following sections will investigate sources of FMA.

2.3.1. Consumer Based Advantages

Consumer based advantage is associated with benefits that can be obtained by being the consumers' first choice when repurchasing a particular product[51]. The first mover influences how customers evaluate the characteristics in the product category and often the first mover may become the standard for that particular product category[52]. Studies have shown that when customers successfully use the pioneering brand in a new product category, they will choose it over later entrants. Consumers have been shown to develop stable preferences for pioneering products over time if they know for certain that the pioneering products meet their requirements[51,53]. Therefore, a first mover can develop a strong customer base early and as a result increase the product switching costs for late movers[53].

2.3.2. Pre-emption of Scarce Assets

Another avenue in which first mover firms may be able to gain advantage is by pre-empting rivals from acquiring scarce assets such as raw materials, space and investment [42]. Gilbert and Newbury were the first to come up with a pre-emptive model in 1982, which analyzed how firms with an early start in research and development can exploit this lead and exclude rivals[54]. Pre-emption of natural resources and raw materials by first movers is a common occurrence since the beginning of trade; an early empirical study into Canadian nickel industry looks into pioneer advantages in controlling high-grade nickel deposits in a single locality, which made it possible for the first movers in that locality to secure rights to almost the entire supply, enabling them to dominate global production for several decades[55].

First movers can prevent competition *via* strategic pre-emption of space, including geographic and product characteristic space[42]. In most markets there is only space for one or limited number of firms to be profitable. Pioneers can pick and choose the most attractive segments or niches (such as preferred geographies or product characteristics), and at the same time take strategic decisions to reduce or limit the amount of space available for later entrants. The targeting by Wal-Mart of small southern townships in United States provides an example of the deterrence competition through pre-emption of spatial assets. Competitors of Wal-Mart initially found these contiguous geographic locations unprofitable to service. However, Wal-Mart was able to maintain high profits and sustain its position for many years by combining spatial pre-emption at the retail level together with a highly effective distribution network [56].

Another method by which first mover advantage is established is by deterrence of competitors from entry *via* pre-emption of investment in plant and equipment[57]. Through continuous investment, first mover can expand and maintain higher outputs after entry and as a result, the first mover is in a position to threaten price discounts and in turn make late entrants unprofitable[58]. Pre-emption by investment in plant and equipment also bring focus onto the role and effect of economies of scale on first mover advantage. First mover advantages are often enhanced in circumstances when economies of scale are large[42].

2.3.3. Technological Leadership

Two ways, identified in literature, in which technological leadership can result in FMA are, firstly, advantages gained from experience or learning curve, where expenditure falls with aggregate product output and, secondly, success in intellectual property races [50].

2.3.4. Experience/Learning Curve based Advantages

Advantages obtained from the 'experience' or 'learning' curve, where expenditure decreases with cumulative output, is a mechanism through which pioneers can gain advantage through sustainable technological leadership[50]. In a groundbreaking study in 1981, it was shown that the learning curve could create extensive barriers to entry if the learning can be kept proprietary[59]. Further, if a pioneering firm is able to keep the learning and experience proprietary, it results in a continuous cost advantage for the firm, which will help, in turn, to maintain its leadership in market share[42]. Some examples of early empirical proof for learning based first mover advantage include a study into European synthetic fiber industry, where late entrants to the market were unsuccessful in achieving low cost or any significant market share, leading many of them to exit the market[60]. Another early example of learning based advantages was evident from a case study of the Lincoln Electric Company, which indicated that Lincoln was able to maintain high profit for decades due to early market entry with strong and superior patented products, along with a managerial system that promoted continual cost decrement during a transformative technological phase[61].

2.3.4.1. Innovations and Intellectual Property

Pioneers often gain a head start *via* sustained technological leadership. One of the ways to achieve sustained leadership and prevent potential competition, is through having a successful and strong intellectual property portfolio[62]. First movers can gain significantly, in circumstances where technological advantage is chiefly a function of research and development expenditure and if this technology can be kept proprietary by patenting and/or maintaining as trade secrets[42]. Often, first movers with an IP portfolio benefit from a temporary market monopoly, which helps them to

strengthen any FMA. This temporary market monopoly can be further lengthened with successful long-term intellectual property management. Further, strong IP can prevent and deter competition from imitators and make it difficult for late movers to be gain market share [40,63]. It is also important to note that second movers and other later market entrants can own intellectual property and use IP to protect their innovations and market position. However, in a study that utilized the Profit Impact of Market Strategies (PIMS) database, it was found that the first mover firms benefitted significantly more (29 percent) from patents than late entrants (13 percent)[64].

Patents are a type of IP that perform an important function in protecting innovations[65]. If a new product or service is largely dependent on a patent protected component or asset of the firm, this firm would likely to dominate the market[62]. The Xerox Corporation and Polaroid Corporations are examples where companies managed to be the only players in the respective photocopier and instant camera markets as a result of owning strong patents[63]. However, in some industries patents do not provide a great degree of protection and often it is relatively easy to "invent around" the patents, or patents only provide a transitory value as the technology changes at a rapid pace[42]. Patent races play an especially important part in few industries; however, pharmaceutical and biopharmaceuticals are two such industries[42,66]. In a sample study of products from pharmaceutical, electrical and chemical industries, it was found that, on average, follow on companies can imitate the patented innovations for about 65 percent of the innovators cost of development[67]. However, it was found that cost of imitation in pharmaceutical industry tends to be relatively higher in comparison to other industries investigated and this was attributed to the fact that most imitators have to go through an extensive regulatory approval process similar to the innovator[67]. This is even with national regulators often allowing for expedited or shortened regulatory approval process for imitator pharmaceutical products.

Nevertheless, patenting is only one method of IP protection and accounts for only a fraction of the advantages enjoyed by first movers and innovations. Research and development need not be confined only to the product, process or hardware. Firms can also innovate and improve in managerial systems and organizational processes, which can be proprietary as well[68]. Innovations

in organizational processes and managerial systems have been shown to be a more durable form of first mover advantage[69]. Many firms such as Campbell Soup, American Tobacco, Procter and Gamble still maintain dominant positions in their respective industries as their managerial innovations allowed them to exploit economies of scale in distribution and manufacturing, starting from the late nineteenth century[40,70].

2.4. Disadvantages to the First Mover and Late Mover Advantage

Not all first movers are successful and sometimes being a late mover in an industry can be advantageous. Microsoft, for example has a history of being successful by being a late mover[71]. So, why is it that sometimes companies are better off to enter the market late?

2.4.1. Free Rider Effects

In the case of Microsoft, one of the company's biggest breaks came when Bill Gates managed to sell an operating system for IBM's personal computers. However, Microsoft was not the first to create a desktop operating system neither did they develop the operating system that was sold to IBM[71.] This example illustrates one of the main disadvantages associated with being a pioneer, known in literature as the "free rider effect".

The free rider effect can be defined as a circumstance where an organization or an individual is able to profit from the work of another without contributing to the expenses associated with such actions[53]. Late entrants have the potential to "free ride" on pioneering firms' investment and progress in number of areas such as research & development, infrastructure development and buyer education[42]. For most products and in most industries cost of imitation is often lower than cost of innovation and often, a late entrant can acquire the same technology as the first mover, but at a lower cost[42,72]. Late movers can further free ride on training and development of human capital carried out by pioneers and gain access to more productive labor force in comparison to the first mover[73]. The ability and extent to which late entrants can free ride decrease the durability and

magnitude of the pioneers' ability to maximize profits. As such, the greater the ease of obtaining free rider effects, the lower the incentive for firms to invest to become a market pioneer[40].

2.4.2. Inter-firm Diffusion of Technology from the First Mover

Inter-firm diffusion of technology results in a decrease in first mover advantage [74]. Diffusion of technology can occur via variety of ways, some of the common mechanisms include research publication, work force mobility, reverse engineering, informal communication and plant tours[42]. Study of a sample of companies in ten industries found that the competitors usually gain detailed information of both processes and product technology within a year of development[75]. In addition, further findings show that product technology leaks faster than process technology[75]. Organizational innovations such as innovations in management systems, often have slow inter-firm diffusion rates compared to process or product innovations[69].

2.4.3. Resolution of Market Uncertainties by the First Mover

First movers have to take on the risk of dealing with market uncertainties such as whether the customers will like the product, or the pricing is accurate. Late entrants may gain by positioning at the "ideal point" in that specific market space, if the first mover had not done so in the first place. Such situations often arise when knowledge of such an "ideal point" comes into light only after the product is widely introduced to the market and when the costs of repositioning is too high for the pioneers[52.] In most new markets, uncertainties are resolved by the appearance of a dominant product and after appearance of such a product, competition will often move to price[42]. As the market matures, inability of the first mover to successfully adapt to changes in competition, demand and environment may hinder it from maintaining their dominant market position[76]. In addition, if the market pioneers are not able to adapt successfully as the market evolves, it may lead to pioneer burnout and they may not have long term success[77].

Being the first mover in a new market is risky and expensive but at the same time potentially very profitable and rewarding. On the other hand, because of the risks and challenges associated

with the pioneering, it can sometimes be advantageous to be a late entrant to a market. If first movers have advantages in costs, information, intellectual property, product line breadth, product quality and long-term market, they are likely to profit from first entry. However, if late entrants have the opportunity to overtake first movers with positioning, branding, and superior technology, firms could gain more by entering after the pioneers.

Section 2.3. and 2.4. of this Chapter looked into first mover advantages and disadvantages recognized in literature and examples from other products and areas of the market. The next section of this chapter looks at how these can be applied to pharmaceutical industry, specifically to post-patent pharmaceutical products such as biosimilars.

2.5. First Mover Advantage in Post-Patent Pharmaceutical Industries

Previously, first mover advantage in post-patent generics market is quantified by looking at market share, pricing and uptake of products based on their time of entry. Evidence of first mover advantage in generic drug market has been observed by the studies carried out by Caves et al (1991), Grabowski and Vernon (1992), Hollis (2002), Yu and Gupta (2014) and Ali et al (2015) and the following sections looks into key findings from these studies [35-37,78].

2.5.1. Pricing and Market Share

Pricing and market share are two widely used indices to analyze first mover advantage, and this applies to the generic market as well. Pricing and market share is not only important in the analysis of first mover advantage but is also a significant determinant in ensuring market competition, since if the generic companies can gain market share without significant price reductions, then there is little incentive for these companies to discount the drug prices[36].

A distinct feature observed in pharmaceutical markets is that even after loss of patent protection and market exclusivity, originators continue to maintain their prices and further, some of the originator drugs even increased their prices by a small percentage, with the entry of first to market generics[35]. Originators rely on their brand positioning to allow for this surge in prices. This increase

in prices is a strategy by originator companies to compensate for the loss in market share that they experience with the entrance of generics into the market[49]. However, previous studies have also identified that originators have eventually drop their prices as the number of generics and competition increases[37,79]. This provides a window of an opportunity for the first generic to enter the market at higher price than the late entrants and maintain a higher selling price before the later generics enters the markets. Given that on average the marginal cost of a small molecule generic drug is only around 5% of the retail price of an originator, higher selling price will certainly increase the profitability for the first mover generics[80]. Hence, this allows the first to market generic firms to ride on the success of the originator and enjoy a first mover advantage in terms of pricing and profitability. A FDA study shows that on average, the first to market generic enters the market at a 6% discount to the originator price and price reduction of 20% is achieved when there are 8 or more generics in the market [81].

Another aspect to consider when looking at price variations is the market share obtained by the first to market generics in comparison to subsequent generic market entrants. A sample study of the generics market in the U.S. in 2014 indicated that the first to market generics and the originators each have equal percentage of the available market share by around the 36th month after generic entry into the market[35]. Furthermore, this study also found that on average the originator and first to market generics each have 30% of market share by the 36th month after generic entry, subsequent second and third generic entrants lagged behind in market share with 12% and 8% respectively[35].

2.5.2. Retail Setting vs. Hospital Setting

Prior first mover literature looking at generics has found that the pioneer advantage differs greatly between the retail and hospital markets[35-37]. First to market generics experience significantly higher share of the market in the retail setting in comparison to the hospital setting. An empirical study data shows that first to market generics enjoyed on average an 80 percent higher market share than the second to market generics and 225 percent higher market share in comparison to the third to market generics[35].

Within the retail space the choice of generics is largely dependent on which of the generic drugs the pharmacies carry and the willingness of the patients to accept the generic version proposed by the pharmacist. Several studies have found that pharmacists choose to continue selling the first to market generic drug[36,37]. This preference is attributed to pharmacists finding it difficult to explain the bio-equivalence of generics to the patients, as some patients find it uncomfortable to switch from one brand to another[35]. Furthermore, although generic drugs are essentially equal products in terms of safety, clinical efficacy and outcome, the differences in shape, size, color and other such branding and packaging between different generic products of the same molecule may also influence patients' preferences and overtime patients would develop preferences due to familiarity[35]. Retail pharmacies have shown preference to products that provide regular delivery on schedule and positive refund policies for redundant inventory[82]. If the first to market generic meets these expectations of the retailer, there is no incentive or necessity for them to switch to a late entrant generic.

In contrast, in a hospital in-patient environment, patients often receive multiple examinations and treatments and prescription drugs are usually not the most expensive component and as a result, patients are less likely to aware of which generic drugs are being given as part of their treatment. Furthermore, most hospital based systems bill the insurance companies a fixed fee based on the patients' illness[36]. Hence, it is expected that hospitals to be much more interested in reducing costs and thus more sensitive to price discounts offered by generics[35]. Furthermore, hospital pharmacies usually obtain their stocks via drug wholesalers, who in turn liaise with the manufacturers for special pricing structures. As such hospitals have less influence in determining the choice of generic product as well as negotiating the prices. These factors have shown to weaken any FMA of first mover generics in the hospital space in comparison to the retail space [35]..

In a study carried out in Netherlands, Norway, Portugal and Slovakia comparing list prices versus actual hospital prices of 12 medicines in 25 hospitals, it was found that the discounts and rebates granted for medicines decreases when there are no therapeutic alternatives (generics) available[83]. This study also demonstrated that hospitals have limited ability to negotiate prices in the

absence of therapeutic alternatives such as generics[83]. Whilst, this study did not explore the extent of discounts or rebates when there are more than 1 generic in the market, it was found that high rebates and discounts tend to present for pharmaceutical products which are likely to continue in primary care once a patient is discharged[83]. This strategy by pharmaceutical companies to provide high rebates for hospitals for products that are continued during primary care, likely sourced directly by patients in retail settings, can be to ensure patients' preference for a particular brand of product early on. As studies have shown that patients develop preferences due to familiarity[35].

As such the difference between retail and hospital market segments can be related to FMA that occurs in retail space may be related to consumer behavior, as well as the degree to which consumer preferences are taken into consideration by retail pharmacy chains. As explained by customer-based pioneer advantages (refer to section 2.3.1), consumers may continue to purchase the product that they are familiar with, thus providing the first to market generic a substantial advantage in the retail space.

It should be noted that in the U.S., the approach to pharmaceutical pricing differs to most industrialized countries, in that it leaves pricing to the market to a much greater extent. In comparison, in other industrialized countries such as Germany, Australia and Canada public health insurance system will determine a maximum allowable price for both originator and post-patent pharmaceutical products[84-86]. Additionally, these countries also use a range of price control mechanisms such as reference-based pricing, in which all therapeutically equivalent products with a drug class would be reimbursed only at the same base price.

2.5.3. Summary – FMA in Post-Patent Pharmaceutical Markets

In summary, FMA for generics post-commercialization in terms of pricing and market share is well established. Furthermore, literature indicates that FMA for generics sold in a retail setting is much greater than in a hospital setting. With limited biosimilar products in the market current, there

is a dearth of literature on first mover advantages focusing on the post-patent biopharmaceutical industry. However, prior experience in other post-patent pharmaceutical markets especially that of the generics provides insight into what might be expected for the biosimilar industry. By simply extrapolating the experience from generics market, it would be predicted that the first to market biosimilar would be likely to gain a degree of FMA in terms of pricing and market share. Yet, it is important to consider that the commercialization processes for biosimilars bear distinct characteristics to that of the generics [24,31-33].

2.6. Biosimilar Commercialization

Initial predictions expected biosimilar industry to have a worth of US$10–25 billion by year 2020[2]. However, biosimilar market entry and acceptance has been slower than what was initially anticipated[28]. Development of biosimilars continues to require extensive resources [24,31-33]. This has led to higher development costs and longer development times for biosimilars in comparison to the other post-patent pharmaceutical product – small molecular generics[87]. The average cost of development of biosimilars is in the range of US$ 100 million with a development time of three to five years[20]. This length of time and cost of development is mainly due to the processes required to align with the regulatory requirements and more extensive clinical data required for biosimilars to gain regulatory approval[20,21]. Unlike the originator biologics industry, emerging pharmaceutical markets in Asia, Eastern Europe and South America are at the forefront of research, development and the bringing of biosimilars to the market[88]. Although, a significant number of companies is working on biosimilars, the number of available reference candidates are limited. This has led to multiple companies developing biosimilars for the same reference product.

2.6.1. Biosimilar Commercialization Challenges

Biosimilars are large, complex molecules and their pharmaceutical functions and resulting clinical outcomes are dependent on the 3-dimensional shape[2]. Due to their structural complexity and molecular weight, biosimilars encounter developmental and commercialization challenges, in particular with analytical characterization and process development (refer to Figure 2-2). As a result,

for biosimilars, unlike generics, the non-clinical analytical results cannot be used as strong evidence to obtain the status of similarity to their comparator originators. Hence, unlike generics, biosimilars must be subjected to more extensive clinical studies to prove their similarity and obtain regulatory approval[17]. The need for extensive clinical trials results in a longer duration and a higher cost of development[17]. The process development of biosimilars is considered to be more technically challenging than generating an originator biologic as biosimilars have to meet constrict comparability requirements[89,90]. While progress in DNA recombinant technology and manufacturing know-how has refined the selection methods for cell lines, reduced bottlenecks in downstream processes, increased production output and reduced the costs of biopharmaceutical production, access to these technologies and the requisite technical knowledge is still limited to a few companies[4,91-93].

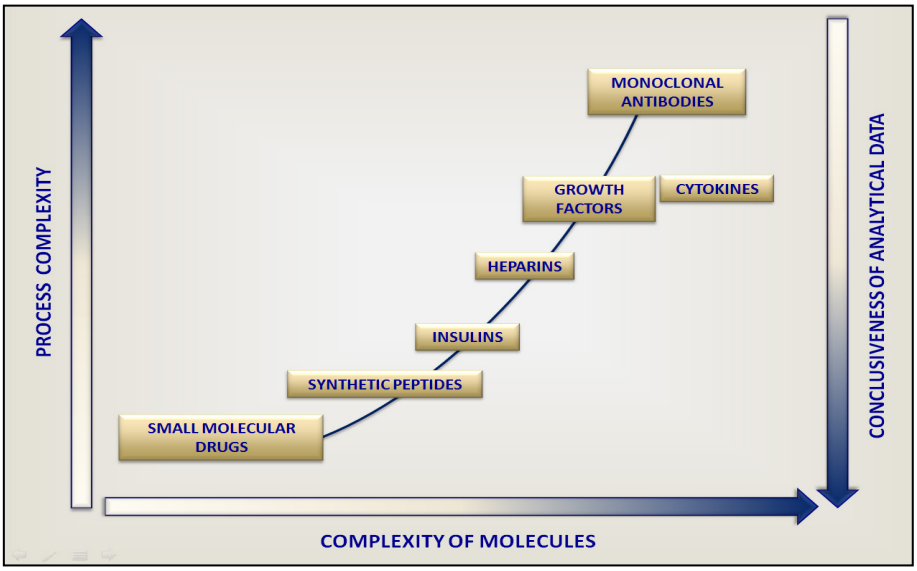


Figure 2-2: How the complexity of different pharmaceutical molecules affects process complexity and conclusiveness of analytical data[28]

In addition to the technical complications associated with complex molecules, evolving regulatory processes, intellectual property issues, legal challenges initiated by originator biopharmaceutical to delay or prevent market entry, resistance from physicians and potential product pricing, and reimbursement issues have further hampered biosimilar development and commercialization process and increased the risk of investment in biosimilars[11,26,28,33,94]. This is clearly reflected by the differences in the cost and time involved in developing a biosimilar in

comparison to a generic drug. On average, development of a biosimilar costs is in the range of US$ 100 million whereas development of a generic costs US$ 3-5 million[17]. The development period of biosimilars is in the range of 3 to 5 years, in comparison a small molecule generic usually takes 2 to 3 years to develop[17]. In the following sections, some of the key challenges faced by biosimilar developers in bringing these products to the market, are discussed in detail.

2.6.1.1. Challenges Faced by Biosimilars due to Molecular Complexities

As biologics, biosimilars are significantly larger and have much more complex molecular structures than small molecular chemical drugs. These complex molecular structures are highly sensitive to changes in manufacturing processes. A small change in production process techniques can result in a structural change that may affect the safety and efficacy of the biosimilar [22]. Biosimilar manufacturers do not have access to complete formulation and manufacturing process information of originator product. As a result, often biosimilar developers have to design and reverse engineer their own processes during the manufacturing[95].

2.6.1.2. Evolving Regulatory Process and Complexities Associated with Managing Different Regulatory Pathways

Another challenge faced by the biosimilar developers is to navigate the uncertainties arising from the evolving regulatory frameworks. Both the FDA and the EMA has established number of biosimilar guidelines in the past few years including molecule specific approvals, manufacturing processes and controls, pre-clinical and clinical testing, and naming[28]. Yet, there are still number of biosimilar guidelines yet to be finalized and inconsistencies between the EMA and the FDA regulatory frameworks continue. Definitions and language used in guidance documents and regulations are examples of such differences between EMA and the FDA regulatory framework for biosimilars[28]. Industry experts have expressed concerns that such variations in terminology used by the EMA and FDA can lead to complications when determining discrepancies related to potential safety problems [22].

2.6.1.3. Challenges with Reference Product Selection

Biosimilar guidelines that determine the selection of originator product that would be the reference biologic is a vital aspect within the current biosimilar regulatory approval process. A reference product is an approved originator biologic drug that is currently authorized to be marketed. Both the FDA and EMA require that the same reference biologic to be used throughout the entire developmental cycle for a particular biosimilar[22]. Both the EMA and the FDA may also permit the use of a reference biologic with foreign regulatory approval for providing in-vivo pre-clinical and clinical data to demonstrate biosimiliarity[96,97]. However, in such scenarios biosimilar developers are required to submit clinical and non-clinical data to scientifically substantiate and validate the biosimilarity of the foreign reference product to a U.S. or EU licensed product. In addition, the EMA requests that such foreign reference biologics are approved by a country that is a member of the International Conference on Harmonization (ICH)[98]. EMA states that this is to ensure the regulatory approval process for the foreign reference biologic is similar to the scientific standards of the EMA[98]. Furthermore, the FDA has suggested that, at present, it is improbable that biosimilars relying on clinical data compared to a foreign reference originator would be sufficient for the FDA to decide on interchangeability status of a biosimilar to a biologic approved by the FDA[96]. These provisions result in a complicated reference product selection process for biosimilars, which adds to development time and cost.

2.6.1.4. Non-Clinical and Pre-Clinical Testing and Data Requirements

The most obvious distinction between the EMA and the FDA with regards to non-clinical and pre-clinical testing requirements is in how the guidance documents have been established. The EMA has published guidance documents for the various product classes such as growth hormones, somatropins, and insulin[22]. The FDA does not have such individual guidance documents based on various product classes. Instead, the FDA applies general guidelines as applicable to each individual biosimilar application[22]. The FDA holds number of in-depth development meetings with the biosimilar developers to facilitate this process[99].

Both the EMA and the FDA require substantial in-vitro data comparing biosimilar to the reference originator[100]. The EMA has expressed that in comparison to in-vivo animal studies, in-vitro assays are often more sensitive and specific to establish comparability between biosimilar and the reference originator. As such, EMA does not necessitate in-vivo pre-clinical data and animal studies, and maintains a risk-based approach to determining the need for such testing[101]. In contrast, the FDA requires data from in-vivo and animal studies as part of the biosimilar application, unless otherwise the FDA decides these studies are not necessary[89]. Both the EMA and the FDA do not require developmental, carcinogenicity and non-clinical safety pharmacology toxicity studies if there is sufficient evidence from structural and functional characterization indicating similarity to the reference originator[22].Hence, biosimilar developers are tasked with identifying the appropriate amount of pre-clinical and non-clinical data that is required the different regulatory approval pathways.

2.6.1.5. Clinical Studies Requirements

Similar to pre-clinical data requirements, the key difference between the EMA and the FDA in regard to clinical data guidelines for biosimilars is how the guidance documents are structured and utilized[22]. The EMA uses guidance documents developed for different product classes of biosimilars whereas the FDA uses a general guidance document[22]. The EMA and the FDA emphasis the requirements for clinical data for biosimilars in both pre-regulatory approval and post-market surveillance conditions. Both the EMA and the FDA have the same opinion that unlike with generics, non-clinical data of biosimilars is insufficient to predict the immunogenicity, hence requiring clinical data to predict the immunogenicity of biosimilars[102]. Both regulatory frameworks require comparative human pharmacodynamics (PD), pharmacokinetics (PK), immunogenicity evaluation via clinical studies, and in some cases comparative data. Therefore, whilst the EMA and the FDA have both indicated possibility for smaller clinical development programs for biosimilars with clinical trials with reduced study size, biosimilars still require extensive clinical data [28,89].

2.6.1.6. Issues with Interchangeability

Interchangeability designations enables substitution to an interchangeable (often post-patent) product by the pharmacy without the intervention of the prescriber/physician[87]. In the U.S., small molecular generics receive interchangeability status with FDA approval. In contrast, biosimilars need further clinical data to gain interchangeability status. Biosimilars are yet to receive the interchangeability status in the U.S. The EU does not have harmonized guidelines on biosimilar interchangeability, instead the interchangeability status is determined by the regulatory frame-work in each member country[103].Due to the need for additional clinical data, biosimilars even with regulatory approval and cost benefits to the payer, cannot be interchanged without the interchangeability status. This adds number of commercialization challenges to biosimilars such as selection of reference product, need for clinical studies, navigating state specific regulatory frameworks, and prescriber and patient education.

2.6.1.7. Manufacturing Challenges

Manufacturing of biosimilars and biologics in general, requires specialized processes such as cell culture and purification, which are often proprietary to the originator companies[4]. Even minor differences can alter the 3-dimensional structure, which can, in turn, lead to adverse consequences for patient health[104]. Often, biosimilar developers have to comprehensively characterize multiple batches of the reference biologic, then plan and actualize a production process that manufactures a similar biologic, usually without the detailed know-how of the production process used for manufacturing the originator biologic[105].

The complex production process and nature of biologics makes identical replication of the originator drug virtually unachievable as a result can lead to many manufacturing challenges for biosimilars that are not present during generic drug manufacturing. Primary amino acid sequence of a biosimilar protein drug is identical to that of the reference product. However, post-translational modifications such as phosphorylation, deamidation or glycosylation often affect the product that can lead to changes in impurity, safety and efficacy profiles in comparison to reference product[16]. In

addition, the utilization of novel expression techniques may introduce new risks like atypical glycosylation patterns, changed impurity profiles and host cell proteins[106].

A proposed formulation for a biosimilar drug has to be tested to ensure that it meets the necessary regulatory guidelines with respect to stability, potency and compatibility with diluents, excipients and packaging materials[107]. Further, potential impact on efficacy and safety must be clearly justified if a chosen formulation, closure system, container or material in contact with biosimilar during the production process varies from that of the reference product. Thus, quality and purity of all biosimilars must be monitored continuously and carefully during the entire manufacturing process to ensure biological activity, immunogenicity and safety profiles are what is expected. Minor differences to existing production lines can result in extensive delays. Because of these challenges only a limited number of companies have the necessary capital funding required to attain such manufacturing expertise, knowledge and current Good Manufacturing Practice (cGMP) facilities necessary to manufacture[108].

2.6.1.8. Intellectual Property Challenges

As detailed in Section 2.6.1.2., the regulatory structure for the biosimilars continues to evolve. Similarly, the legal framework for biosimilar industry is being established. As such there is still room for varying interpretations of regulatory and legal requirements by the different stakeholders resulting in uncertainty [87]. The “patent dance” procedure in the U.S. for new biosimilars, provides an excellent example to demonstrate the complications arising for such varying interpretations.

With regards to potential IP infringements related to biosimilar developments, the BPCIA provisions that once aBLA has been submitted to the FDA by a biosimilar sponsor, the sponsors for the reference originator and the biosimilar must exchange information with respect to patents that are regarded to be potentially infringed. The sponsors must recognize which of these patents the originator would be prepared to license to the biosimilar sponsor. This process of information disclosure and negotiation around the originator patents is commonly known as the “patent dance”, has already led to debate and litigation with in the biopharmaceutical industry[28]. Sandoz, the first

biosimilar sponsor to obtain FDA approval for its biosimilar Zarxio, was sued by the originator sponsor Amgen in relation to provisions around the patent dance [109]. Amgen alleged that by refusing to disclose the aBLA and manufacturing information related to Zarxio to Amgen, Sandoz did not follow the rules set by the BPCIA in regard to information disclosure by the biosimilar sponsor [109]. The District Court's decision was in favour of Sandoz, that the BPCIA does not require Sandoz to disclose information related to Zarxio's aBLA as well as manufacturing information to the originator company. Amgen appealed this decision, the U.S. Federal Court decided to partly uphold the decision by the District Court, stating that a biosimilar developer is not absolutely required to engage in the "patent dance" [28,109,110]. Furthermore, biosimilar applications to the FDA require assurance by the biosimilar company that there are no intellectual property infringements of relevant patents of the reference originator biologic. As such it is important for biosimilar applicants to consider that if it was decided not to share their applications, they are potentially risking an immediate declaratory judgement action by the originator to claim patent infringements.

Similar patent disputes can be seen in Europe as well. Celltrion's Remicade biosimilar for infliximab was the first biosimilar monoclonal antibody approved in Europe in September 2013 for reference originator Remsima (refer to Figure 2-3). However, the reference originator company Janssen Biotech received a paediatric extension for Remsima until 24th February 2015 in twelve of the leading European markets[111]. As a result of this extension, the effective patent life for Remicade was extended for all approved indications, both paediatric and adult. This delayed the market entry of Celltrion's Remicade until 2015[111].

In addition, originator biopharmaceuticals usually have number of subsidiary patents or double patenting to ensure extensive intellectual property protection. An example of such subsidiary patents is patents protecting manufacturing process[28]. An example of allegations of "double patenting" by a biosimilar company was seen in the US court case Celltrion Healthcare Co. Ltd. et al. vs Janssen Biotech, Inc., case number 1:14-cv-11613-MLW, requesting a declaratory judgement that Janssen's prevailing patents were unenforceable and invalid[28,112]. According to Celltrion, Janssen's previous owner, Centacor Biotech, had applied for patents, all of which protected the

same invention of cA2 and its applications, “or obvious variations of that purported invention” [113]. Thus, in this case, Celltrion alleged that Janssen “double patented” and purposely delayed the entry of Remsima™ [113]. There is a very strong tradition in the pharmaceutical market of 'evergreening' strategies to extend patent protection and these subsidiary and double patents often are a part of such strategies. Biosimilar companies have to spend resources to understand the scope and the strength of the intellectual property related to the reference originator as well as estimate the best time for to file regulatory applications and market entry[20]. Patent disputes have become increasingly common for biosimilar products, further increasing the cost and time taken for product commercialization [20,87,114].

2.6.2. Summary - Biosimilar Commercialization Challenges in the U.S. and the EU

The review of literature on the biosimilar industry in the U.S. and EU has shown that biosimilar commercialization is fraught with challenges. Whilst, some of these challenges are common to both originator biologics and biosimilars, other challenges are unique to biosimilars. For the originator biopharmaceutical and generic first mover applicants, market exclusivity provisions in regulatory frameworks have allowed them to create a market monopoly to ensure that they can recoup their initial investment and incentivizes the risks associates being first. Examples of such regulatory provisions include a 12-year period of market exclusivity for originator biopharmaceuticals in the U.S.[115], an 8-year period of data-exclusivity in Europe for originator biopharmaceuticals followed by a 2-year market-exclusivity period[116], provided they meet certain requirements according to the EU guidelines[117]. In comparison for biosimilars, these developmental challenges will potentially reduce the extent of price savings provided by biosimilars. Since biosimilars do not provide any additional therapeutic benefits over the reference biologic, price of biosimilars is expected to be a key incentive to switch from the known reference originator biologic to the biosimilar product[17]. Hence developmental challenges that reduce the ability of biosimilar products to provide sufficient price discounts can affect the degree of market uptake and commercial success of these products[17].

The next section discusses the primary research question of the thesis, formulated based on the literature review.

2.7. Research Setting: Biosimilar Industry in the EU and the U.S.

The thesis aims to answer the research question in relation to biosimilar products commercialized in the EU and the U.S. Biosimilars are biopharmaceutical drugs designed to have the same clinical outcome as previously licensed reference originator biologics (refer to Table 1-1 for U.S. FDA and EMA definitions of biosimilars). This focus stems from the realization that literature applicable to understanding FMA within the biosimilar industry is still in its nascent stages and biosimilars are facing a complex commercialization environment filled with special challenges[31,32,118,119]. Some of these challenges include complications arising due to the complex nature of the molecules (detailed in section 2.6.1.1.), the evolving nature of the regulatory framework (detailed in section 2.6.1.2.), the need to manage different regulatory pathways in different jurisdictions (detailed in section 2.6.1.2.), difficulties associated with reference product selection (detailed in section 2.6.1.3.), the need to resolve complex challenges in manufacturing such as maintenance of batch-to-batch consistency (detailed in section 2.6.1.4.), the navigation of complex pre-clinical and clinical development (detailed in section 2.6.1.5. and section 2.6.1.6.) and intellectual property challenges (detailed in section 2.6.1.8.). Furthermore, post-commercialization challenges exist with respect to naming, labeling and interchangeability of biosimilars[28]. It is thus imperative that not only the biosimilar commercialization process become better understood, but also that potential policy interventions be identified to stimulate the growth of this industry. The literature review also revealed that although originator and post-patent pharmaceutical products share the same product characteristics, the originator and post-patent pharmaceutical regulatory approval pathways differ considerably. Moreover, the steps preceding market entry, and the changes in the market size and product pricing could be reasonably expected to be different for originators and post-patent pharmaceuticals.

To provide background to this research, the following subsections present a brief overview of the regulatory approval process for biosimilars in the U.S. and the EU as well as the roles of the

two different regulatory bodies, the FDA and the EMA. Both the EMA and the FDA will only approve a biosimilar once the market exclusivity periods allocated to the reference originator *via* regulatory provisions have been expired. New product approval process for the biosimilar industry is a highly regulated process. Any new biosimilar product must go through a stringent and government mandated clinical development program prior to gaining regulatory approval for market launch. In the EU, the EMA is the appointed government body responsible for granting approval for new biosimilar products for market entry. In the U.S., the FDA is the government body responsible for assessing whether a biosimilar product meets the necessary requirements to obtain regulatory approval.

Any firm that is intending to sell biosimilars in the EU or the U.S. must comply with the EMA or FDA regulations, which includes clinical development and comprehensive regulatory approval process. Furthermore, as leading regulatory agencies for pharmaceutical products, regulatory frameworks developed by these two agencies are often mirrored by other regulatory bodies across the world.

The EU was the first of the locations to develop a regulatory framework specific for biosimilars. The EU directive 2003/63/EC published on the 25th of June 2003, created a regulatory approval pathway for biosimilars and the first biosimilar was approved in the EU in 2006. According to this legislation, biosimilar products applying for regulatory approval in the EU can refer and use the originators' clinical data. Whilst the regulatory approval process is harmonized across all the EU countries, the interchangeability status of approved biosimilars is dependent on the legislation and regulatory framework of individual member states[32].

In the United States, biosimilar legislation for biosimilars is governed by the Biologics Price Competition and Innovation Act of 2009 (BPCIA). Formally established under Title VII of the Patient Protection and Affordable Care Act in March 2010[16], the BPCIA creates an abbreviated and dedicated approval pathway known as the 351(k) pathway[120] in the U.S. for biopharmaceuticals that are highly similar to, or potentially interchangeable with, a FDA approved reference, originator

biologic. Figure 2-3 depicts the history of biosimilar guidelines in the U.S. by the FDA and the EU by the EMA.

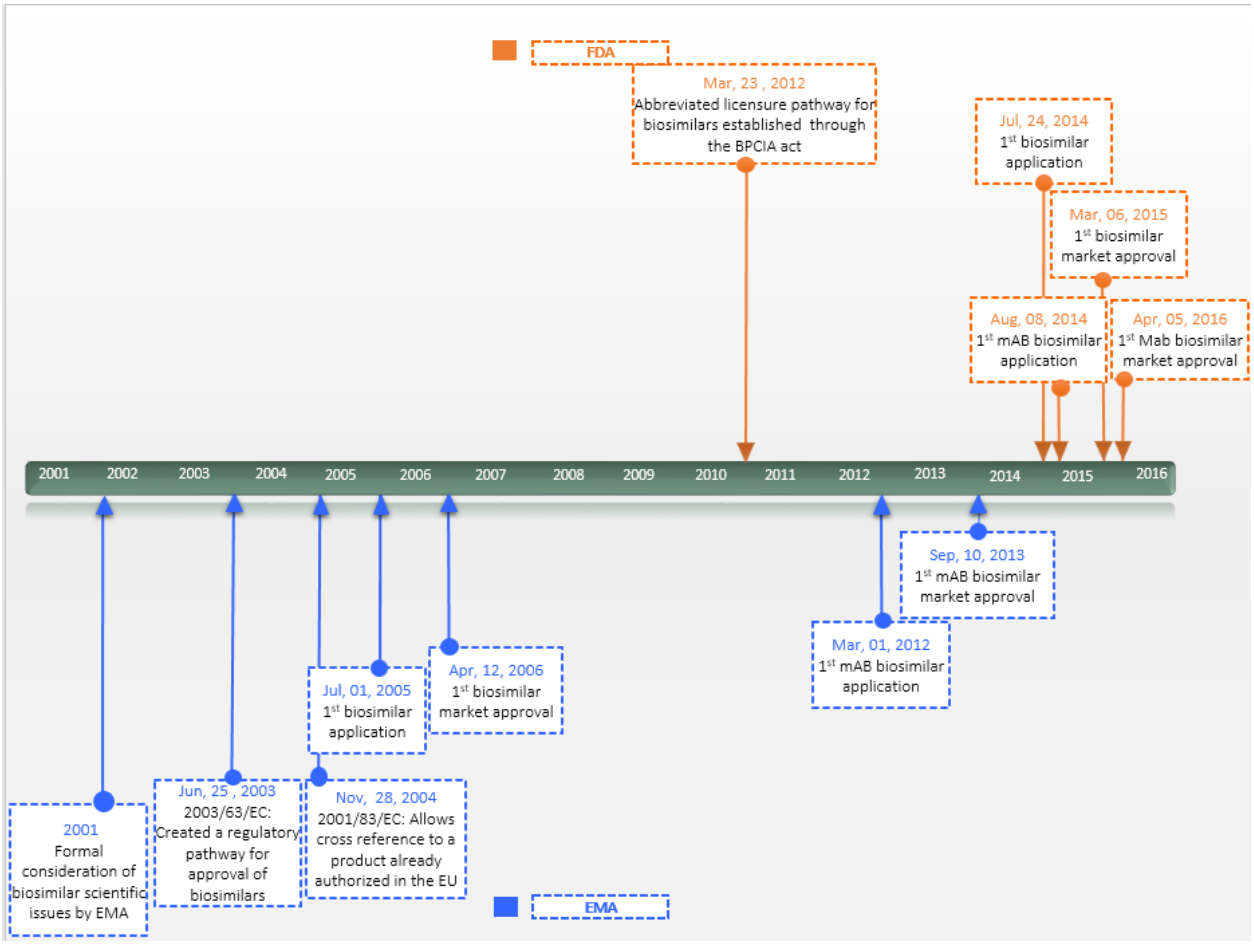


Figure 2-3: Comparison between the U.S. and EU biosimilar regulatory milestones[28]

The two timelines represent the history of establishing biosimilar guidelines by the FDA (orange arrows and boxes) and the EMA (blue arrows and boxes) and key biosimilar regulatory milestones in the U.S. and the EU.

The 351(k) pathway (in the U.S.A.) permits companies developing biosimilars to use and extrapolate clinical data from originator biologics to show clinical safety and efficacy. Furthermore, the BPCIA provides that the first biosimilar to obtain interchangeability status with its reference product is eligible for a 12-month market exclusivity period[115]. This exclusivity period is designed to recover the substantial research and development expenditure that the first mover biosimilar developers incur during biopharmaceutical development and to encourage further innovation and investment into drug development. The provisions provided by the BPCIA are summarized in table 2-2.

Key Elements	BPCIA
Abbreviated approval pathway for follow-on imitators	Yes, via 351(k) pathway for biosimilars
Ability to use originators' clinical data	Yes – extrapolation of reference drug's clinical data
Interchangeability	Yes – requires demonstration that the biosimilar can be expected to produce same clinical result as the reference product
Exclusivity period for biosimilar products	Yes – 1-year period of market exclusivity for the first biosimilar to obtain interchangeability status with its reference product.
Market exclusivity for originators	Yes, 4-year period of data exclusivity upon FDA approval. During this time a 351(k) application for a biosimilar cannot be submitted to the FDA 12-year market exclusivity to originator biologic upon FDA approval. FDA can accept a biosimilar 351(k) application during this time, however FDA approval can only be granted after this market exclusivity period has elapsed. Market exclusivity and data exclusivity periods run concurrently. Exclusivity is independent of any available patent protection.

Table 2-2: Summary of incentives provided the BPCIA Act (2009)

A new biosimilar product will gain regulatory approval based on clinical data showing sufficient similarity to the reference originator biologic. Clinical development is carried out in phases of I, II and III. Phase I, II and III clinical trials are a series of experiments aimed at testing the safety, toxicity and efficacy of a new medicinal product in a sample population of humans prior to regulatory approval and subsequent wider usage by public. Phase I clinical trials are conducted in small number of human subjects, often 20-30 healthy volunteers to aimed at testing the pharmacologic and metabolic effects of the product being tested. Phase II clinical trials develop on phase I trials, increasing number of participants up to about 200. Often phase II clinical trials are conducted on patients with the treated condition, aimed at evaluating the effectiveness of the product being tested against its target as well as understanding any side effects and risks. Phase III clinical trials expand on phase I and II trials, to further evaluate the safety, risks and side effects of the product being evaluated. Phase III trials can enroll large number of patients up to several thousands. Clinical

development is often long and costly. Clinical trial data and performance has a definite impact on the regulatory approval.

The biosimilar commercialization process can be broadly categorized into a few sequential processes namely (1) research and development, (2) pre-clinical development (3) clinical development (4) regulatory approval and, culminating in (5) market launch. Information about the first two stages is often not disclosed by most organizations to the public domain. As such it is difficult to analyze and measure the performance of products in these two stages. Phases 3 to 5 account for the bulk of time and expenditure spent on commercializing biosimilars[33,114,121]. Furthermore, clinical development and regulatory approval are considered the riskiest phases in the commercialization process of new pharmaceutical products, with only about 10 percent success rate[122,123]. This thesis will focus on phase 4 – regulatory approval phase of the commercialization process. Furthermore, given that one of the research objectives is to identify potential policy and regulatory interventions that can accelerate the growth of the biosimilar industry, this thesis concentrates on phase 4 of the commercialization process.

2.8. Research Question

Often, the first biosimilar entrant of a product category would go through a challenging development process whilst accounting for the uncertainties in the regulatory approval process. If, during the commercialization process of biosimilars the first biosimilar to apply for regulatory approval process is likely to lose its FMA due to time delays, then the incentive for a company to invest and go through the risky development process is reduced. As such for the biosimilar market to show an increased number of market entrants, it is vital that the first biosimilar to apply for regulatory approval retains its time advantage till market entry to reap the benefits of being the first to market.

With lack of patent protection and regulatory provisions for exclusivity periods, biosimilars at present rely on market performance to recoup their investment. Hence, if the FMA is lost, because of delays during the regulatory process, it will weaken the incentives for a biosimilar developer to

overcome the market entry barriers and navigate the challenging development process. This can result in a lack of competition in the biosimilar market, as it will reduce the number of products aiming for market entry. Lack of competition will reduce the anticipated systemic cost savings that biosimilars can potentially provide to payers. Within this context, the research question of this thesis is to find out whether first mover biosimilars have an advantage during the regulatory approval phase in the EU and the U.S. and how this may have an impact on market entry. The answers to the research question will lead to a discussion into potential policy and regulatory interventions that may be necessary to assist the biosimilar industry.

2.9. Chapter Conclusion

First mover has been defined in several different ways in the literature (refer to the table). Most of these definitions are based on either being the first organization (or individual) to invent the product or the first organization to introduce a new product and/or new market or a combination of these. Being the first mover in a new market is risky and expensive but at the same time potentially profitable and rewarding[53]. If first movers have advantages in costs, information, intellectual property, product line breadth, product quality and long-term market share, companies may profit from first entry [53,64]. However, if late entrants can overtake first movers with positioning, branding, and/or superior technology firms could gain more by entering after the pioneers[40].

In literature, FMA is often measured and analyzed after market entry in terms of market uptake, positioning and price structures. However, pharmaceutical products go through a unique commercialization process where the market entry of products is often dependent on the clinical development and regulatory approval process. Whilst, FMA in biosimilar industry is not yet analyzed in the literature, previous studies into the generics industry show that post-patent pharmaceutical markets can enjoy FMA.

However, due to their complex molecular nature biosimilars face a heightened degree of technical, manufacturing, and analytical challenges in comparison to generics. Other than the implications of the molecular complexity of biosimilars for both production processes and regulatory

compliance, biosimilar developers also face a multitude of other commercialization challenges such as labeling, naming and interchangeability, which are unique to them. Due to these challenges, biosimilar developers face number of market unique market entry barriers and have to navigate a complex commercialization process to bring a product to the market. For first mover biosimilars applicants, with lack of patent protection and market exclusivity, the length of the regulatory approval process will be a critical determinant of (1) the timing of market entry, (2) whether they enter the market prior to later applicants, and (3) the length of time they are present in the market as the only available therapeutic alternative to an originator if they enter the market first. The findings of this research can hence promote a discussion into potential policy and regulatory interventions that may be necessary to promote market entry. The next chapter, Chapter 3, develops a research methodology to test whether there is first mover advantage during the regulatory approval phase for biosimilars commercialized in EU and the U.S.

CHAPTER 3: RESEARCH METHODS

3.1. Introduction

The present chapter describes the research methods that will be used to answer the research question presented in the previous chapter, namely: "is a first mover advantage observed during the regulatory approval phase for biosimilars commercialized in EU and the U.S.?" This chapter focuses on the decision-making processes, conceptual basis of the investigation and the methods of analysis utilized to answer the research question of the thesis. A quantitative approach was utilized to analyze data on biosimilars commercialized in the EU and the U.S.

3.2. Research Design

Figure 3-1 below provides schematic image of how the research question for this study is designed. The following section will discuss the various aspects of the research design.

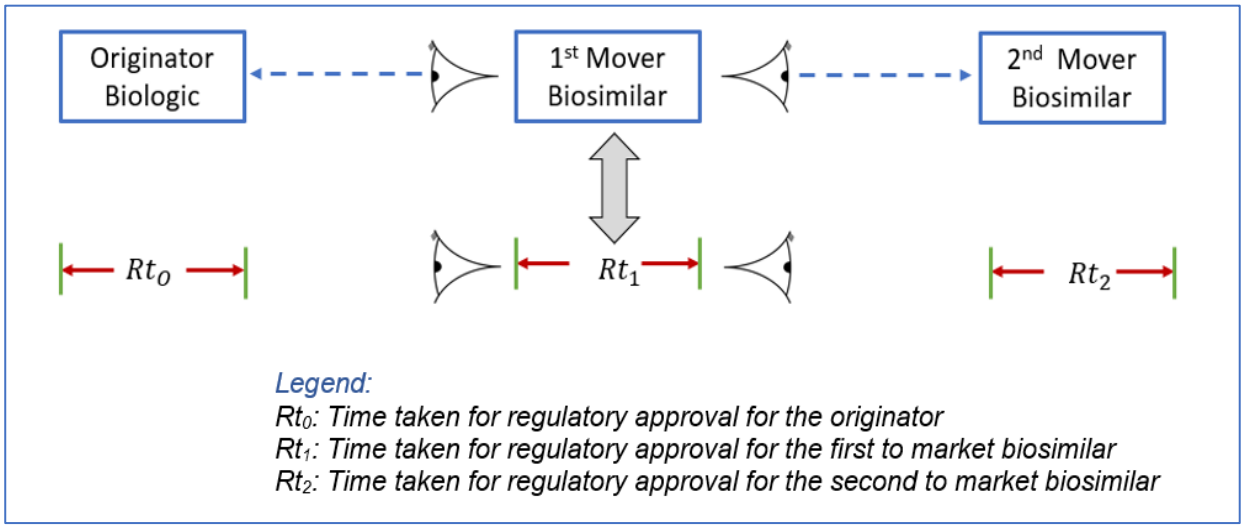


Figure 3-1: Overview of the research question

3.2.1. Theory

This research commenced by reviewing the current literature on the biosimilar industry as well as on first mover advantage (presented in Chapter 2). The primary reason for looking at the biosimilar industry is to gain an understanding of the current state and the issues currently identified by scholars. The main goal for looking at the first mover literature was to trace its evolution as well as to build a theoretical framework for the current research. The literature review revealed that (i)

the biosimilar industry is facing unique challenges in comparison to other pharmaceutical and post-patent pharmaceutical market, (ii) lack of a conceptual and theoretical framework to understand the first mover advantage in the post-patent pharmaceutical industry, (iii) lack of understanding of how the presence or absence of first mover advantage is affecting the biosimilar industry and (iv) the possible public policy interventions and changes. These considerations guided the research process, the design of the research question (refer to Chapter 2 section 2.9) and the research objectives (refer to section 3.1). Hence, the literature review acted as a starting point for the current research, aided with the formulation of a research methodology and suggested what data needed to be collected and analyzed.

3.2.2. Level of Analysis

The main level of analysis for the present study is micro level (refer to Figure 3-2 and Figure 3-3 below).

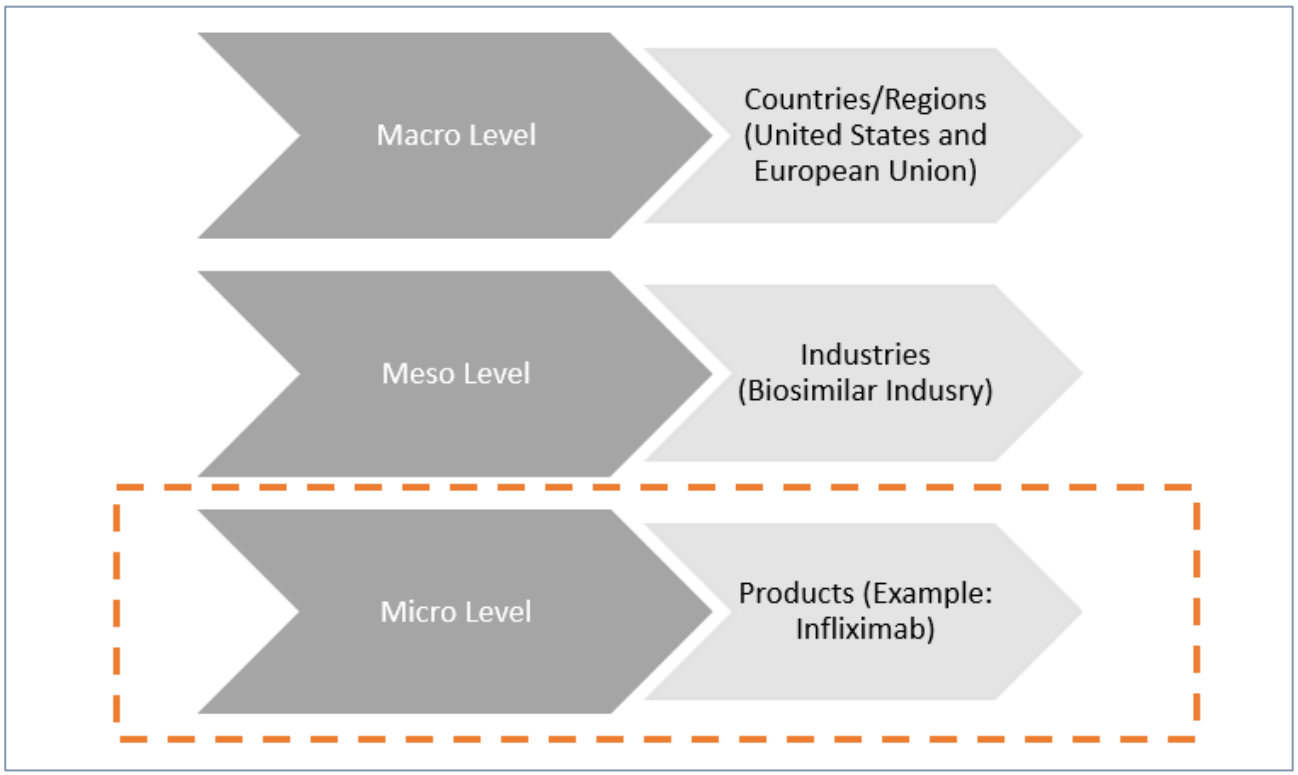


Figure 3-2: Overview of different levels of analysis

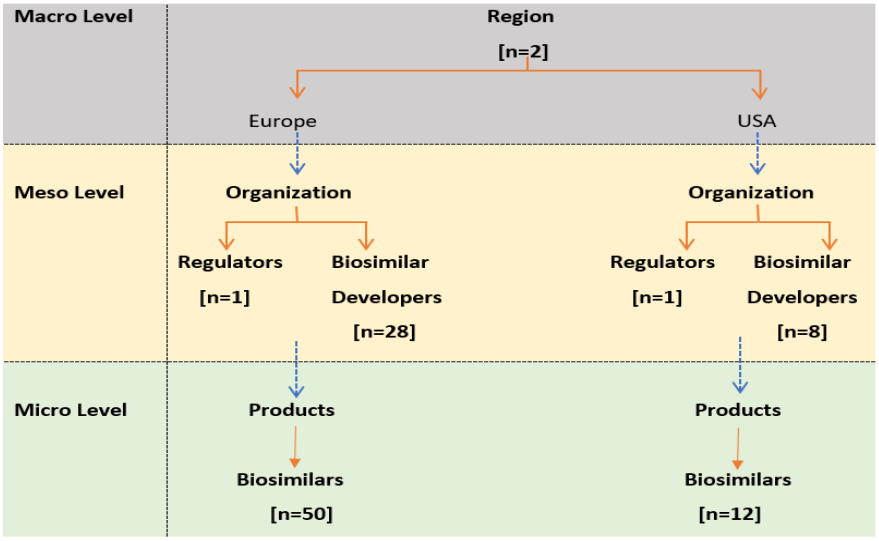


Figure 3-3: Number of variants at each level of analysis for the present study

3.2.3. Types of Data

The current study is an observational study since data is collected without manipulation to the study environment. In general, there are two types of observational studies, longitudinal and cross sectional. Longitudinal studies collect data through time, whereas a cross sectional study will look data at a single point of time. A longitudinal study can distinguish and identify changes over time, which cross sectional studies cannot.

For the current study, the data is required to be longitudinal. This is because the research question requires analysis of date related to biosimilars that are introduced at different times. The data will be sourced from biosimilar products that have received regulatory approval in the EU or in the U.S., on or before 31st July 2018. This is to ensure that the all the steps with in the regulatory approval phase for biosimilars are being captured. The primary benefit of a longitudinal study is its ability to measure and to study change[124]. Another advantage of longitudinal studies is the ability to identify the degree of variation in the dependent variable across time for one product[124].

For a longitudinal study, data can be collected via two main methods; historical data (batch data) or real-time data. Given that this study is only focused at looking products that have been

commercialized, this thesis looks only at collecting historical longitudinal data. Longitudinal historic data offers the ability to interpret dynamic account of past events[125].

3.2.4. Sources of Data

To answer the present research question secondary sources of data were chosen considering (i) secondary data related to the study is available freely in the public domain, (ii) the need for the current study to analyze the entire population of data as the number of products available for analysis is a relatively small number, (iii) primary data sources will most likely restrict the access to entire population of data and (iv) secondary data obtained from recognized reliable sources are likely to eliminate any biases and personal opinions. Reanalysis of data have often resulted in unexpected discoveries and secondary data is widely used to come up with new relevant conclusions.

Secondary data has multiple advantages over primary data sources for the current study. One of the advantages of secondary data that it is less time consuming to collect than primary data[126]. In comparison, secondary sources often allow greater accessibility which is likely to result in a more efficient and less expensive data collection process and allows for data collection on larger samples and entire populations[126,127]. In addition, since secondary data has been collated for motives other than to answer a study specific questions, it would eliminate and avoid any biases[128].

When selecting the secondary sources of data, attention was given to (i) identification and location of data sources that are applicable to answer the current research question, (ii) ability to retrieve the applicable data and (iii) how well the data meets the quality needs of the current study. The main sources of secondary data used for quantitative data collection were publicly available information from the regulatory bodies such as the FDA and the EMA, and from press releases from companies that have developed biosimilars.

The FDA is a federal agency under the United States Department of Health and Human Services, responsible for “protecting and promoting public health”[129]. This is achieved by supervision, regulation and control of a range of products including biopharmaceuticals, pharmaceutical products,

medicines, vaccines and dietary supplements[129]. Among other laws, FDA is responsible for the enforcement of the Federal Food, Drug and Cosmetic (FD&C) Act enacted in 1938[130], Section 361 of the Public Health Services Act enacted in 1944[47] and the Biologics Price Completion and Innovation Act (BPCIA) enacted in 2009[115]. The FDA consist of several Centers responsible for regulating different classes of products. Center for Drug Evaluation and Research (CDER) is responsible for assessing and granting regulatory approval for biosimilars[129].

The EMA is an EU agency responsible for the evaluation and approval of medicinal products. EMA is setup via directive Regulation EC No. 726/2004[131]. Prior to 2004, EMA was known as the European Agency for Evaluation of Medicinal Products (EMEA). The EMA (then known as EMEA) was established in 1995, funded by the EU, the pharmaceutical industry and with the support from the EU member states as indirect subsidies[132]. This agency was set up as an attempt to harmonize the regulatory activities carried out by the individual regulatory bodies of EU member states[132]. The main objectives of setting up this centralized agency were to increase competition by eliminating the protectionist susceptibility of member states to approve novel medicinal products that might compete with medicines produced by domestic companies and reduce the time and expenditure spent by pharmaceutical companies to obtain separate approvals from each member state[133]. The centralized processing of applications allowed pharmaceutical companies to submit one application to gain marketing authorization in countries recognized as part of the EU and the EEA[131]. New biosimilar applications are assessed by the Committee for Medicinal Products for Human Use (CHMP). If the CHMP finds that the safety, efficacy and quality of medicinal product sufficiently meets the requirements, it provides a positive opinion[133]. This opinion is then sent to the European Commission to be considered and translated a marketing authorization enabling the product to be marketed in the EU[133].

3.2.5. Sampling Process

For the locations selected for this study (the U.S. and the EU), the data on the entire population of biosimilars that have undergone the regulatory approval process until 31st July 2018 have been analyzed. The first biosimilar application was submitted to the EMA on 01st July 2005 and

the first biosimilar approval by the EMA took place on 12th April 2006 (refer to Figure 2-3 in Chapter 2). In comparison in the U.S, the 1st biosimilar application was submitted to the FDA on 24th July 2014 and the 1st biosimilar approval by the FDA was on 06th March 2015 (refer to Figure 2-3 in Chapter 2). This study included all biosimilar approvals by the EMA from 01st July 2005 to 31st July 2018 and all biosimilar approvals by the FDA from 06th March 2015 to 31st July 2018. Thus, the findings are representative of the entire population. Studies of entire populations minimize selection bias[134].

3.2.6. Ethics Approval and Considerations

This study has received ethics approval from The University of Queensland Science, Low & Negligible Risk Ethics Sub-Committee on the 02nd of August 2017 (Approval Number 2017001050).

This study only utilized de-identified, product related secondary data that is publicly available at free of charge. There were no enrolments of participants to this study. Hence, the researcher's main responsibility was to ensure that the data collection, collation, observation and analysis were honest, trustworthy and had no conflict of interest in terms of financial or any personal gain. This research complies with these guidelines and the researcher made sure that the data was collected from valid sources, reliability of the data was ensured and where necessary citations were carried out.

3.2.7. Limitations of the Research Design

Numerous studies have examined limitations of using secondary sources of data. These include questions regarding missing information, quality of data, and lack of information on confounding variables[134]. However, given the constraints of time and hurdles that can be faced in gaining access to primary data, secondary sources of data provided a more viable option for conducting a comprehensive population study. Furthermore, to ensure that the quality of data is maintained in the quantitative analysis, the study has obtained data only from reliable third-party organizations such as regulatory bodies. Another possible criticism of the current research design is

in relation to the limited number of data points. Whilst, this aspect is beyond the control of the researcher given the emerging nature of the biosimilar industry, it means that there is a low number of biosimilars that have completed the regulatory approval phase. Hence, a whole population quantitative study has been designed to provide a more comprehensive analysis.

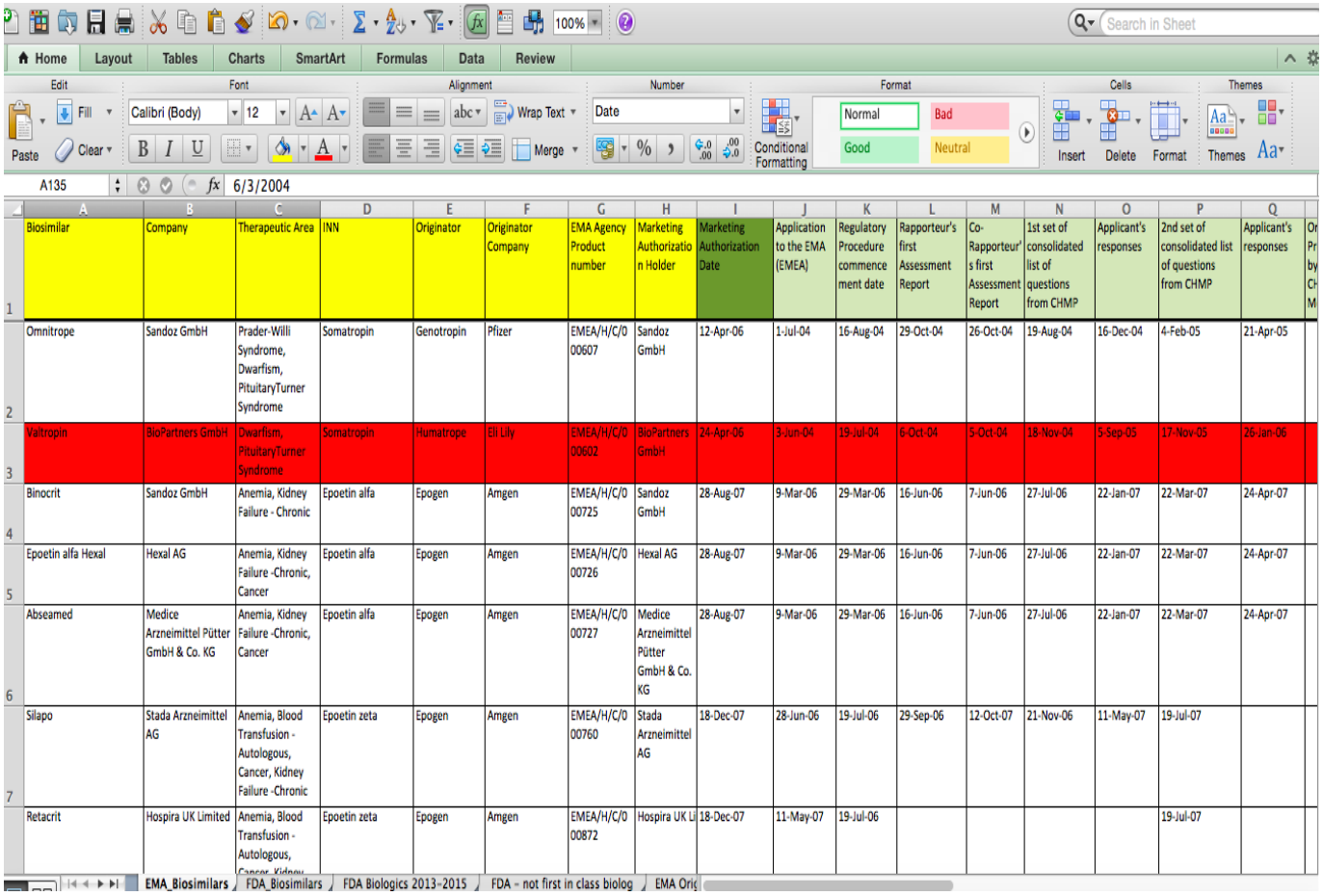
3.3. Data Collection and Data Analysis

3.3.1. Data Collection

Data collection commenced by identifying the biosimilars approvals by the EMA and the FDA. Press releases and periodic reports by the EMA and the FDA were searched and analyzed to accumulate a list of biosimilar approvals by each regulatory body. This was an ongoing process from the point the research commenced in March 2015 until the end of the research period in 31st July 2018. Since the study was designed as a population study it was vital to capture all biosimilars approved (refer to Appendix 3-1 for summary of websites used to collect this information). The list of biosimilars approved was the basis for the rest of data collection. The second step was to cross check the collated list of approved biosimilars with industry and journal publications such as the lists of Biosimilars approved in Europe[135] and Biosimilars approved in the US[136] maintained by the Generics and Biosimilar Initiative. The final step in the data collection process for this study was to collect data relevant to the regulatory approval process for each biosimilar. Relevant data such as the application date, the approval date, International Nonproprietary Name (INN), names of the biosimilars and biosimilar developers were collected (refer to Appendix 3-1 for summary of the data points collected as part of this study). A single coder extracted all of the required data using standardized data collection forms (refer to Figure 3-4 below).

Reliability and validity of the data collected, and information presented are an important consideration in research. Since secondary data was used for this thesis, traditional methods of reliability testing such as test-retest method were not applicable, however, the FDA and the EMA have procedures in place to ensure that the records present are accurate. However, further internal validation was carried out to ensure that the data collected was correct. Examples of such measures include (1) cross validating the data collected from the FDA and EMA databases with the regulatory

dossiers submitted to the EMA or the FDA by the biosimilar sponsor companies as well as EMA and FDA product detail pages; (2) cross checking the regulatory approval information presented on EMA and FDA product detail pages with press releases of the regulatory agencies and of the respective biosimilar companies; and (3) validating biosimilar approvals by collating information from industry journals as well as checking the records with FDA and EMA.



Biosimilar	Company	Therapeutic Area	INN	Originator	Originator Company	EMA Agency Product number	Marketing Authorization Holder	Marketing Authorization Date	Application to the EMA (EMEA)	Regulatory Procedure commencement date	Rapporteur's first Assessment Report	Co-Rapporteur's first Assessment Report	1st set of consolidated list of questions from CHMP	Applicant's responses	2nd set of consolidated list of questions from CHMP	Applicant's responses
Omnitrope	Sandoz GmbH	Prader-Willi Syndrome, Dwarfism, PituitaryTurner Syndrome	Somatropin	Genotropin	Pfizer	EMEA/H/C/000607	Sandoz GmbH	12-Apr-06	1-Jul-04	16-Aug-04	29-Oct-04	26-Oct-04	19-Aug-04	16-Dec-04	4-Feb-05	21-Apr-05
Valtropin	BioPartners GmbH	Dwarfism, PituitaryTurner Syndrome	Somatropin	Humatrope	Eli Lily	EMEA/H/C/000602	BioPartners GmbH	24-Apr-06	3-Jun-04	19-Jul-04	6-Oct-04	5-Oct-04	18-Nov-04	5-Sep-05	17-Nov-05	26-Jan-06
Binocrit	Sandoz GmbH	Anemia, Kidney Failure - Chronic	Epoetin alfa	Epogen	Amgen	EMEA/H/C/000725	Sandoz GmbH	28-Aug-07	9-Mar-06	29-Mar-06	16-Jun-06	7-Jun-06	27-Jul-06	22-Jan-07	22-Mar-07	24-Apr-07
Epoetin alfa Hexal	Hexal AG	Anemia, Kidney Failure -Chronic, Cancer	Epoetin alfa	Epogen	Amgen	EMEA/H/C/000726	Hexal AG	28-Aug-07	9-Mar-06	29-Mar-06	16-Jun-06	7-Jun-06	27-Jul-06	22-Jan-07	22-Mar-07	24-Apr-07
Abseamed	Medice Arzneimittel Pütter GmbH & Co. KG	Anemia, Kidney Failure -Chronic, Cancer	Epoetin alfa	Epogen	Amgen	EMEA/H/C/000727	Medice Arzneimittel Pütter GmbH & Co. KG	28-Aug-07	9-Mar-06	29-Mar-06	16-Jun-06	7-Jun-06	27-Jul-06	22-Jan-07	22-Mar-07	24-Apr-07
Silapo	Stada Arzneimittel AG	Anemia, Blood Transfusion - Autologous, Cancer, Kidney Failure -Chronic	Epoetin zeta	Epogen	Amgen	EMEA/H/C/000760	Stada Arzneimittel AG	18-Dec-07	28-Jun-06	19-Jul-06	29-Sep-06	12-Oct-07	21-Nov-06	11-May-07	19-Jul-07	
Retacrit	Hospira UK Limited	Anemia, Blood Transfusion - Autologous,	Epoetin zeta	Epogen	Amgen	EMEA/H/C/000872	Hospira UK Li	18-Dec-07	11-May-07	19-Jul-06					19-Jul-07	

Figure 3-4: Excerpt of regulatory approval data downloaded from EMA website and collated in Microsoft Excel

3.3.2. Data Analysis Methodology

The data analysis was commenced by cataloguing and organizing the collected secondary data files. The data collected were tabulated into forms (refer to figure 3-4 for an example). After which, further analysis was conducted.

To answer the research question, measures, as well as statistical analysis of the duration of regulatory approval phase were carried out. The measurement of historical variations in duration of

the regulatory approval phase required an application date and an approval date. The EMA records the application date as the “Application to the EMA or EMEA (EMA is previously known as EMEA – European Agency for the Evaluation of Medicinal Products) and the approval date as the “Marketing Authorization Date”. In a similar way, the FDA records the application date of a biosimilar as the “Application to the FDA” and the approval date simply as "Approval Date”. Statistical Analysis was then conducted to identify trends in the duration of regulatory approval phase.

3.3.3. Data Presentation

The eventual databases were both complex and voluminous. As such, the researcher investigated ways and tried different methods to collate data into a more manageable format. Such attempts resulted in the formulation of tables and graphical representations dividing the data into subsets which allowed for further statistical analysis and build-up of case studies.

3.4. Chapter Conclusion

This chapter presented the research methods considered to be best suited for examination of the research question proposed in this thesis. Given the early stage of development of the biosimilar industry and limited literature on first mover advantage on post-patent pharmaceutical markets, a quantitative strategy investigating the trends in the regulatory approval phase for biosimilars, was selected. The quantitative design is a longitudinal population study utilizing historical data from secondary sources, which allowed the measurement and monitoring of changes over time. The next chapter, Chapter 4 presents and discusses the results of the quantitative analysis.

CHAPTER 4: FINDINGS

4.1. Introduction

By investigating trends in the duration of the regulatory approval phase for biosimilar drugs in the European Union and the United States of America, this research was directed to answering the question posed in Chapter 2 (refer to Chapter 2 section 2.9.). The previous chapter also detailed that a longitudinal, population study of biosimilars that have received regulatory approval till 31st July 2018 was conducted to answer the research question. The current chapter describes the findings based on the data analysis.

4.2. Biosimilar Regulatory Approvals in the European Union

For this study the date on which the EMA receives the Marketing Authorization Application is considered as the date on which the regulatory approval process commences. Once a biosimilar has received marketing authorization, it is considered to have obtained regulatory approval within the countries in the EU and EEA. Hence, for the current study, the date of marketing authorization by the European Commission is considered as the regulatory approval date for biosimilars in Europe.

4.2.1. Number of biosimilars that have received regulatory approval in the European Union

A dedicated regulatory approval pathway for biosimilars was established through the EU directive 2003/63/EC in June 2003 (refer to Figure 2-3 in Chapter 2, Section 2.7.) From June 2003 to July 2018, 50 biosimilars have received regulatory approval from the EMA (refer to Table 4-1).

Three biosimilars have been withdrawn from the market at the request of the marketing authorization holder after receiving marketing authorization (refer to the Status column in Table 4-1). The reasons for these withdrawals were stated as “commercial” by the marketing authorization holder[137]. These three biosimilars are Valtropin, Filgrastim ratiopharm and Biograstim. Marketing authorization for Valtropin were withdrawn voluntarily in October 2011 and the withdrawn was formalized in 10th May 2012[137,138]. European Union withdrew the marketing authorization for Filgrastim ratiopharm on 20th April 2011 and for Biograstim on 15th September 2018[139,140]. The

withdrawal notifications by the EMA for Valtropin and Filgrastim ratiopharm further states that these two products were never marketed in the EMA[138,140]. These three biosimilars are not removed from the data set used to answer the research question since they underwent the regulatory approval process as with other biosimilars and were only withdrawn later for commercial reasons.

Biosimilar	INN	Reference Originator	Originator Company	EMA Agency Product number for the Biosimilar	Marketing Authorization Holder of the Biosimilar	Biosimilar Application Date to the EMA	Biosimilar Marketing Authorization Date	Status
Valtropin**	Somatropin	Humatrope	Eli Lily	EMEA/H/C/000602	BioPartners GmbH	3-Jun-04	24-Apr-06	Withdrawn
Omnitrope	Somatropin	Genotropin	Pfizer	EMEA/H/C/000607	Sandoz GmbH	1-Jul-04	12-Apr-06	Authorized
Binocrit	Epoetin alfa	Epogen	Amgen	EMEA/H/C/000725	Sandoz GmbH	9-Mar-06	28-Aug-07	Authorized
Epoetin alfa Hexal	Epoetin alfa	Epogen	Amgen	EMEA/H/C/000726	Hexal AG	9-Mar-06	28-Aug-07	Authorized
Abseamed	Epoetin alfa	Epogen	Amgen	EMEA/H/C/000727	Medice Arzneimittel Pütter GmbH & Co. KG	9-Mar-06	28-Aug-07	Authorized
Silapo	Epoetin zeta	Epogen	Amgen	EMEA/H/C/000760	Stada Arzneimittel AG	28-Jun-06	18-Dec-07	Authorized
Filgrastim ratiopharm **	Filgrastim	Neupogen	Amgen	EMEA/H/C/000824	Ratiopharm GmbH	29-Jan-07	15-Sep-08	Withdrawn
Ratiograstim	Filgrastim	Neupogen	Amgen	EMEA/H/C/000825	Ratiopharm GmbH	29-Jan-07	15-Sep-08	Authorized
Tevagrastim	Filgrastim	Neupogen	Amgen	EMEA/H/C/000827	Teva GmbH	29-Jan-07	15-Sep-08	Authorized
Biograstim **	Filgrastim	Neupogen	Amgen	EMEA/H/C/000826	AbZ-Pharma GmbH	29-Jan-07	15-Sep-08	Withdrawn
Retacrit	Epoetin zeta	Epogen	Amgen	EMEA/H/C/000872	Hospira UK Limited	11-May-07	18-Dec-07	Authorized
Filgrastim Hexal	Filgrastim	Neupogen	Amgen	EMEA/H/C/000918	Hexal AG	6-Sep-07	6-Feb-09	Authorized
Zarzio	Filgrastim	Neupogen	Amgen	EMEA/H/C/000917	Sandoz GmbH	6-Sep-07	6-Feb-09	Authorized
Nivestim	Filgrastim	Neupogen	Amgen	EMEA/H/C/001142	Hospira UK Limited	27-Feb-09	8-Jun-10	Authorized
Ovaleap	Follitropin alfa	Gonal-f	Merck	EMEA/H/C/002608	Teva Pharma B.V.	28-Feb-12	27-Sep-13	Authorized
Remsima	Infliximab	Remicade	Janssen Biologics B.V., NL	EMEA/H/C/002576	Celltrion Healthcare Hungary Kft.	1-Mar-12	10-Sep-13	Authorized
Grastofil	Filgrastim	Neupogen	Amgen	EMEA/H/C/002150	Apotex Europe BV	30-Apr-12	18-Oct-13	Authorized
Inflectra	Infliximab	Remicade	Janssen Biologics B.V., NL	EMEA/H/C/002778	Hospira UK Limited	26-Jun-12	10-Sep-13	Authorized
Bemfola	Follitropin - alfa	Gonal-f	Merck	EMEA/H/C/002615	Finox Biotech AG	30-Oct-12	27-Mar-14	Authorized
Abasaglar (previously Absaria)	Insulin glargine	Lantus	Sanofi-Aventis Deutschland GmbH	EMEA/H/C/002835	Eli Lilly Regional Operations GmbH	3-Jun-13	9-Sep-14	Authorized

Biosimilar	INN	Reference Originator	Originator Company	EMA Agency Product number for the Biosimilar	Marketing Authorization Holder of the Biosimilar	Biosimilar Application Date to the EMA	Biosimilar Marketing Authorization Date	Status
Accofil	Filgrastim	Neupogen	Amgen	EMEA/H/C/3956	Accord Healthcare Ltd	24-Mar-14	18-Sep-14	Authorized
Benepali	Etarnacept	Enbrel	Pfizer Limited	EMEA/H/C/004007	Samsung Bioepis UK Limited (SBUK)	3-Dec-14	14-Jan-16	Authorized
Thorinane	Enoxaparin sodium	Clexane	Sanofi Aventis	EMEA/H/C/003795	Pharmathen S.A.	6-Feb-15	15-Sep-16	Authorized
Flixabi	Infliximab	Remicade	Janssen Biologics B.V., NL	EMEA/H/C/004020	Samsung Bioepis UK Limited	3-Mar-15	26-May-16	Authorized
Inhixa	Enoxaparin sodium	Clexane	Sanofi Aventis	EMEA/H/C/004264	Techdow Europe AB	27-May-15	15-Sep-16	Authorized
Truxima	Rituximab	MabThera	Roche Registration Limited	EMEA/H/C/004112/0000	Celltrion Healthcare Hungary Kft.	9-Oct-15	17-Feb-17	Authorized
Erelzi	Etarnacept	Enbrel	Pfizer Limited	EMEA/H/C/004192/0000	Sandoz GmbH	11-Nov-15	27-Jun-17	Authorized
Terrosa	Teriparatide	Forsteo	Eli Lilly Nederland B.V.	EMEA/H/C/003916	Gedeon Richter Plc.	27-Nov-15	4-Jan-17	Authorized
Movymia	Teriparatide	Forsteo	Eli Lilly Nederland B.V	EMEA/H/C/004368/0000	STADA Arzneimittel AG	30-Nov-15	11-Jan-17	Authorized
Amgevita	Adalimumab	Humira	AbbVie Ltd	EMEA/H/C/004212/0000	Amgen Europe B.V.	3-Dec-15	22-Mar-17	Authorized
Solymbic	Adalimumab	Humira	AbbVie Ltd	EMEA/H/C/004373/0000	Amgen Europe B.V.	3-Dec-15	22-Mar-17	Authorized
Lusduna	Insulin glargine	Lantus	Sanofi-Aventis Deutschland GmbH	EMEA/H/C/004101	Merck Sharp & Dohme Limited	4-Dec-15	4-Jan-17	Authorized
Rixathon	Rituximab	MabThera	Roche Registration Limited	EMEA/H/C/003903/0000	Sandoz GmbH	11-Apr-16	19-Jun-17	Authorized
Imraldi	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	EMEA/H/C/004279/0000	Samsung Bioepis UK Limted	21-Jun-16	24-Aug-17	Authorized
Semglee	Insulin glargine	Lantus	Sanofi-Aventis Deutschland GmbH	EMEA/H/C/004280/0000	Mylan S.A.S	1-Aug-16	23-Mar-18	Authorized
Ontruzant	Trastuzmab	Herceptin	Roche Registration Limited	EMEA/H/C/004323	Samsung Bioepis UK Limted	30-Aug-16	15-Nov-17	Authorized
Insulin lispro Sanofi	Insulin lispro	Humalog	Eli Lilly Nederland B.V.	EMEA/H/C/004303	Sanofi-Aventis Groupe	7-Sep-16	19-Jul-17	Authorized
Herzuma	Trastuzmab	Herceptin	Roche Registration Limited	EMEA/H/C/002575	Celltrion Healthcare Hungary Kft.	10-Oct-16	9-Feb-18	Authorized
Cyltezo	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	EMEA/H/C/004319/0000	Boehringer Ingelheim	27-Oct-16	10-Nov-17	Authorized

Biosimilar	INN	Reference Originator	Originator Company	EMA Agency Product number for the Biosimilar	Marketing Authorization Holder of the Biosimilar	Biosimilar Application Date to the EMA	Biosimilar Marketing Authorization Date	Status
Mvasi	Bevacizumab	Avastin	Roche Registration Limited	EMEA/H/C/004728	Amgen Europe B.V.	1-Dec-16	15-Jan-18	Authorized
Riximyo	Rituximab	MabThera	Roche Registration Limited	EMEA/H/C/004729/0000	Sandoz GmbH	9-Dec-16	15-Jun-17	Authorized
Kanjinti	Trastuzmab	Herceptin	Roche Registration Limited	EMEA/H/C/004361/0000	Amgen Europe B.V., Breda	1-Mar-17	16-May-18	Authorized
Ritemvia	Rituximab	MabThera	Roche Registration Limited	EMEA/H/C/004725/0000	Celltrion Healthcare Hungary Kft.	3-Mar-17	13-Jul-17	Authorized
Blitzima	Rituximab	MabThera	Roche Registration Limited	EMEA/H/C/004723/0000	Celltrion Healthcare Hungary Kft.	6-Mar-17	13-Jul-17	Authorized
Rituzena (previously Tuxella)	Rituximab	MabThera	Roche Registration Limited	EMEA/H/C/004724/0000	Celltrion Healthcare Hungary Kft.	6-Mar-17	13-Jul-17	Authorized
Zessly	Infliximab	Remicade	Janssen Biologics B.V., NL	EMEA/H/C/004647/0000	Sandoz GmbH	21-Apr-17	18-May-18	Authorized
Hyrimoz	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	EMEA/H/C/004320/0000	Sandoz GmbH	24-Apr-17	26-Jul-18	Authorized
Trazimera	Trastuzmab	Herceptin	Roche Registration Limited	EMEA/H/C/004463/0000	Pfizer Europe MA EEIG	27-Jun-17	26-Jul-18	Authorized
Halimatoz	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	EA/H/C/004866/0000	Sandoz GmbH	23-Nov-17	26-Jul-18	Authorized
Hefiya	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	EMEA/H/C/004865/0000	Sandoz GmbH	23-Nov-17	26-Jul-18	Authorized

*Table 4-1: List of biosimilar approvals in Europe (Updated on 31st July 2018). The above list is in arranged from the earliest marketing authorization application to the latest application. **European Union withdrew marketing authorization for these biosimilars at the request of their respective marketing authorization holders*

4.2.1.2 Unique and Non-Unique Biosimilar Regulatory Approvals in Europe

During the data collection, it was observed that certain biosimilars that applied under different marketing authorization holders in Europe underwent an identical regulatory approval process. For this study such biosimilars are grouped together as non-unique biosimilars. A biosimilar approval is categorized as non-unique if all the following criteria were met:

- Submission of identical clinical data in the application as another biosimilar (recorded in the Committee for Medical Products for Human Use (CHMP) Assessment Report),

- Same application date as the other biosimilar
- Same approval date as the other biosimilar
- Have the same reference originator as the other biosimilar

Such non-unique biosimilar approvals are grouped as one unique approval. This grouping was carried out to ensure that such non-unique approvals do not skew the statistical analysis of data. Table 4-2 provides a list of biosimilar approvals with the non-unique approvals grouped into unique approvals. Grouping of non-unique approvals led to 6 groupings resulting in a remaining 41 unique biosimilar approvals. These 41 unique approvals were then used for further statistical analysis to answer the research question.

Biosimilars	INN	Reference Originator	Originator Company	Biosimilar Application Date	Biosimilar Marketing Authorization Date
Valtropin	Somatropin	Humatrope	Eli Lily	3-Jun-04	24-Apr-06
Omnitrope	Somatropin	Genotropin	Pfizer	1-Jul-04	12-Apr-06
Binocrit/ Epoetin alfa Hexal/ Abseamed	Epoetin alfa	Epogen	Amgen	9-Mar-06	28-Aug-07
Silapo	Epoetin zeta	Epogen	Amgen	28-Jun-06	18-Dec-07
Filgrastim ratiopharm/ Ratiograstim/ Tevagrastim/ Biograstim	Filgrastim	Neupogen	Amgen	29-Jan-07	15-Sep-08
Retacrit	Epoetin zeta	Epogen	Amgen	11-May-07	18-Dec-07
Filgrastim Hexal/ Zarzio	Filgrastim	Neupogen	Amgen	6-Sep-07	6-Feb-09
Nivestim	Filgrastim	Neupogen	Amgen	27-Feb-09	8-Jun-10
Ovaleap	Follitropin alfa	Gonal-f	Merck	28-Feb-12	27-Sep-13
Remsima (**Note 1)	Infliximab	Remicade	Janssen Biologics B.V., NL	1-Mar-12	10-Sep-13
Grastofil	Filgrastim	Neupogen	Amgen	30-Apr-12	18-Oct-13
Inflectra (**Note 1)	Infliximab	Remicade	Janssen Biologics B.V., NL	26-Jun-12	10-Sep-13
Bemfola	Follitropin - alfa	Gonal-f	Merck	30-Oct-12	27-Mar-14
Abasaglar (previously Absaria)	Insulin glargine	Lantus	Sanofi-Aventis Deutschland GmbH	3-Jun-13	9-Sep-14
Accofil	Filgrastim	Neupogen	Amgen	24-Mar-14	18-Sep-14
Benepali	Etarnacept	Enbrel	Pfizer Limited	3-Dec-14	14-Jan-16
Thorinane	Enoxaparin sodium	Clexane	Sanofi Aventis	6-Feb-15	15-Sep-16
Flixabi	Infliximab	Remicade	Janssen Biologics B.V., NL	3-Mar-15	26-May-16
Inhixa	Enoxaparin sodium	Clexane	Sanofi Aventis	27-May-15	15-Sep-16
Truxima	Rituximab	MabThera	Roche Registration Limited	9-Oct-15	17-Feb-17

Erelzi	Etarnacept	Enbrel	Pfizer Limited	11-Nov-15	27-Jun-17
Terrosa	Teriparatide	Forsteo	Eli Lilly Nederland B.V.	27-Nov-15	4-Jan-17
Movymia	Teriparatide	Forsteo	Eli Lilly Nederland B.V	30-Nov-15	11-Jan-17
Amgevita/ Solymbic	Adalimumab	Humira	AbbVie Ltd	3-Dec-15	22-Mar-17
Lusduna	Insulin glargine	Lantus	Sanofi-Aventis Deutschland GmbH	4-Dec-15	4-Jan-17
Rixathon	Rituximab	MabThera	Roche Registration Limited	11-Apr-16	19-Jun-17
Imraldi	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	21-Jun-16	24-Aug-17
Semglee	Insulin glargine	Lantus	Sanofi-Aventis Deutschland GmbH	1-Aug-16	23-Mar-18
Ontruzant	Trastuzmab	Herceptin	Roche Registration Limited	30-Aug-16	15-Nov-17
Insulin lispro Sanofi	Insulin lispro	Humalog	Eli Lilly Nederland B.V.	7-Sep-16	19-Jul-17
Herzuma	Trastuzmab	Herceptin	Roche Registration Limited	10-Oct-16	9-Feb-18
Cyltezo	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	27-Oct-16	10-Nov-17
Mvasi	Bevacizumab	Avastin	Roche Registration Limited	1-Dec-16	15-Jan-18
Riximyo	Rituximab	MabThera	Roche Registration Limited	9-Dec-16	15-Jun-17
Kanjinti	Trastuzmab	Herceptin	Roche Registration Limited	1-Mar-17	16-May-18
Ritemvia	Rituximab	MabThera	Roche Registration Limited	3-Mar-17	13-Jul-17
Blitzima/Rituzena (previously Tuxella)	Rituximab	MabThera	Roche Registration Limited	6-Mar-17	13-Jul-17
Zessly	Infliximab	Remicade	Janssen Biologics B.V., NL	21-Apr-17	18-May-18
Hyrimoz	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	24-Apr-17	26-Jul-18
Trazimera	Trastuzmab	Herceptin	Roche Registration Limited	27-Jun-17	26-Jul-18
Halimatoz/ Hefiya	Adalimumab	Humira	Abbvie Deutschland GmbH & Co. KG	23-Nov-17	26-Jul-18

Table 4-2: Non-Unique biosimilar approvals grouped. The above list is in arranged from the earliest marketing authorization application to the latest application.

**Note 1: Inflectra and Remsima are both manufactured at Celltrion Inc and are the same product (also referred to as CTP-13 which was the code used during the development clinical trials)[141,142]

4.2.2. Trends in Time Taken for Biosimilar Regulatory Approvals vs. Date of Application

The time taken for the regulatory approval process was determined by calculating the number of days between the EU marketing authorization application date to the date which marketing authorization is granted for each biosimilar. Figure 4-1 below shows the time taken for regulatory approval for biosimilar approvals until July 2018 as per Table 4-1. Figure 4-2 is a variation of Figure 4-1 with the non-unique biosimilars grouped as *per* Table 4-2.

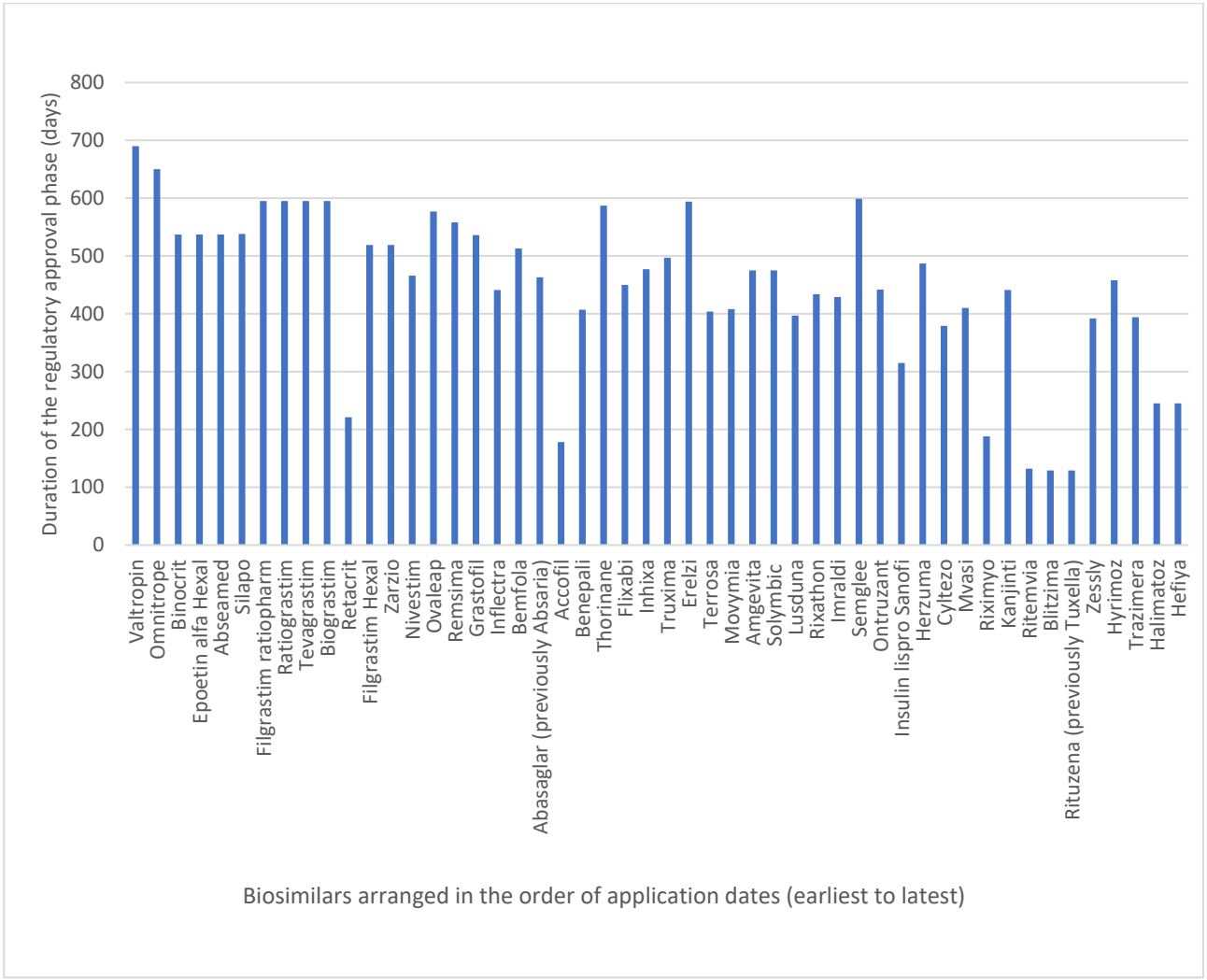


Figure 4-1: Time taken for regulatory approval for biosimilar approvals till July 2018. The biosimilars were arranged in the order of application dates but not on a linear timescale.

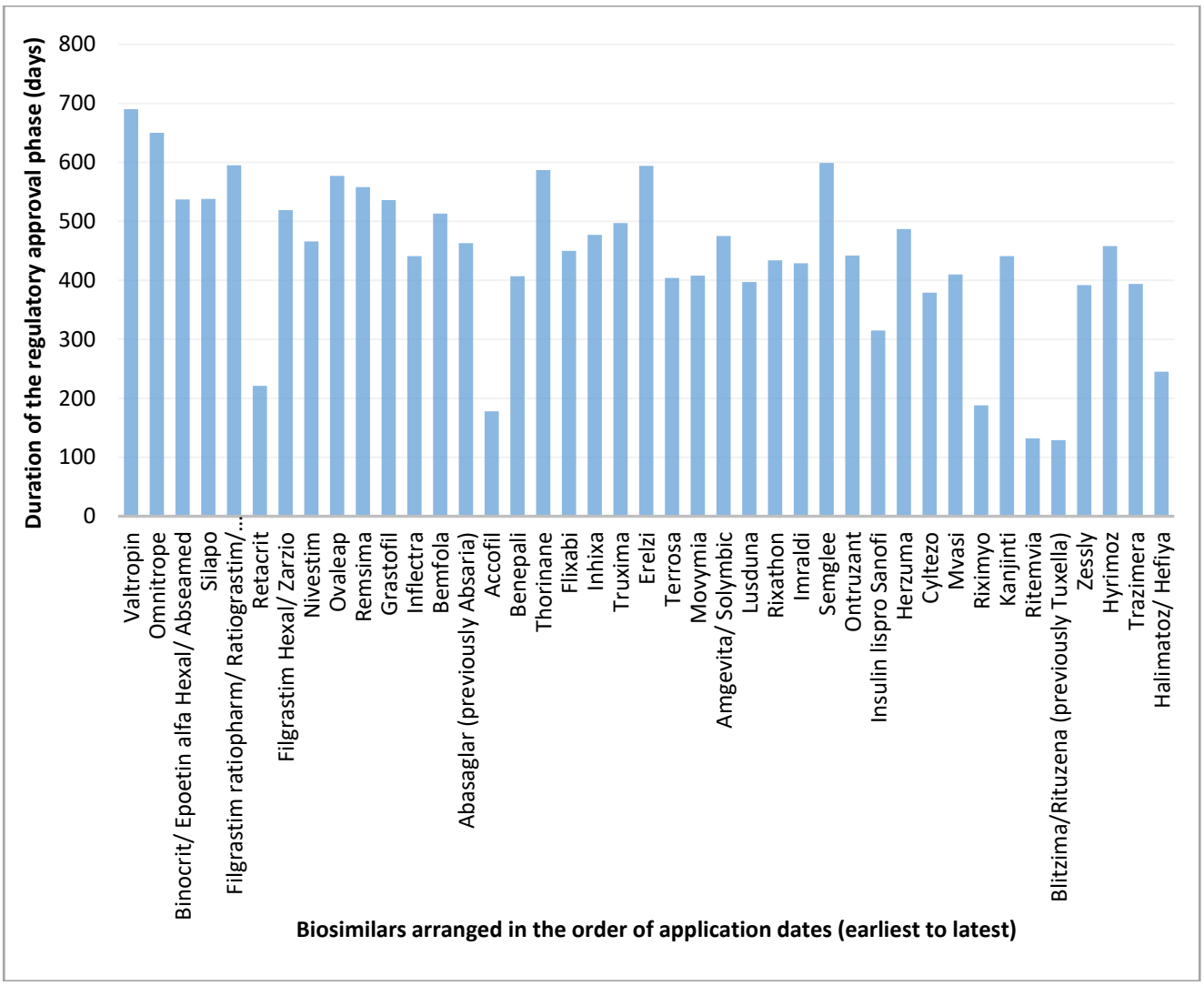


Figure 4-2: A variation of Figure 4-2, depicting the time taken for regulatory approval for biosimilar approvals till July 2018, but with the non-unique applications grouped. The biosimilars were arranged in the order of application dates but not on a linear timescale.

The mean, standard deviation, median and interquartile range calculated for the time taken for regulatory approvals (till 31st July 2018) of unique biosimilar applications in the EU are presented in Table 4-3.

Number of data points	**41**
Mean	440.29 days
Population standard deviation	125.89 days
Median	450.00 days
Quartile 1	397.00 days
Quartile 3	536.00 days
Interquartile Range (Quartile 3 minus Quartile 1)	139.00 days

Table 4-3: Mean, standard deviation, median and interquartile range calculated for unique biosimilar applications in the EU.

A single-factor (also commonly known as one-way) Analysis of Variance analysis (ANOVA) is used to test the null hypothesis that the means of several populations are equal. A single factor ANOVA was conducted to see whether the mean time taken for regulatory approval differed significantly between the different populations. The data was arranged as shown in Table 4-4, whereby each application year column was taken as one population.

Application year	2004	2006	2007	2009	2012	2013	2014	2015	2016	2017
Duration of the regulatory approval phase	690	537	595	466	577	463	178	587	434	441
	650	538	221		558		407	450	429	132
			519		536			477	599	129
					441			497	442	392
					513			594	315	458
								404	487	394
								408	379	245
								475	410	
								397	188	

Table 4-4: Duration of the regulatory approval phase arranged by each application year to conduct a single factor ANOVA.

The null hypothesis tested is that the mean duration of the regulatory approval phase for each application year is the same. The results show that the F value of 3.046985 is greater than F critical value of 2.199355 (refer to Table 4-5 below). Since the F calculated is greater than the F critical, the null hypothesis can be rejected. This indicates that there is a statistically significant difference in the mean duration of the regulatory approval phase for different application years (P-value = 0.009923).

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	*338893*	*9*	*37654.78*	*3.046985*	*0.009923*	*2.199355*
Within Groups	*383099.4*	*31*	*12358.05*			
Total	*721992.4*	*40*				

Table 4-5: Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for each year of application.

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric

tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test are as follows:

- K statistic : 19.819878
- Degree of freedom : 9
- P-value calculated : 0.019057

The null hypothesis tested is that the duration of the regulatory approval phase for each application year is the same. As the P-value calculated is less than 0.05, the null hypothesis is rejected. The results from the Kruskal-Wallis test are in congruence with the results from the ANOVA test.

Furthermore, a scatter plot was drawn to examine whether there is a relationship between the date of regulatory application and the time taken for regulatory approval (refer to Figure 4-3). The linear trendline in Figure 4-3 indicates that the duration of the pre-market regulatory approval phase decreases over time. Correlation co-efficient, R calculated using the data sets from the two variables (dependent variable being duration for regulatory approval phase and independent variable being the application dates) was -0.47. To further examine this trend the coefficient of determination, R^2, was calculated. R^2 value describes the “proportion of the variance in the dependent variable” (time taken for regulatory approval phase) “that is predictable from the independent variable” (date of application). The R^2 value was calculated to be 0.229, which corresponds to a 22.9% of the variability in the linear model. This indicates a weak to moderate negative linear relationship between the two variables. P-value calculated using this data was 0.00155. Hence, the P-value calculated is less than or equal 0.05, indicating evidence rejecting the null hypothesis, that the duration of the regulatory approval phase does not change over time. Hence, the duration of the regulatory approval phase does change (decreases) over time.

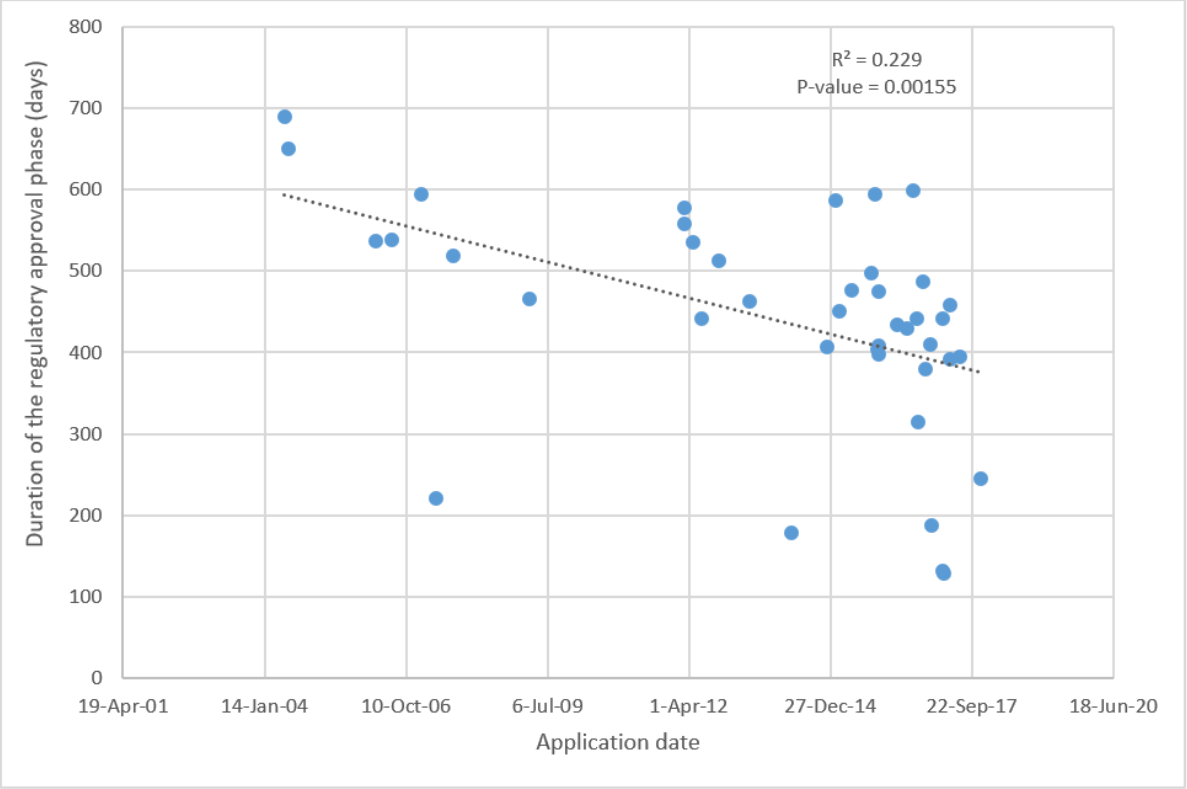


Figure 4-3: Duration of the pre-market regulatory approval phase vs. application date, without any adjustment of cut-off date for inclusion of data points.

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : -0.62286
- Number of data points : 41
- P-value calculated : 0.00014

The null hypothesis tested is that the duration of the regulatory approval phase does not change over time. As the P-value calculated is less than 0.05, the null hypothesis is rejected. This indicates that there is a statistically significant change in the duration of the regulatory approval phase over time. Spearman's rank correlation coefficient is negative, indicating that as the year of application increases, the duration of review decreases. The results from the Spearman's Rank correlation test are in congruence with the results from the regression analysis above.

4.2.2.1. Sensitivity Analysis via Right Censoring

Looking at Figure 4-3 above, there are two factors that can potentially have an impact on the results presented. Firstly, ,there are biosimilar applications prior to 31st July 2018 (study sample) that are currently being reviewed by the EMA and hence not captured in Figure 4-3. According to the EMA as of July 2018, there are 14 biosimilar applications that were under review and yet to be approved (refer to Appendix 4-1)[143]. As a result, in the latter years, Figure 4-3 may only have captured biosimilars that have taken shorter duration of time to progress through the regulatory approval process. Secondly, a potential change to the regulatory approval process affecting duration of the regulatory approval phase, for example the increase in the product (INN) specific guidelines being published by the EMA since December 2012, especially related to approval of monoclonal antibodies with the approval of Infliximab in December 2013, accelerating the regulatory approval process[144]. This approval of Infliximab was a landmark in biosimilar approvals, marking a shift from relatively simple growth factor type molecules (Erythropoietin and Granulocyte-colony stimulating factors) to molecules of much greater complexity both in terms of molecular structure and pharmacological action but also clinical indication. Thus, statistical analysis conducted using Figure 4-3 is potentially require right censoring.

To investigate if these factors are biasing the results, sensitivity analysis was conducted using an earlier cut-off date for data collection. This eliminates data points that are potentially biasing (right censoring) the results. To identify the earlier cut-off date the following steps were carried out:

1. The population standard deviation (refer to Table 4-3) was multiplied by a factor of 2 (M1 days). For an approximately normal set of data it is widely accepted that two standard deviations account for about 95% of the data.
2. The new cut-off date (here in referred to as the Adjusted Cut-Off Date) was then calculated by subtracting M1 days from 31st July 2018 (refer to Figure 4-4 below). Table 4-7 below summarizes the calculations related to the Adjusted Cut-Off Date. Using the Adjusted Cut-Off Date, further statistical analysis was conducted (refer to following sections 4.2.2.2., 4.2.3.1., and 4.2.4.1. in this chapter).

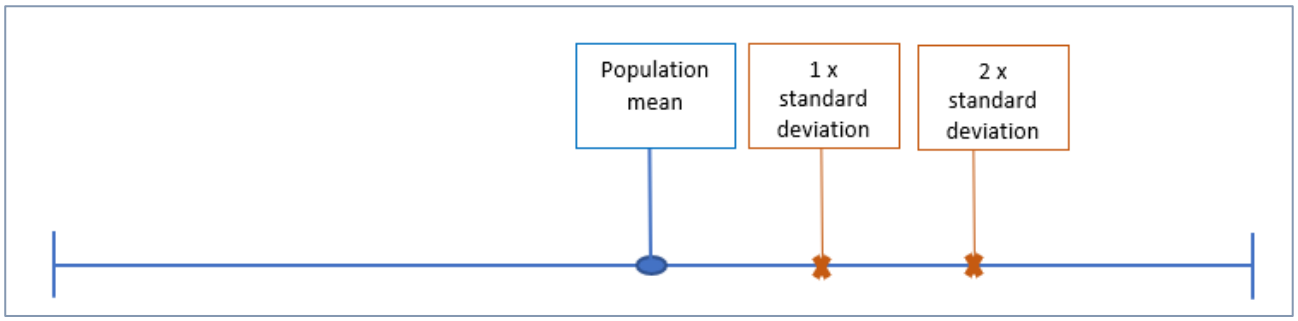


Figure 4-4: Schematic diagram showing how the Adjusted Cut-Off Date is calculated

Population standard deviation (refer to Table 4-3)	**125.89 days**
2 x Population standard deviation (M1 days)	**251.78 days**
Data collection cut-off date	**31st July 2018**
Adjusted Cut-Off Date	**21st November 2017 (251.78 days prior to 31st July 2018)**

Table 4-7: Summary of calculations to identify Adjusted Cut-Off Date.

4.2.2.2. Trends in Time Taken for Biosimilar Regulatory Approvals vs. Date of Application in the EU, using Adjusted Cut-Off Date

As discussed in the previous section the Adjusted Cut-Off Date for biosimilar approvals was calculated to be 21st November 2017. The mean, standard deviation, median and interquartile range calculated for the time taken for regulatory approval of unique application on or prior to the Adjusted Cut-Off Date are presented in Table 4-8. Whilst, the mean time taken for regulatory approval for the population of biosimilar applications on or prior to the Adjusted cut-off date was lower than the mean for the total population of the study (application till 31st July 2018), the difference was not great.

Details	Biosimilar application on or prior to Adjusted Cut-Off Date	Biosimilar applications on or prior to 31st July 2018
Number of data points to Adjusted Cut-Off Date	33	41
Mean	443.21 days	440.29 days
Population standard deviation	133.40 days	125.89 days
Median	463.00 days	450.00 days
Interquartile range	133.00 days	139.00 days

Table 4-8: Mean, standard deviation, median and interquartile range calculated for biosimilars applications on or prior to the Adjusted Cut-Off Date.

A single factor ANOVA was conducted to see whether the mean time taken for regulatory approval differed significantly over the years for the biosimilar applications approved on or prior to the Adjusted Cut-Off Date. The data was arranged whereby each application year column was taken as one population (refer to Table 4-9).

Application year	2004	2006	2007	2009	2012	2013	2014	2015	2016	2017
Duration of the regulatory approval phase	690	537	595	466	577	463	178	587	434	132
	650	538	221		558		407	450	429	129
			519		536			477	442	
					441			497	315	
					513			594	379	
								404	188	
								408		
								475		
								397		

Table 4-9: Duration of the regulatory approval phase in the EU arranged by each application year, for the biosimilar applications approved on or prior to the Adjusted Cut-Off Date, to conduct a single factor ANOVA.

The null hypothesis tested is that the mean duration of the regulatory approval phase for each application year is the same. The results show that the F calculated value 5.431928 is greater than the F critical value 2.32010 (refer to Table 4-10 below). Since the F calculated is greater than F critical, the null hypothesis is rejected. This indicates that there is a statistically significant difference between the mean duration of the regulatory approval phase for the different years (P-value is 0.000496). The result of the ANOVA test for the population of biosimilar applications on or prior to the Adjusted Cut-Off Date is in congruence with the total population of biosimilar applications until 31st July 2018 (refer to tables 4-5 and 4-10).

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	443198.3	9	49244.25	5.431928	0.000496	2.320105
Within Groups	208511.2	23	9065.705			
Total	651709.5	32				

Table 4-10: Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for each year of application, for biosimilar applications on or prior to the Adjusted Cut-Off Date.

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 20.074272
- Degree of freedom : 9
- P-value calculated : 0.017460

The null hypothesis tested is that the duration of the regulatory approval phase for each application year is the same. As the P-value calculated is less than 0.05, the null hypothesis is rejected. This indicates that there is a statistically significant difference between the mean duration of the regulatory approval phase for the different years. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test.

A regression analysis was then conducted to examine whether there was a correlation between the date of regulatory application and the time taken for regulatory approval (refer to Figure 4-5). The R^2 value was calculated to be 0.27579, which corresponds to a 27.58% of the variability in the linear model. Whilst the R^2 value for the population of biosimilar applications approved on or prior to the Adjusted cut-off date was higher than the R^2 value of 0.229 (refer to Figure 4-3) for the total population of the study (application till 31st July 2018), however the difference was not great. P-value calculated using this data is 0.001528. Similar to the to the entire data set, the P-value calculated for biosimilar applications on or before the Adjusted Cut-Off Date is less than 0.05, providing statistical evidence to reject the null hypothesis, that the duration of the regulatory approval phase does not change over time. Hence, the duration of the regulatory approval phase does change (decreases) over time. This is in congruence to the results from the analysis from the entire study population of biosimilars approved on or before 31st July 2018 (refer to Section 4.2.2 above).

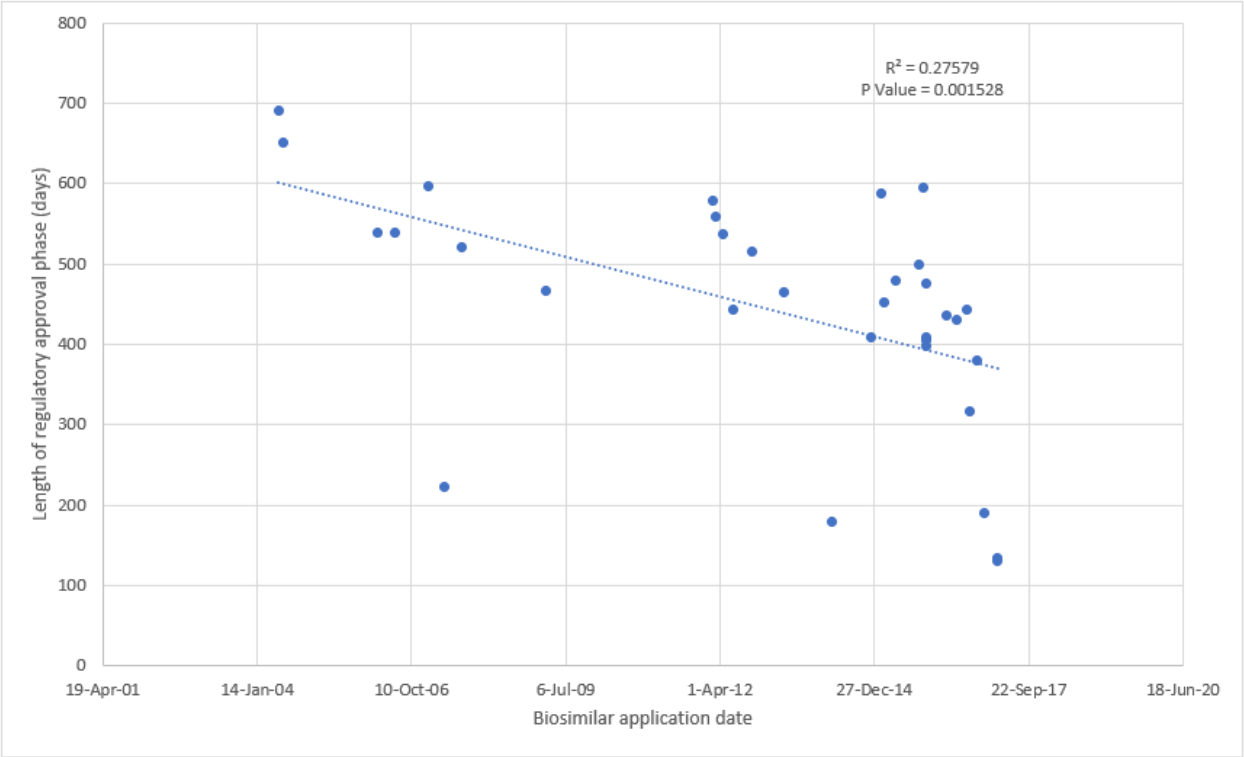


Figure 4-5: Duration of the regulatory approval phase vs. application date for biosimilar applications on or prior to the Adjusted Cut-Off Date

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : -0.696
- Number of data points : 33
- P-value calculated : <0.00001

The null hypothesis tested is that the duration of the regulatory approval phase does not change over time. As the P-value calculated is less than 0.05, the null hypothesis is rejected. This indicates that there is a statistically significant decrease in the duration of the regulatory approval phase over time. The results from the Spearman's Rank correlation test is in congruence with the results from the regression analysis above.

4.2.3. Trends in Time Taken for Biosimilar Regulatory Approvals vs. Generation in the EU

For the current study, the first biosimilar that applies for regulatory approval is defined as the first generation or generation one (1), the second biosimilar applying for regulatory approval referencing the same originator as generation two (2) and hence forth. As such for the current study a generation is defined as all the biosimilars that are at the same position of regulatory application, relative to their respective originators. Table 4-11 below shows the unique biosimilars applications grouped under each generation and the corresponding durations of their regulatory approval phase. From Table 4-11, it can be observed that there are fifteen unique 1st generation biosimilar approvals showing that biosimilars have been developed using fifteen reference originators. Table 4-11 further shows that there are eleven 2nd generation, seven 3rd generation, five 4th generation, and three 5th generation unique biosimilar approvals.

Generation	Name of Biosimilar	Duration of the regulatory approval phase (days)
1st mover biosimilars	1.1 Valtropin	690
	1.2 Omnitrope	650
	1.3 Binocrit/ Epoetin alfa Hexal/ Abeamed	537
	1.4 Filgrastim Ratiopharm/ Ratiograstim/ Tevagrastim/ Biograstim	595
	1.5 Remsima	558
	1.6 Ovaleap	577
	1.7 Absalgar	463
	1.8 Benepali	407
	1.9 Thorinane	587
	1.10 Terrosa	404
	1.11 Truxima	497
	1.12 Amgevita/ Solymbic	475
	1.13 Ontruzant	442
	1.14 Insulin lispro Sanofi	315
	1.15 Mvasi	410
2nd mover biosimilars	2.1 Silapo	538
	2.2 Fligrastim Hexal/Zarzio	519
	2.3 Inflectra	441
	2.4 Bemfola	513
	2.5 Inhixa	477
	2.6 Lusduna	397
	2.7 Movymia	408
	2.8 Rixathon	434
	2.9 Erelzi	594
	2.10 Imraldi	429
	2.11 Herzuma	487
3rd mover biosimilars	3.1 Retacrit	221
	3.2 Nivestim	466
	3.3 Flixabi	450
	3.4 Semglee	599
	3.5 Cyltezo	379
	3.6 Kanjinti	441
	3.7 Ritemvia	132
4th mover biosimilars	4.1 Grastofil	536
	4.2 Blitzima/Rituzena	129

Generation	Name of Biosimilar	Duration of the regulatory approval phase (days)
	4.3 Zessly	392
	4.4 Hyrimoz	458
	4.5 Trazimera	394
5th mover biosimilars	5.1 Accofil	178
	5.2 Riximyo	188
	5.3 Halimatoz/Hefiza	245

Table 4-11: Unique biosimilar applications grouped in generations and corresponding duration of their regulatory approval phase. The rows highlighted in blue represents non-unique applications grouped as unique applications.

Means, standard deviations and medians of each generation were calculated (refer to Table 4-12) and then graphically represented (refer to Figure 4-6) to observe whether there are variations and/or trends in the time taken for regulatory approval across the different generations.

Generation	Number of Applications	Mean (days)	Standard Deviation (days)	Median (days)
1	15	507	103.73	497
2	11	476	60.20	477
3	7	384	158.46	441
4	5	382	153.09	394
5	3	204	36.14	188

Table 4-12: Means, standard deviations and medians calculated for each generation.

Figure 4-6 below, indicates a possible decrease in mean time taken for regulatory approval against ascending order of generations.

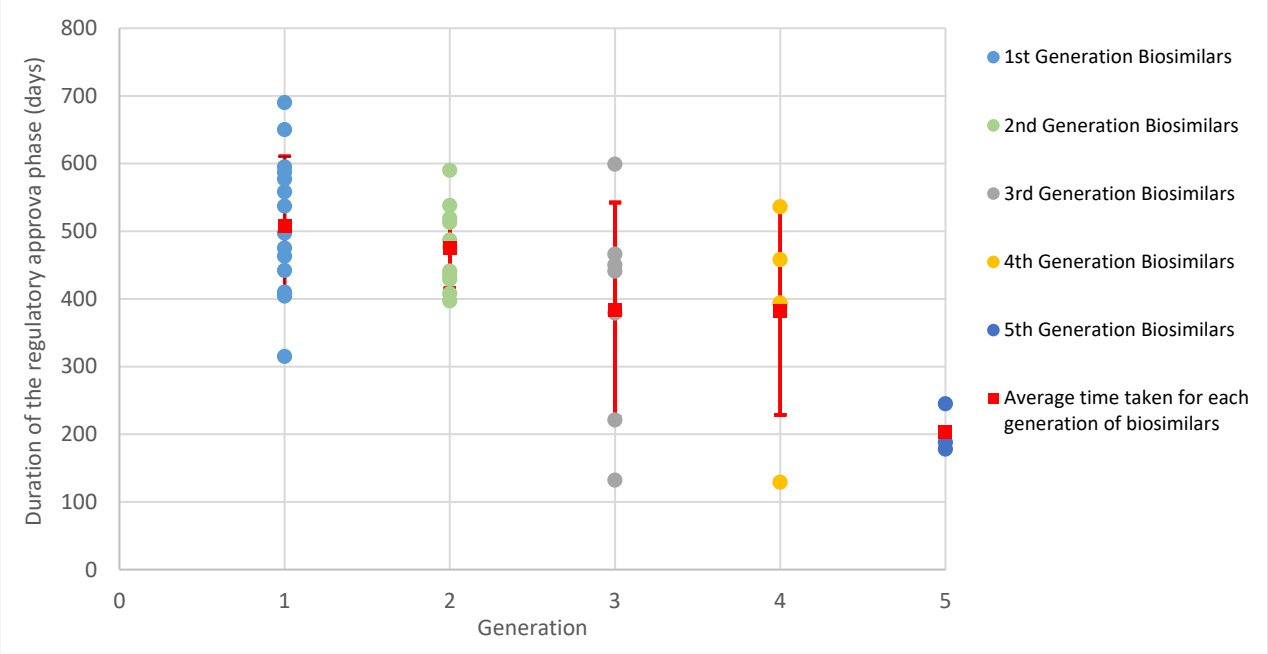


Figure 4-6: Time taken for regulatory approvals of unique application vs. generation. Means and standard deviations calculated for each generation is indicated in red.

Furthermore, a single factor ANOVA was conducted to test the null hypothesis that the mean duration of the regulatory approval phase for each generation is the same. To conduct a single factor ANOVA the data was arranged as shown in Table 4-13, whereby each generation column was taken as one population. The results show that the calculated F value 5.976 is greater than the F critical value 2.634 (refer to Table 4-14 below). Since the F calculated is greater than F critical, null hypothesis is rejected. This indicates a statistically significant difference in the mean duration of the regulatory approval phase between the different generations (P-value 0.00085572).

1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation
690	538	221	536	178
650	519	466	129	188
537	441	450	392	245
595	513	599	458	
558	477	379	394	
577	397	441		
463	408	132		
407	434			
587	594			
404	429			
497	487			
475				
442				
315				
410				

Table 4-13: Duration of the regulatory approval phase arranged by each generation to conduct a single factor ANOVA.

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	288091.0572	4	72022.7643	5.975596353	0.00085572	2.63353209
Within Groups	433901.3818	36	12052.81616			
Total	721992.439	40				

Table 4-14: *Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for each generation.*

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do

not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 11.858906
- Degree of freedom : 4
- P-value calculated : 0.018432

The null hypothesis tested is that the duration of the regulatory approval phase for each generation is the same. As the P-value calculated is less than 0.05, the null hypothesis is rejected. This indicates that there is a statistically significant difference between the duration of the regulatory approval phase for the different generations. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test.

Results from the single factor ANOVA and Kruskal-Wallis test were confirmed with a regression analysis (refer to Figure 4-7 below) to see whether there is trend in duration of regulatory approval time over generations. P-value calculated using this data is 0.00004. As the P-value calculated is less than 0.05, this indicates statistically strong evidence against the null hypothesis. Hence, the duration of the regulatory approval phase does change (decreases) over the generations.

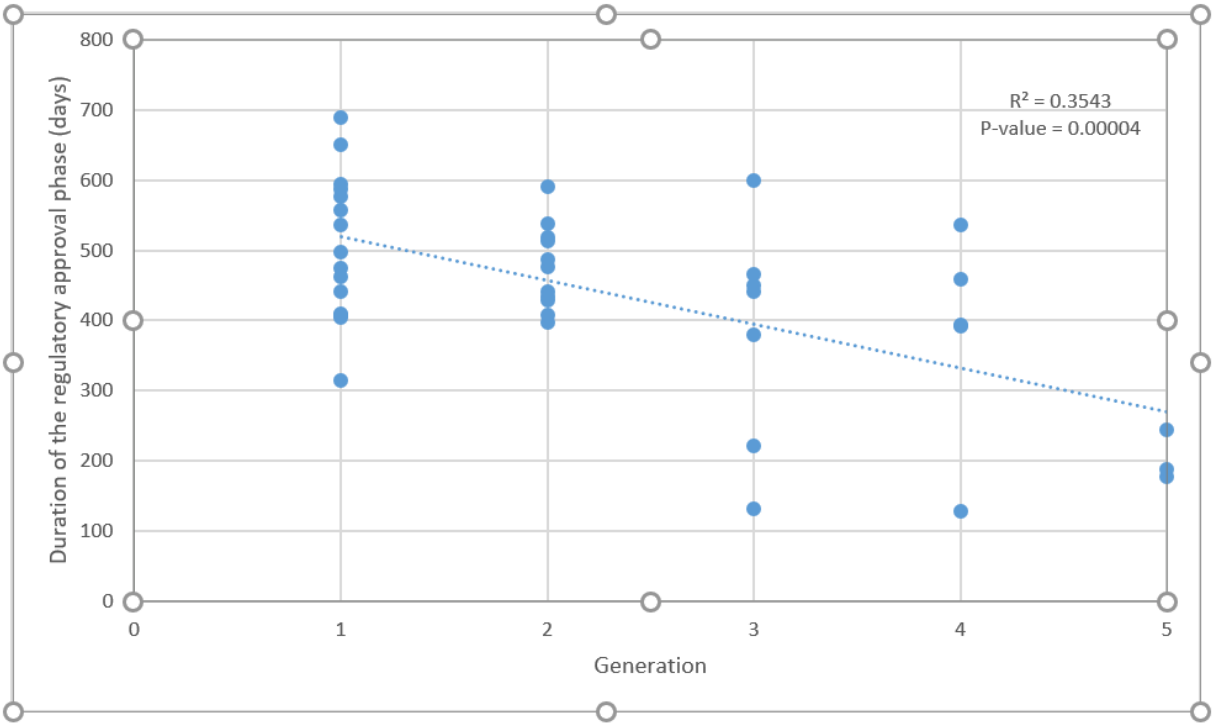


Figure 4-7: Time taken for regulatory approvals of unique application on or before 31st July 2018 vs. generation.

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : -0.50493
- Number of data points : 41
- P-value calculated : 0.00076

The null hypothesis tested is that the duration of the regulatory approval phase does not change over generations. As the P-value calculated is less than 0.05, the null hypothesis is rejected. This indicates that there is a statistically significant decrease in the duration of the regulatory approval phase over generations. The results from the Spearman's Rank correlation test is in congruence with the results from the regression analysis above.

4.2.3.1 Trends in Time Taken for Biosimilar Regulatory Approvals vs. Generation in the EU, using Adjusted Cut-Off Date

The Adjusted Cut-Off Date was calculated to be 21st November 2017 (refer to Section 4.2.2.1). Table 4-15 below shows a variation of Table 4-11, where the unique biosimilars applications grouped under each generation and the corresponding durations of their regulatory approval phase for biosimilar applications on or prior to the Adjusted Cut-Off Date.

Generation	Name of Biosimilar	Duration of the regulatory approval phase (days)
1st mover biosimilars	1.1 Valtropin	690
	1.2 Omnitrope	650
	1.3 Binocrit/ Epoetin alfa Hexal/ Abeamed	537
	1.4 Filgrastim Ratiopharm/ Ratiograstim/ Tevagrastim/ Biograstim	595
	1.5 Remsima	558
	1.6 Ovaleap	577
	1.7 Absalgar	463
	1.8 Benepali	407
	1.9 Thorinane	587
	1.10 Terrosa	404
	1.11 Truxima	497
	1.12 Amgevita/ Solymbic	475
	1.13 Ontruzant	442
	1.14 Insulin lispro Sanofi	315
	2.1 Silapo	538

Generation	Name of Biosimilar	Duration of the regulatory approval phase (days)
2nd mover biosimilars	2.2 Fligrastim Hexal/Zarzio	519
	2.3 Inflectra	441
	2.4 Bemfola	513
	2.5 Inhixa	477
	2.6 Lusduna	397
	2.7 Movymia	408
	2.8 Rixathon	434
	2.9 Erelzi	594
	2.10 Imraldi	429
3rd mover biosimilars	3.1 Retacrit	221
	3.2 Nivestim	466
	3.3 Flixabi	450
	3.4 Cyltezo	379
	3.5 Ritemvia	132
4th mover biosimilars	4.1 Grastofil	536
	4.2 Blitzima/Rituzena	129
5th mover biosimilars	5.1 Accofil	178
	5.2 Riximyo	188

Table 4-15: Unique biosimilar applications on or prior to the Adjusted Cut-Off Date, grouped in generations and corresponding duration of their regulatory approval phase. The rows highlighted in blue represents non-unique applications grouped as unique applications.

Means and standard deviations of each generation was calculated for biosimilar applications on or prior to the Adjusted Cut-Off Date (refer to Table 4-16 below).

Generation	Biosimilar application on or prior to Adjusted cut-off date			Biosimilar applications on or prior to 31st July 2018		
	Number	Mean (days)	Standard Deviation (days)	Number	Mean (days)	Standard Deviation (days)
1	14	514.07	103.98	15	507	103.73
2	10	475	64.15	11	476	60.20
3	5	329.6	146.95	7	384	158.46
4	2	332.50	287.79	5	382	153.09
5	2	183	7.07	3	204	36.14

Table 4-16: Mean and standard deviation calculated for biosimilars applications on or prior to the Adjusted Cut-Off Date.

Furthermore, a single factor ANOVA was conducted to test the null hypothesis that the mean duration of the regulatory approval phase for each generation is the same for biosimilar applications on or prior to the Adjusted Cut-Off Date. The results show that the calculated F calculated value 6.15307 is greater than the F critical value 2.714076 (refer to Table 4-17 below). Since the F calculated is greater than F critical, null hypothesis is rejected, which indicates a statistical difference in the duration of the regulatory approval phase between the different generations of biosimilars (P-

value 0.001104). This is the same trend as was discovered when the total population of biosimilar applications till 31st July 2018 was used. (refer to Section 4.2.3), but with a slightly smaller F calculated value (as might be expected because data which might spuriously increase the trend have been trimmed).

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	304872.9	4	76218.22	6.15307	0.001104	2.714076
Within Groups	346836.6	28	12387.02			
Total	651709.5	32				

Table 4-17: *Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for each generation for biosimilar applications on or prior to the Adjusted Cut-Off Date.*

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 10.475630
- Degree of freedom : 4
- P-value calculated : 0.033134

The null hypothesis tested is that the duration of the regulatory approval phase for each generation is the same. As the P-value calculated is less than 0.05, the null hypothesis is rejected. This indicates that there is a statistically significant difference between the duration of the regulatory approval phase for the different generations. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test above (Refer to Table 4-17)

Results from the single factor ANOVA and Kruskal-Wallis test were confirmed with a regression analysis (refer to Figure 4-8 below) to see whether there is trend in duration of regulatory approval time over generations. P-value calculated using this data is less than 0.00001. As the P-

value calculated is less than 0.05, this indicates statistically strong evidence against the null hypothesis. Hence the duration of the regulatory approval phase does change over the generations.

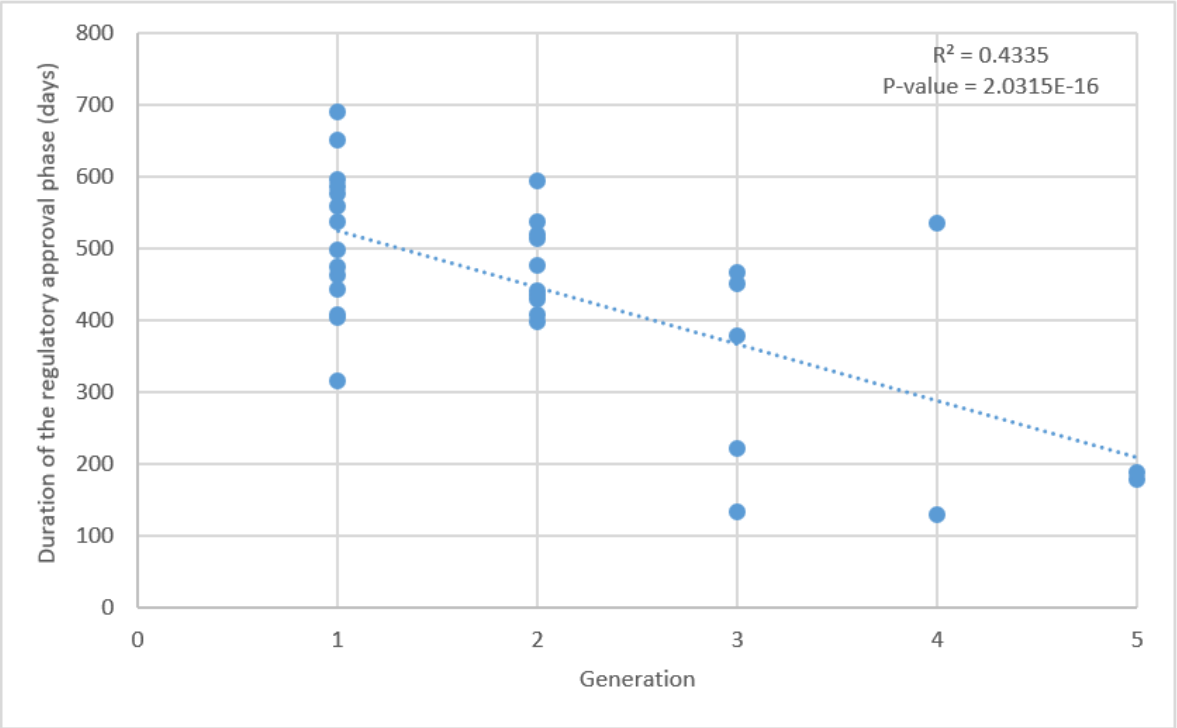


Figure 4-8: Time taken for regulatory approvals of unique application on or before Adjusted Cut-Off Date vs. generation.

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : -0.52902
- Number of data points : 33
- P-value calculated : 0.00155

The null hypothesis tested is that the duration of the regulatory approval phase does not change over generations. As the P-value calculated is less than 0.05, the null hypothesis is rejected. This indicates that there is a statistically significant decrease in the duration of the regulatory approval phase over generations. The results from the Spearman's Rank correlation test is in congruence with the results from the regression analysis above.

4.2.4. Trends in Time Taken for Biosimilar Regulatory Approvals for each Reference Originator in the EU

This section details the findings from the data analysis conducted to investigate whether the molecular nature or class of drugs affects the duration of the regulatory approval phase of biosimilars. To identify whether the molecular nature or class of drugs had any effect on the regulatory approval duration, biosimilar approvals were grouped against their reference originator. Biosimilars must show similarity to the originator in terms of quality, biological activity, tolerability, and efficacy[145]. As such grouping biosimilars referencing the same originators, there is a direct comparison of molecules of similar attributes. Table 4-18 shows unique biosimilar approvals against their reference originator. Table 4-18 also shows that as of 31st July 2018 there have been biosimilar applications and subsequent regulatory approvals for biosimilars referencing 15 different originator biopharmaceuticals. Out of these 15 reference originators:

- 3 reference originators have five generations of biosimilars (highlighted in yellow),
- 2 reference originators have four generations of biosimilars (highlighted in grey),
- 2 reference originators have three generations of biosimilars (highlighted in blue),
- 4 reference originators have two generations of biosimilars (highlighted in green), and
- 4 reference originators have only one generation of biosimilars (highlighted in orange).

#	Originator	1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation
1	Humatrope	Valtropin				
2	Genotropin	Omnitrope				
3	Eprex/Erypo	Binocrit/ Epoetin alfa Hexal/ Abseamed	Silapo	Retacrit		
4	Neupogen	Filgrastim Ratiopharm/Ratiograstim/ Tevagrastim/ Biograstim	Filgrastim Hexal /Zarzio	Nivestim	Grastofil	Accofil
5	Remicade	Remsima	Inflectra	Flixabi	Zessly	
6	Gonal-f	Ovaleap	Bemfola			
7	Lantus	Absalgar	Lusduna	Semglee		
8	Enbrel	Benepali	Erelzi			
9	Clexane	Thorinane	Inhixa			
10	Forsteo	Terrosa	Movymia			
11	MabThera	Truxima	Rixathon	Ritemvia	Blitzima/Rituzena	Riximyo
12	Humira	Amgevita/Solymbic	Imraldi	Cyltezo	Hyrimoz	Halimatoz/Hefiya
13	Herceptin	Ontruzant	Herzuma	Kanjinti	Trazimera	
14	Humalog	Insulin lispro Sanofi				
15	Avastin	Mvasi				

Table 4-18: Summary of reference originators and the corresponding generations of biosimilars.

The duration of the regulatory approval phase for each generation of biosimilars developed referencing the various originators was graphically represented to identify any characteristic trends (refer to Figure 4-9 below). Based on Figure 4-9, it can be observed that when there is more than one generation of biosimilars for a reference originator, the first generation appears to have the longest duration regulatory approval phase. Furthermore, in general the durations of the regulatory approval phase appear to decrease through the subsequent generations as confirmed by the statistical analysis in the previous section (refer to section 4.2.2.).

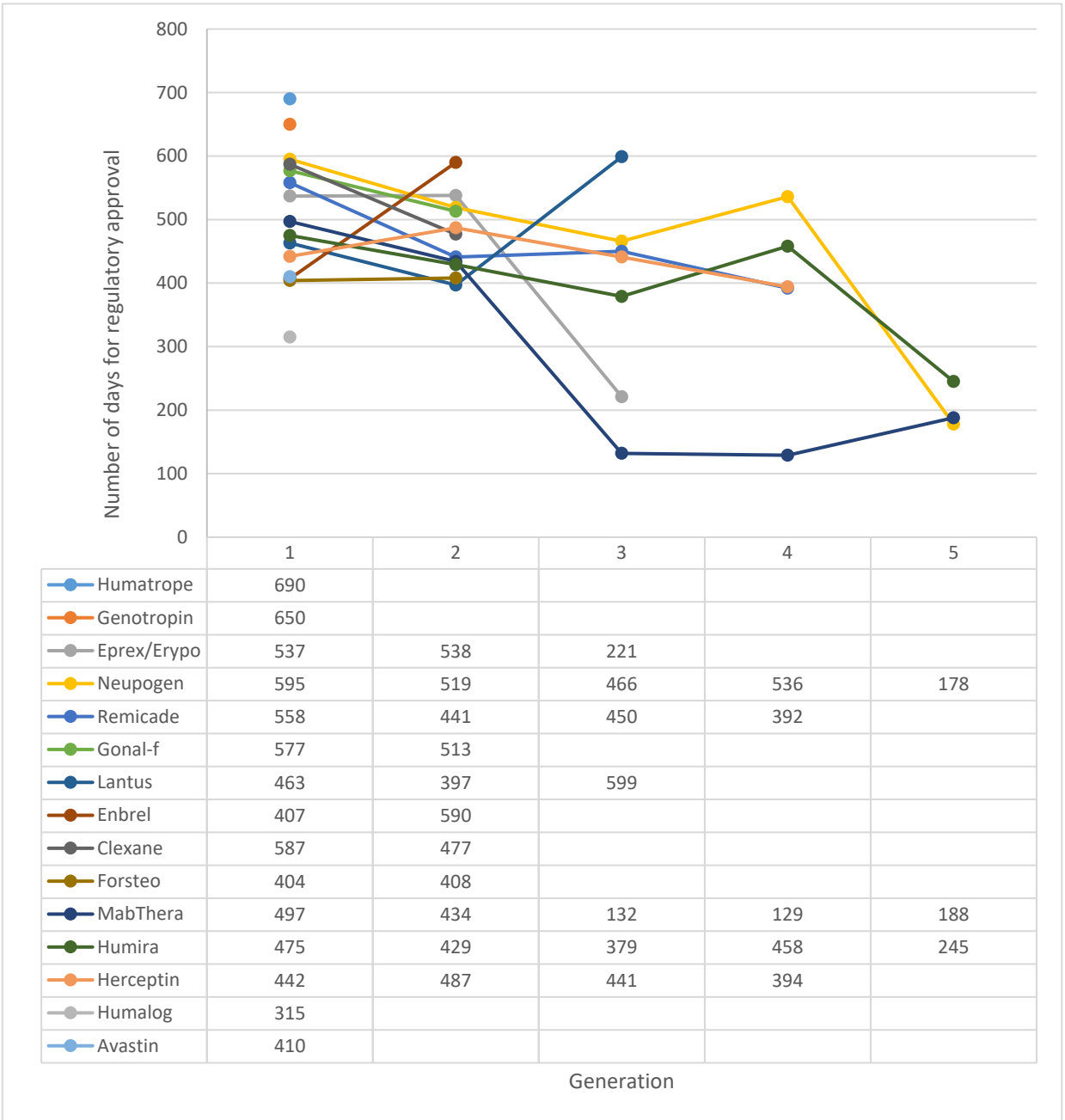


Figure 4-9: Number of days taken for regulatory approval of each generation of biosimilars developed using the different reference originators.

Initially a single factor ANOVA was conducted to see whether the mean time taken for regulatory approval (considering all generations from a given originator) differed significantly between for biosimilars, using the entire population of data. However, it was decided that this was not feasible, as the effect of the different number of generations for different originators would confound the results. Thus, it was decided to conduct a single factor ANOVA, with each ANOVA conducted with only the reference originators with the *same number* of biosimilar descendants.

- **ANOVA - originators with 2 biosimilar descendants**

The results of the single factor ANOVA show that the calculated F value 1.2664 is less than the F critical value 6.5914 (refer to Table 4-20 below). Since the F calculated is less than F critical, null hypothesis is accepted(P-value 0.39845129), which indicates that there is no statistical difference in the mean duration of the regulatory approval phase between the biosimilar descendants referencing the four different reference originators (Gonal-f, Enbrel, Clexane and Forsteo).

Descendants	Gonal-f	Enbrel	Clexane	Forsteo
1	577	407	587	404
2	513	590	477	408

Table 4-19: Duration of the regulatory approval phase, arranged by each reference originator (column) for originator biologics with two biosimilar descendants, to conduct a single factor ANOVA.

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	23603.375	3	7867.79167	1.26641986	0.39845129	6.59138212
Within Groups	24850.5	4	6212.625			
Total	48453.875	7				

Table 4-20: *Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for biosimilar decedents of reference originators with two biosimilar descendants.*

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the

statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 2.83333
- Degree of freedom : 3
- P-value calculated : 0.418042

The null hypothesis tested is that the duration of the regulatory approval phase between the descendants referencing the four different reference originators (Gonal-f, Enbrel, Clexane and Forsteo) is the same. As the P-value calculated is more than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference between duration of the regulatory approval phase of the biosimilar descendants of these four different reference originators. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test.

- **ANOVA - originators with 3 biosimilar descendants**

The results of the single factor ANOVA show that the calculated F value 0.2012 is less than the F critical value 7.7086 (refer to Table 4-22 below). Since the F calculated is less than F critical, null hypothesis is accepted (P-value 0.20127878), which indicates that there is no statistical difference in the mean duration of the regulatory approval phase between the biosimilar descendants referencing the two different reference originators (Eprex/Erypo and Lantus). However, due to the limited availability of data this finding should only be considered preliminary.

Descendants	Eprex/Erypo	Lantus
1	537	463
2	538	397
3	221	599

Table 4-21: Duration of the regulatory approval, arranged by each reference originator (column) for originator biologics with three biosimilar descendants, to conduct a single factor ANOVA.

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	4428.16667	1	4428.16667	0.20127878	0.67692154	7.70864742
Within Groups	88000.6667	4	22000.1667			
Total	92428.8333	5				

Table 4-22: *Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for biosimilar decedents of reference originators with three biosimilar descendants.*

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 0.47619
- Degree of freedom : 1
- P-value calculated : 0.827259

The null hypothesis tested is that the duration of the regulatory approval phase between the descendants referencing the two different reference originators (Eprex/Erypo and Lantus) is the same. As the P-value calculated is more than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference between duration of the regulatory approval phase of the biosimilar descendants of these two different reference originators. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test.

However, it should be noted that in the example of Semglee (3rd biosimilar descendent to Lantus originator), that there is a potential for technical issues related to manufacturing site, rather than the biosimilarity evaluation per se, influenced the duration of regulatory review[146].

- **ANOVA - originators with 4 biosimilar descendants**

  As there was only the originator Remicade with 4 biosimilar descendants, an ANOVA could not be conducted (refer to Table 4-18).

- **ANOVA - originators with 5 biosimilar descendants**

The results of the single factor ANOVA show that the calculated F value 1.9571 is less than the F critical value 3.8852 (refer to Table 4-24 below). Since the F calculated is less than F critical, null hypothesis is accepted (P-value 0.18381209), which indicates that there is no statistical difference in the mean duration of the regulatory approval phase between the biosimilar descendants referencing the three different reference originators (Neupogen, MabThera, and Humira).

Descendants	Neupogen	MabThera	Humira
1	595	497	475
2	519	434	429
3	466	132	379
4	536	129	458
5	178	188	245

Table 4-23: Duration of the regulatory approval phase, arranged by each reference originator (column) for originator biologics with two biosimilar descendants, to conduct a single factor ANOVA.

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	86499.7333	2	43249.8667	1.95711381	0.18381209	3.88529383
Within Groups	265185.6	12	22098.8			
Total	351685.333	14				

Table 4-24: *Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for biosimilar decedents of reference originators with five biosimilar descendants.*

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 3.9800
- Degree of freedom : 2
- P-value calculated : 0.136695

The null hypothesis tested is that the duration of the regulatory approval phase between the descendants referencing the three different reference originators (Neupogen, MabThera, and Humira) is the same. As the P-value calculated is more than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference between duration of the regulatory approval phase of the biosimilar descendants of these three different reference originators. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test.

4.2.4.1. Trends in Time Taken for Biosimilar Regulatory Approvals for each Reference Originator in the EU, with the Adjusted Cut-Off Date

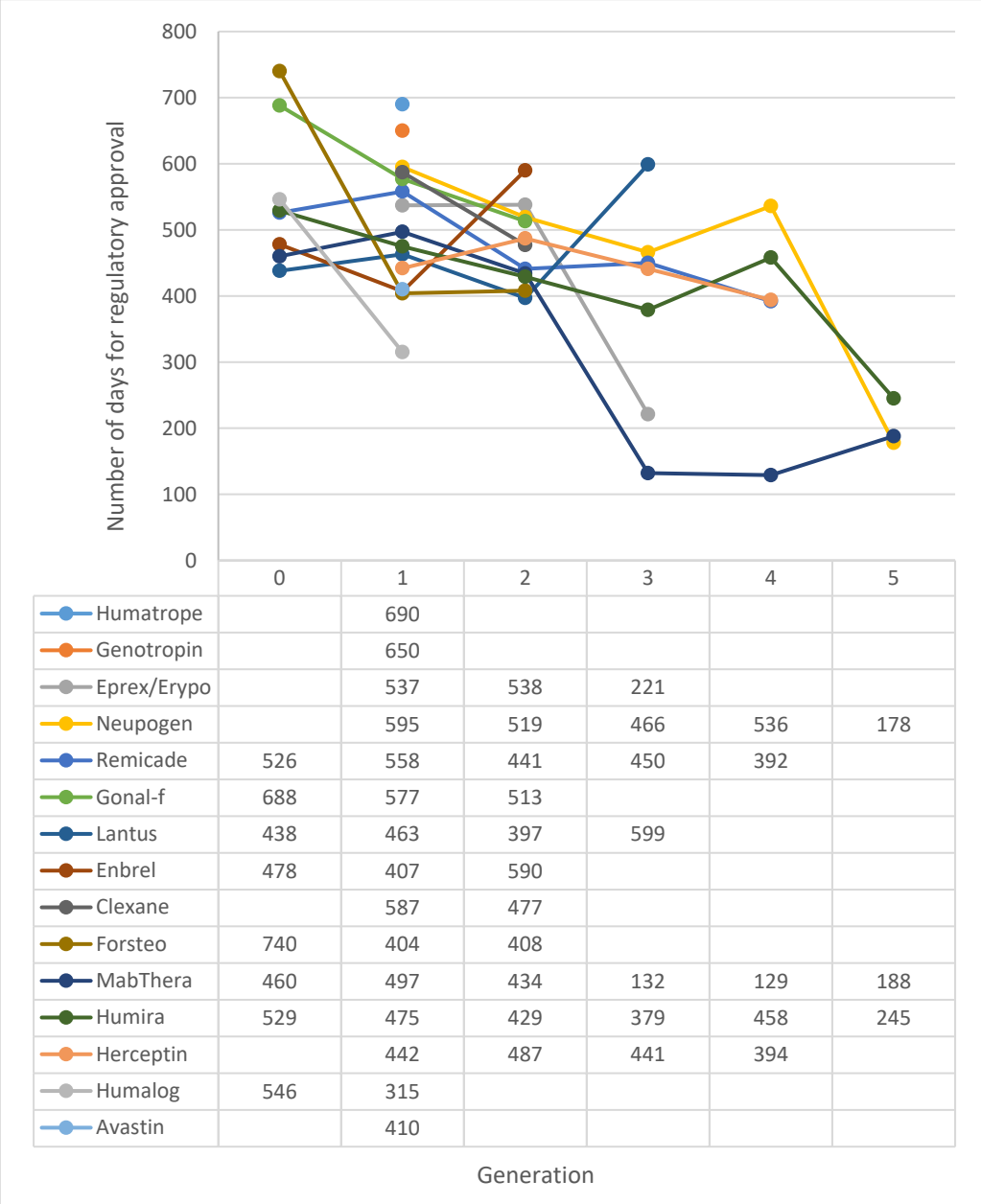
In the trend analysis of time taken for biosimilar regulatory approval for each reference originator, the analysis compared originators with same number of descendants irrespective of the time of application by the first biosimilar. As such the effect of any pending application was not considered as a factor that could potentially have skewed the trend analysis. Hence, it was decided that the Adjusted Cut-Off Date would not be considered.

4.2.4.2. Trends in Time Taken for Biosimilar Regulatory Approvals for each Reference Originator in the EU, Including Available Reference Originator Approval Times

Based on the results of the ANOVA conducted (refer to Tables 4-20, 4-22 and 4-24), a potential trend observed is that the duration of regulatory approval phase for biosimilars approved in the EU does not vary significantly between the different reference originators.

The researcher then investigated the possibility of collating data on the duration of regulatory approval phase for each of the 15 reference *originators*. The duration of regulatory approval phase for 8 out of the 15 reference originators could be calculated from the available data in the publicly available EMA databases. These data points along with data points from Figure 4-9 were then graphically represented in Figure 4-10.

Figure 4-10 shows that based on this limited data set, the duration of the regulatory approval phase for 3 originators (refer to generation 0 in Figure 4-10) was shorter in comparison to the duration of the regulatory approval for their corresponding first generation biosimilars. These 3 originators are Remicade, Lantus and MabThera.



	0	1	2	3	4	5
Humatrope		690				
Genotropin		650				
Eprex/Erypo		537	538	221		
Neupogen		595	519	466	536	178
Remicade	526	558	441	450	392	
Gonal-f	688	577	513			
Lantus	438	463	397	599		
Enbrel	478	407	590			
Clexane		587	477			
Forsteo	740	404	408			
MabThera	460	497	434	132	129	188
Humira	529	475	429	379	458	245
Herceptin		442	487	441	394	
Humalog	546	315				
Avastin		410				

Figure 4-10: Number of days taken for regulatory approval of each generation of biosimilars developed using the different reference originators and their reference originators. Column 0 represents the number of days taken for regulatory approval for reference originators.

4.2.5. 95% Confidence Interval Calculations for Biosimilar Approvals in the EU

4.2.5.1. 95% Confidence Interval Calculation, without the Adjusted Cut-Off Date

To further understand the distribution of time taken for biosimilar regulatory approval, 95% confidence interval was calculated for biosimilar approvals on or prior to 31st July 2018 (entire study population). Refer to Table 4-25 below for the results of this calculation.

Mean	440.2927 days
Standard Deviation	134.4624
Population size	41
Standard Error of the Mean	20.9995 days
Lower Limit (Mean – 1.96*Standard Error of the Mean)	399.1336 days
Upper Limit (Mean + 1.96*Standard Error of the Mean)	481.4517 days

Table 4-25: Results from 95% confidence interval calculation for biosimilar approvals in the EU, on or prior to 31st July 2018.

Results show that 95% confidence interval falls between 399 to 481 days. Looking at the time it took for biosimilar regulatory approvals in Table 4-2 above, 25 out of the 41 biosimilars (60.9% of regulatory approvals) fall outside of the 95% confidence level. This indicates a tight cluster of a subset of data points around the mean, with 60.9% of the falling outside of the 95% confidence interval (refer to Figure 4-11 below).

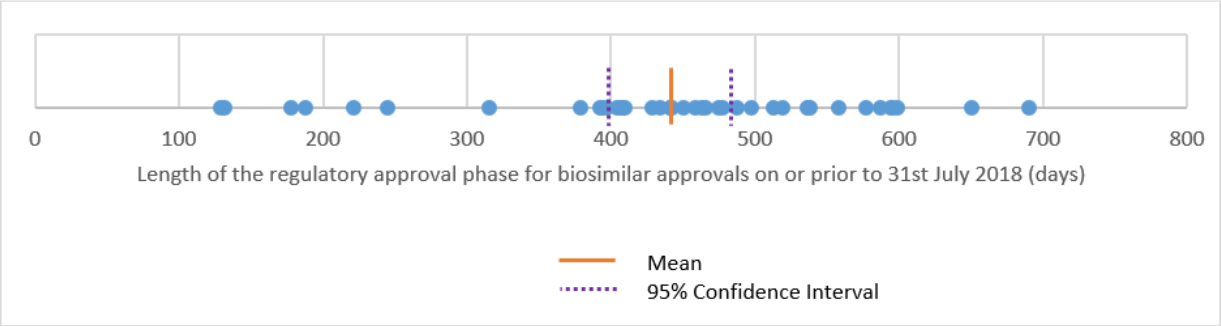


Figure 4-11: Mean and 95% confidence interval for biosimilar approvals in the EU, on or prior to 31st July 2018.

4.2.5.2. 95% Confidence Interval Calculation, using the Adjusted Cut-Off Date

The 95% Confidence Interval was then calculated for biosimilar approvals using the Adjusted Cut-Off Date. Refer to Table 4-26 below for the results of this calculation.

Mean	443.21 days
Standard Deviation	142.71 days
Population size	33
Standard Error of the Mean	24.8425 days
Lower Limit (Mean – 1.96*Standard Error of the Mean)	394.5208 days
Upper Limit (Mean + 1.96*Standard Error of the Mean)	491.9034 days

Table 4-26: Results from 95% confidence interval calculation for biosimilar approvals in the EU, on or prior to the Adjusted Cut-Off Date.

Results show that 95% confidence interval falls between 394 to 491 days. Looking at the time it took for biosimilar regulatory approvals in Table 4-2 above, 20 out of the 33 biosimilars (58.8% of regulatory approvals) falls outside of the 95% confidence level. Similar to the analysis in Section 4.2.51, this indicates tight cluster of a subset of data points around the mean are clustered around the mean, with the balance percentage of the data falling outside of the 95% confidence interval (refer to Figure 4-12 below).

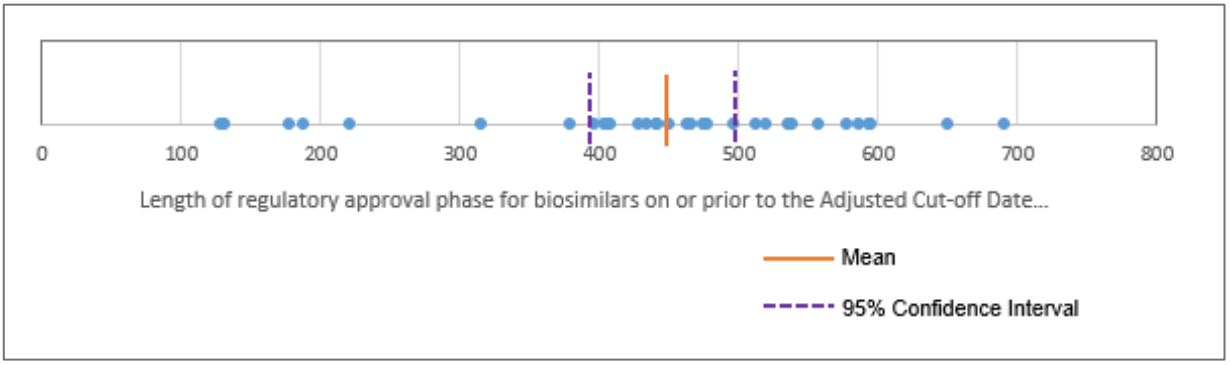


Figure 4-12: Mean and 95% confidence interval for biosimilar approvals in the EU, on or prior to the Adjusted Cut-Off Date.

4.2.6. Summary of Key Findings - Biosimilar Regulatory Approvals in the European Union

Based on the data analysis conducted indicate the following potential trends and findings for biosimilar regulatory approvals for 41 unique biosimilars:

- durations of regulatory approval phase for biosimilars approved in the EU vary significantly between the different application years, with the duration of regulatory approval phase decreasing in the later years,
- durations of regulatory approval phase for biosimilars approved in the EU shows significant variation between each subsequent generation of biosimilars, with the duration of regulatory approval phases decreasing with each subsequent generation
- durations of regulatory approval phase for biosimilars approved in the EU does not differ significantly between the different reference originators, and
- close to 60% of the data points were found to be outside of the 95% confidence interval, so it is going to be difficult to predict the expected duration of time a biosimilar application will take to gain regulatory approval phase in the EU.

The above trends and findings were found to be consistent when the investigation was conducted with sensitivity analysis using the Adjusted Cut-off Date to prevent right censoring by recent data points. The sensitivity analysis was conducted using 33 of the 41 unique biosimilar approvals in the EMA. In addition to the above trends, it is interesting to note that some of the 1st generation biosimilars had a lengthier regulatory approval phase compared to their reference originator biopharmaceuticals.

The next section of this chapter will summarize the findings from a similar data analysis conducted for biosimilar approvals in the United States, on or prior to 31st July 2018.

4.3. Biosimilar Regulatory Approvals in the United States

In the United States, all medicines including biosimilars, must be approved by the FDA and receives a license number from the Department of Health and Human Services USA, prior to being marketed and made available to patients. For biosimilars, the pathway to FDA approval commences when a biosimilar developer files for an aBLA using the 351(k) pathway (refer to Chapter 2, Section 2.5). For this study the date on which the FDA receives the aBLA is considered as the date on which the regulatory approval process commences (application date), and the date of FDA approval and licensure is considered as the regulatory approval date for biosimilars in Europe. The following sections look into the regulatory approval phase of biosimilars that have received FDA approval on or prior to 31st July 2018 with the aim of answering the current research question.

4.3.1. The Number of Biosimilars that have Received Regulatory Approval in the United States of America

In February 2012, the FDA issued three guidelines that paved the pathway for biosimilar applications and subsequent approvals[147]. From February 2012 to July 2018, twelve biosimilars have received FDA approvals (refer to Table 4-27 below).

Biosimilar (Proprietary Name)	Product (Proper) Name - as per FDA Definition	INN	Originator	Originator Company	Biosimilar Company	aBLA number	Date of aBLA (application date)	Biosimilar Date of Licensure (approval date)
Zarxio	filgrastim-sndz	filgrastim	Neupogen	Amgen Inc.	Sandoz Inc.	(BLA) 125553	8-May-14	6-Mar-15
Inflectra	infliximab-dyyb	infliximab	Remicade	Janssen Biotech	Celltrion Inc.	(BLA) 125544	8-Aug-14	5-Apr-15
Retacrit	epoetin alfa-epbx	epoetin alfa	Epogen/Procrit	Amgen Inc.	Hospira Inc.	(BLA) 125545	16-Dec-14	15-May-18
Erelzi	etanercept-szzs	etanercept	Enbrel	Amgen Inc	Sandoz Inc.	(BLA) 761042	30-Jul-15	30-Aug-16
Amjevita	adalimumab-atto	adalimunab	Humira	Abbvie Inc	Amgen Inc.	(BLA) 761024	25-Nov-15	23-Sep-16
Renflexis	infliximab-abda	infliximab	Remicade	Janssen Biotech	Samsung Bioepis Co. Ltd	(BLA) 761054	21-Mar-16	21-Apr-17
Cyltezo	adalimumab-adbm	adalimunab	Humira	Abbvie Inc	Boehringer Ingelheim Pharmaceuticals, Inc.	(BLA) 761058	27-Oct-16	25-Aug-17
Ogivri	trastuzumab-dkst	trastuzumab	Herceptin	Genentech, Inc.	Mylan GmbH	(BLA) 761074	3-Nov-16	1-Dec-17
Mvasi	bevacizumab-awwb	bevacizumab	Avastin	Genentech, Inc.	Amgen Inc.	(BLA) 761028	14-Nov-16	14-Sep-17
Fulphila	pegfilgrastim-jmdb	pegfilgrastim	Neulasta	Amgen Inc.	Mylan GmbH	(BLA) 761075	9-Dec-16	4-Jun-18
Ixifi	infliximab-qbtx	infliximab	Remicade	Janssen Biotech	Pfizer Inc.	(BLA) 761072	13-Feb-17	13-Dec-17
Nivestim	filgrastim-aafi	filgrastim	Neupogen	Amgen Inc.	Hospira Inc.	(BLA) 761080	21-Sep-17	20-Jul-18

Table 4-27: List of biosimilars approvals in the U.S., (Updated on 31st July 2018). The above list is in arranged from the earliest application to the latest application.

4.3.2. Trends in Time Taken for Biosimilar Regulatory Approvals vs. Date of Application

The time taken for the regulatory approval process was determined by calculating the number of days between the application date to the date which FDA notifies approval and licensure. Figure 4-13 below shows the time taken for regulatory approval for biosimilar approvals till 31st July 2018 as per Table 4-27. As there are only 12 available data points, the results are only interpreted as preliminary.

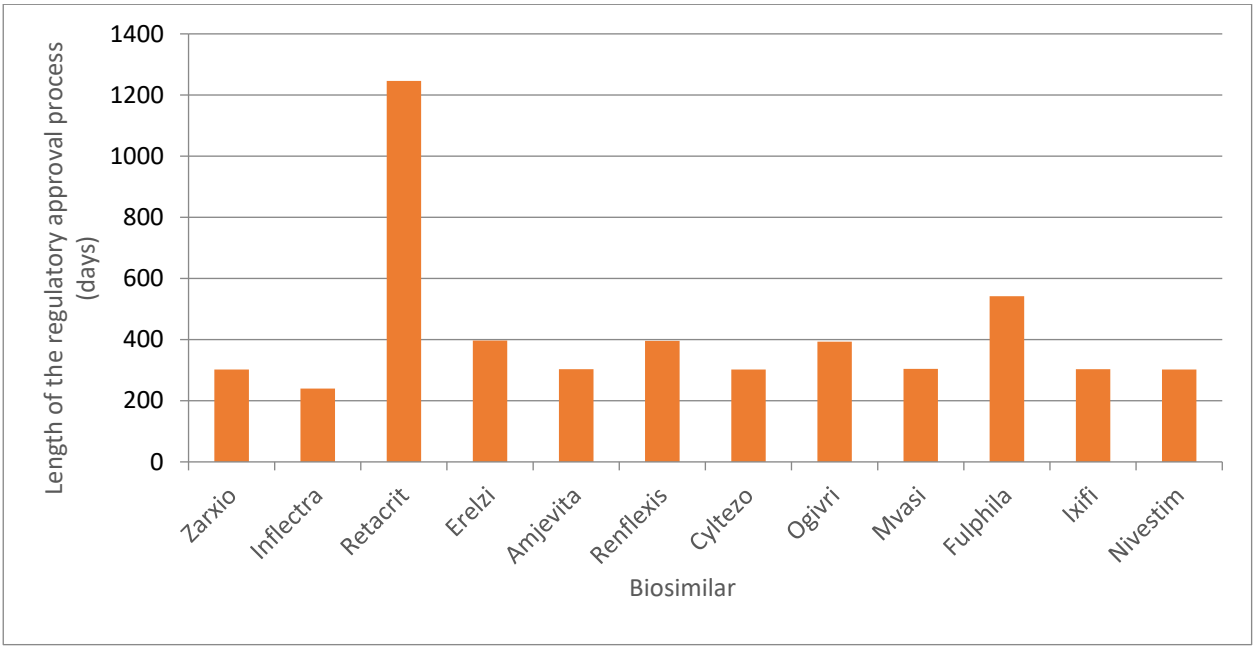


Figure 4-13: Time taken for regulatory approval for biosimilar approvals till 31st July 2018. The biosimilars were arranged in the order of application dates but not on a linear timescale.

The mean, standard deviation, median and interquartile range calculated for the time taken for regulatory approval are presented in Table 4-28.

Number of data points	**12**
Mean	419 days
Population standard deviation	260.45 days
Median	304.00 days
Quartile 1	302.00 days
Quartile 3	396.00 days
Interquartile range (Quartile 3 minus Quartile 1)	94.00 days

Table 4-28: Mean, standard deviation, median and interquartile range calculated.

A single factor ANOVA was conducted to see whether the mean time taken for regulatory approval differed significantly between the different application years. The data was arranged as shown in Table 4-29, whereby each application year column was taken as one population.

2014	2015	2016	2017
302	397	396	303
240	303	302	302
1246		393	
		304	
		542	

Table 4-29: Duration of the regulatory approval phase arranged by each application year to conduct a single factor ANOVA.

The null hypothesis tested is that the mean duration of the regulatory approval phase for each application year is the same. The results show that the F calculated value 0.5332 is less than the F critical value 4.0662 (refer to Table 4-30 below). Since the F calculated < F critical, null hypothesis is accepted. This indicates that between the different application years there is no statistically significant difference in the mean duration of the regulatory approval phase and hence the time taken for regulatory approval (P-value = 0.672232)

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	135646	3	45215.32	0.533242	0.672232	4.066181
Within Groups	678345.7	8	84793.21			
Total	813991.7	11				

Table 4-30: Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for each year of application.

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 1.830724
- Degree of freedom : 3
- P-value calculated : 0.608272

The null hypothesis tested is that the duration of the regulatory approval phase for each application year is the same. As the P-value calculated is more than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference between the duration of the regulatory approval phase for the different years. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test (refer to Table 4-30).

Results from the single factor ANOVA and Kruskal-Wallis test were confirmed with a regression analysis. A scatter plot was drawn to examine whether there was a correlation between the date of regulatory application and the time taken for regulatory approval (refer to Figure 4-14).

The linear trendline in Figure 4-14 indicates that the duration of the pre-market regulatory approval phase has decreased over time. The R^2 value was calculated to be 0.0665, which corresponds to 6.65% of the variability in the linear model. P-value calculated using this data is 0.4183 (refer to Figure 4-14 below). As the P-value calculated is greater than 0.05, this indicates statistically strong evidence to accept the null hypothesis, that the duration of the regulatory approval phase does not change over the years.

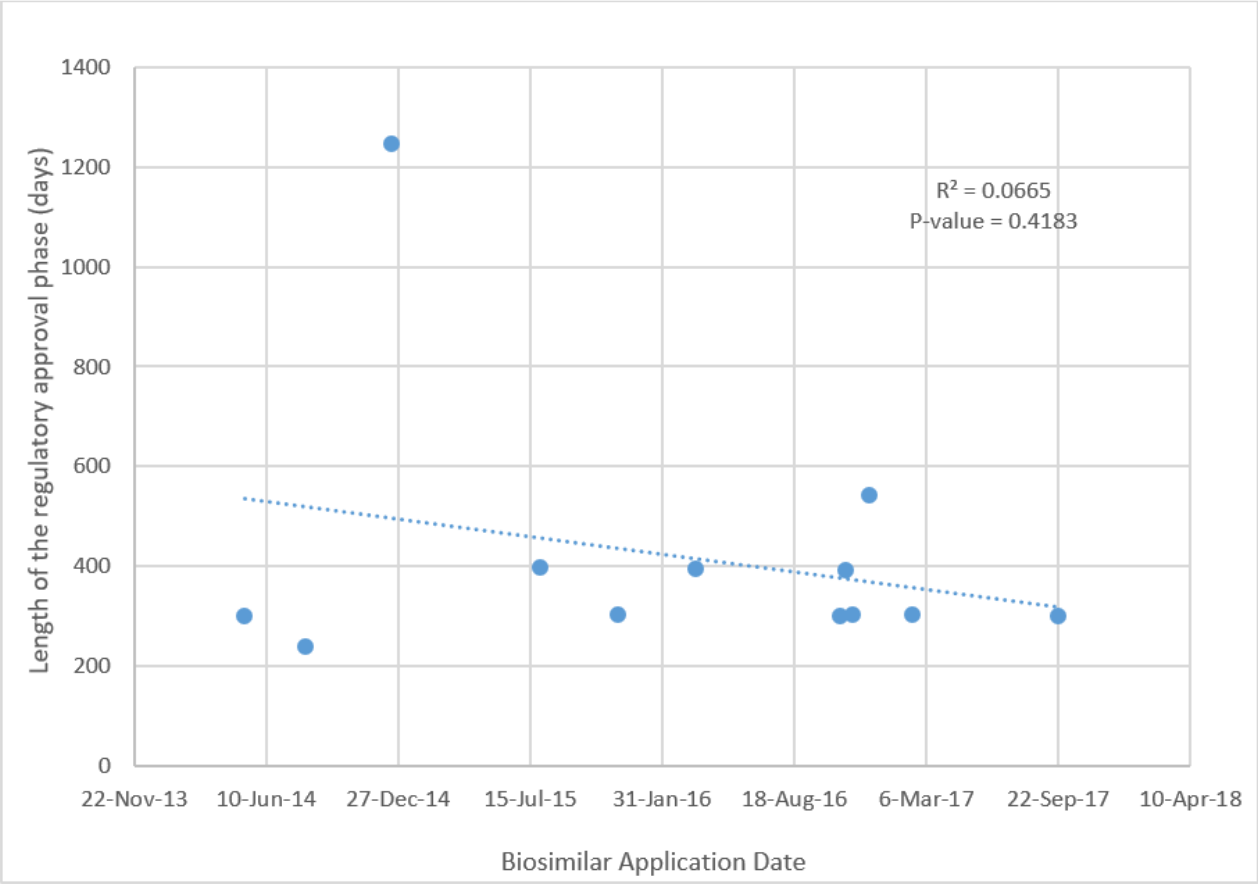


Figure 4-14: Duration of the pre-market regulatory approval phase vs. application date.

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : 0.07861
- Number of data points : 12
- P-value calculated : 0.808155

The null hypothesis tested is that the duration of the regulatory approval phase does not change with different application date. As the P-value calculated is greater than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference in the duration of the regulatory approval phase over time. The results from the Spearman's Rank correlation test is in congruence with the results from the regression analysis above.

4.3.2.1. Sensitivity Analysis : Investigation of the need for an Adjusted Cut-Off Date

Unlike in the European Union, the scatter diagram looking at regulatory approval phase versus the application date for biosimilars approved in the United States did not indicate any obvious potential right-censoring of data. However, to statistically examine whether there is a skewing sensitivity of R^2 value was calculated at different time points to compare with overall R^2. This was conducted to identify whether there is an inflection point in R^2 value over this time period. Figure 4-15 below shows the different dates selected for calculation of R^2. Table 4-31 summarizes the variation in R^2 sensitivity in comparison to overall R^2 value.

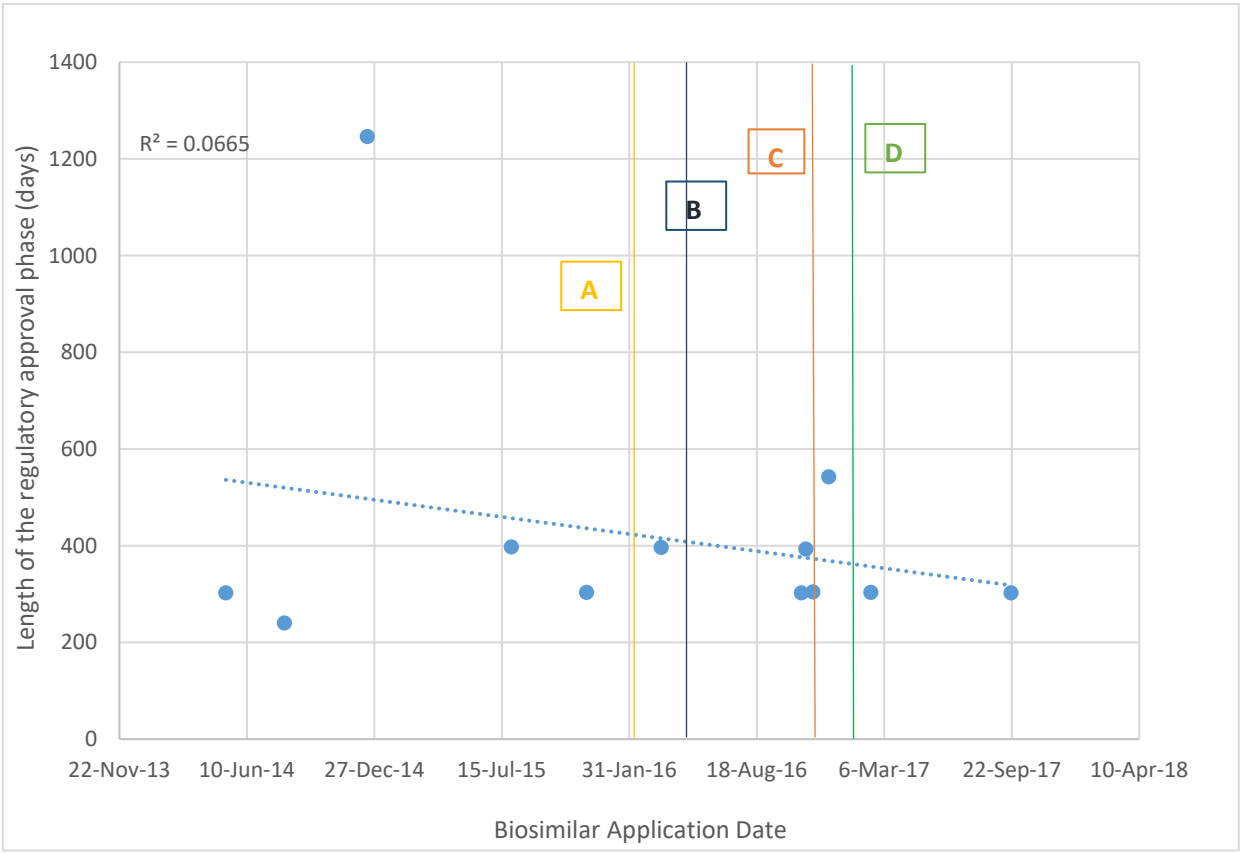


Figure 4-15: Indicates the different dates selected to calculate the sensitivity of R^2 values.

Corresponding Figure 4-15 Indicator	Details	R^2 Values
Not Applicable	Overall R^2 value	R^2 = 0.0665
A	Biosimilar Applications prior to 01st Feb 2016	R^2 = 0.001
B	Biosimilar Applications prior to 01st Apr 2016	R^2 = 0.0086
C	Biosimilar Applications prior to 01st Dec 2016	R^2 = 0.0598
D	Biosimilar Applications prior to 01st Jan 2017	R^2 = 0.0335

Table 4-31: Summary of R^2 values at different cut-off dates.

Based on the calculated values for R^2 in Table 4-31, there is an inflection point for R^2 values in the period between 01st April 2016 to 01st December 2016. There were three biosimilar applications in this period of time (refer to Table 4-27). It is interesting to note that with the removal of the very recent approvals the time taken for regulatory approval seem to be consistent (refer to Figures 4-16 and 4-17 below).

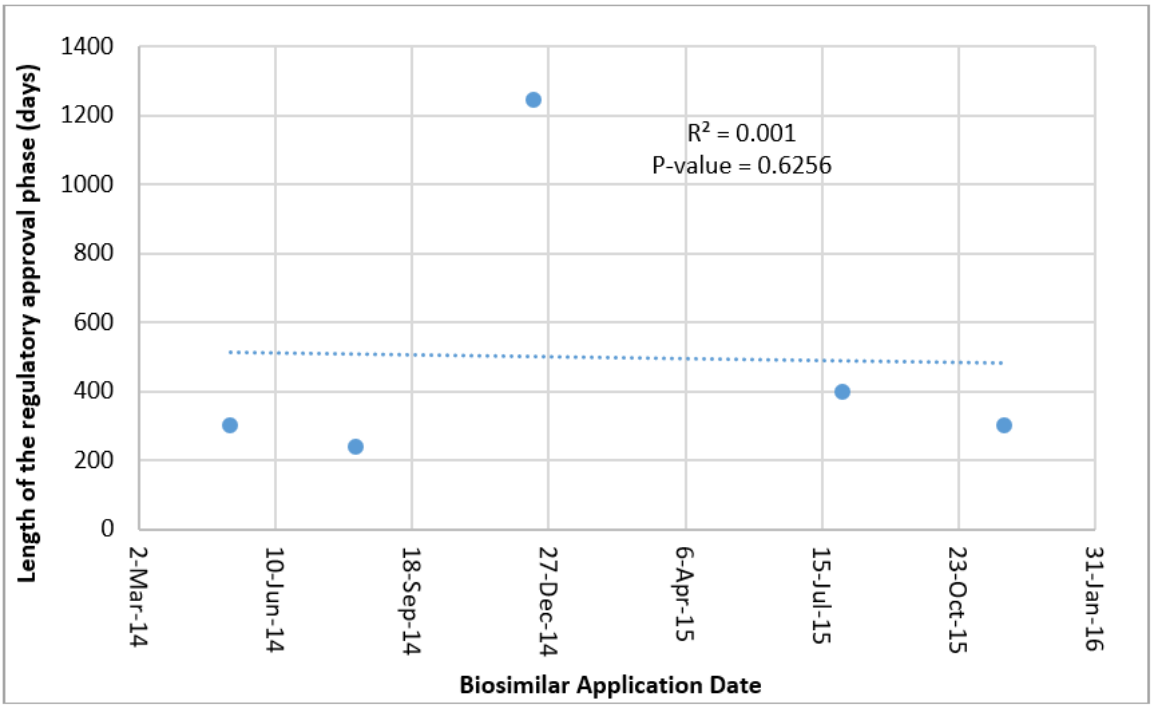


Figure 4-16: Duration of the pre-market regulatory approval phase vs. application date, for biosimilar approvals till 01st February 2016.

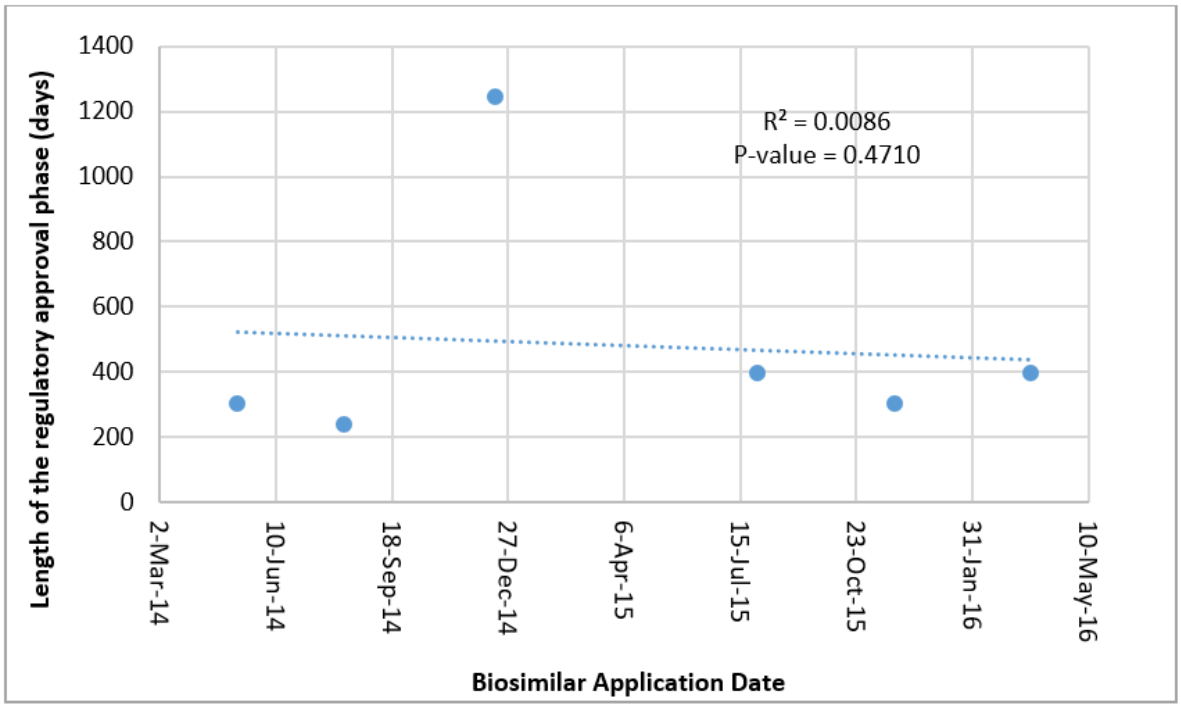


Figure 4-17: Duration of the pre-market regulatory approval phase vs. application date, for biosimilar approvals till 01st April 2016.

Whilst, the R^2 potential inflection after 01st April 2016, it was decided that for generational (Section 4.3.3) and reference originator analysis (Section 4.3.4) an Adjusted Cut-Off Date is not necessary as the explanatory variable in these scenarios is categorical rather than linear. It should however be noted here that there was one extreme outlier (Retacrit) (2.37 times of standard deviations from the mean of the first mover biosimilars) that was considered likely to skew the data. This is dealt with below (see 4.3.2.2).

4.3.2.2. Trends in Time Taken for Biosimilar Regulatory Approvals vs. Date of Application, after removing Retacrit from the Study Population

The time taken for regulatory approval of Retacrit was 1,246 days, which is 2.972 times the population average and 4.788 times the population standard deviation. Retacrit was developed and marketed by Pfizer Inc. The regulatory approval for Retacrit was delayed due to a request for more data by the FDA after the initial evaluation of the application in 2015[148] and was further delayed due to regulatory concerns over the manufacturing site in 2017[149]. The data analysis was conducted with and without Retacrit, as these delays due to the regulatory concerns at the manufacturing plant may

potentially confound the data analysis. The mean, standard deviation, median and interquartile range calculated for the time taken for regulatory approval, without Retacrit, are presented in Table 4-32.

Number of data points	**11**
Mean	344.00 days
Population standard deviation	78.73 days
Median	303.00 days
Interquartile range	93.00 days

Table 4-32: Mean and standard deviation calculated, without Retacrit.

A single factor ANOVA was conducted to see whether the mean time taken for regulatory approval differed significantly between the different application years. The data was arranged as shown in Table 4-33, whereby each application year column was taken as one population.

2014	2015	2016	2017
302	397	396	303
240	303	302	302
		393	
		304	
		542	

Table 4-33: Duration of the regulatory approval phase, without Retacrit, arranged by each application year to conduct a single factor ANOVA.

The null hypothesis tested is that the mean duration of the regulatory approval phase for each application year is the same. The results show that the F calculated value 1.2344 is less than the F critical value 4.3468 (refer to Table 4-34 below). Since the F calculated < F critical, null hypothesis is accepted (P-value = 0.3668). This indicates that there is no statistically significant difference in the mean duration of the regulatory approval phase between the different application years. As such removing Retacrit has not changed the outcome from the single-factor ANOVA calculations (refer to section 4.3.2). However, it must be remembered that this finding must be regarded as provisional and could change in the next few years, with more biosimilar applications.

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	23592.3	3	7864.1	1.234395	0.3668	4.346831
Within Groups	44595.7	7	6370.814			
Total	68188	10				

Table 4-34: Results from the single-factor ANOVA, without Retacrit, testing the differences in mean duration of regulatory phase for each year of application.

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 5.306977
- Degree of freedom : 3
- P-value calculated : 0.150650

The null hypothesis tested is that the duration of the regulatory approval phase for each application year is the same. As the P-value calculated is more than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference between the duration of the regulatory approval phase for the different years, without Retacrit. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test (refer to Table 4-34).

Furthermore, the results from the single factor ANOVA and Kruskal-Wallis test were confirmed with this regression analysis. A scatter plot was drawn to examine whether there was a correlation between the date of regulatory application and the time taken for regulatory approval (refer to Figure 4-18). The R^2 value was calculated to be 0.079, which corresponds to 7.9% of the variability in the linear model. P-value calculated using this data is 0.4024 (refer to Figure 4-18 below). As the P-value calculated is greater than 0.05, this indicates statistically strong evidence to accept the null hypothesis, that the duration of the regulatory approval phase does not change over the years.

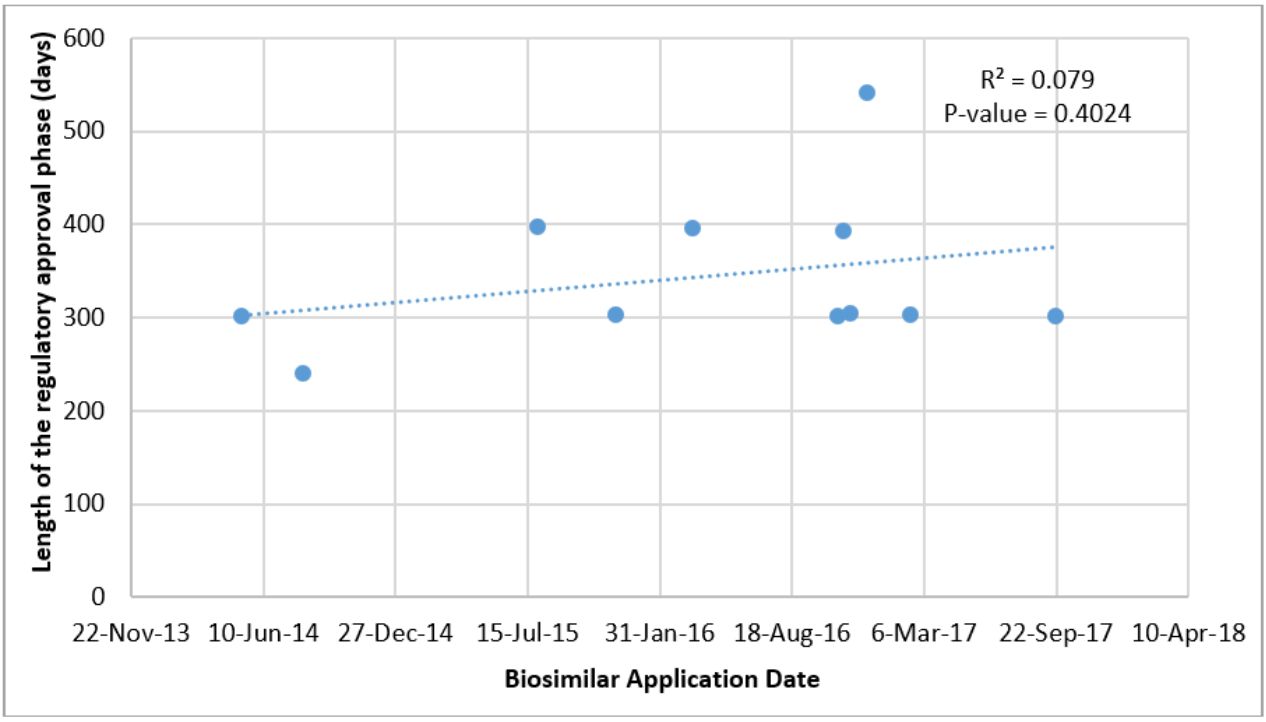


Figure 4-18: Duration of the pre-market regulatory approval phase vs. application date, with Retacrit removed.

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression test assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : 0.220455
- Number of data points : 11
- P-value calculated : 0.5149

The null hypothesis tested is that the duration of the regulatory approval phase does not change with different application date. As the P-value calculated is greater than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference in the duration of the regulatory approval phase over time, without Retacrit. The results from the Spearman's Rank correlation test is in congruence with the results from the regression analysis above.

4.3.3. Trends in Time Taken for Biosimilar Regulatory Approvals vs. Generation

As discussed in the analysis for biosimilars approvals by the EMA, biosimilar applications to the FDA must show high similarity to and no clinically meaningful differences from an existing FDA approved originator[150]. As such grouping biosimilars referencing the same originators, there is a direct comparison of molecules of similar attributes. Table 4-35 below shows the biosimilars applications in the U.S. grouped under each generation and the corresponding durations of their regulatory approval phase. From Table 4-35, it can be observed that there are eight 1st generation biosimilar approvals showing that biosimilars have been developed using eight reference originators. Furthermore, there are three 2nd generation and one 3rd generation biosimilar applications and subsequent approvals.

Generation	Name of Biosimilar	Duration of regulatory approval phase (days)
1st mover biosimilars	1.1 Zarxio	302
	1.2 Inflectra	240
	1.3 Retacrit	1246
	1.4 Erelzi	397
	1.5 Amjevita	303
	1.6 Ogivri	393
	1.7 Mvasi	304
	1.8 Fulphila	542
2nd mover biosimilars	2.1 Renflexis	396
	2.2 Cyletzo	302
	2.3 Nivestim	302
3rd mover biosimilars	3.1 Ixifi	303

Table 4-35: Biosimilar applications grouped in generations and corresponding duration of their regulatory approval phase.

Means, standard deviations and medians of each generation was calculated (refer to Table 4-36) to observe whether there are variations and/or trends in the time taken for regulatory approval across the different generations. Means and standard deviations are also graphically represented in Figure 4-19 below.

Generation	Number of biosimilars	Mean (days)	Standard Deviation (days)	Median (days)
1	8	466	328.43	348.5
2	3	333	54.27	302
3	1	Not Applicable	Not Applicable	Not Applicable

Table 4-36: Means, standard deviations and medians calculated for each generation.

Figure 4-19 below, indicates a possible decrease in mean time taken for regulatory approval against ascending order of generations. It should be noted that biosimilar Ixifi is the only 3rd generation biosimilar approved by the FDA as of 31st July 2018.

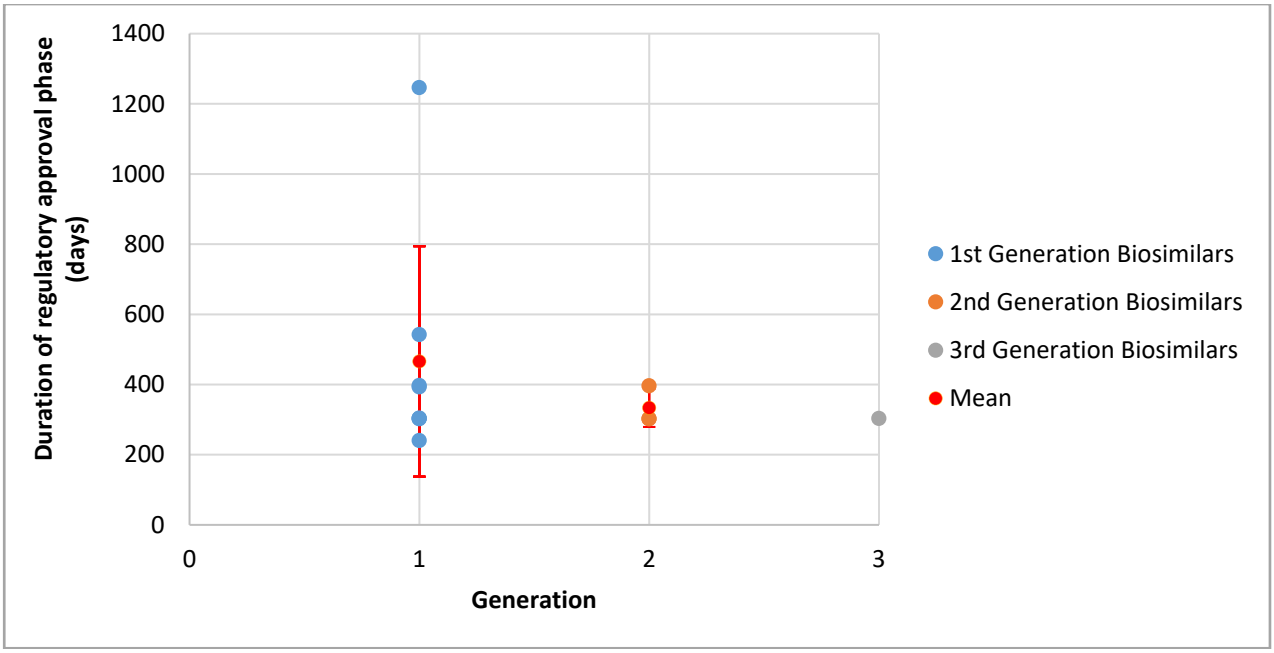


Figure 4-19: Time taken for regulatory approvals vs. generation. Means and standard deviations calculated for each generation is indicated in red.

Furthermore, a single factor ANOVA was conducted to test the null hypothesis that the mean duration of the regulatory approval phase for each generation is the same. To conduct a single factor ANOVA the data was arranged as shown in Table 4-37, whereby each generation column was taken as one population. The results show that the calculated F value 0.3137 is less than the F critical value 4.2565 (refer to Table 4-38 below). Since the F calculated is less than F critical, null hypothesis is accepted, indicating that there is no statistical difference in the mean duration of the regulatory approval phase between the different generations (P-value 0.738399).

1st mover biosimilars	2nd mover biosimilars	3rd mover biosimilars
302	396	303
240	302	
1246	302	
397		
303		
393		
304		
542		

Table 4-37: Duration of the regulatory approval phase arranged by each generation to conduct a single factor ANOVA.

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	53050.125	2	26525.06	0.313724	0.738399	4.256495
Within Groups	760941.5417	9	84549.06			
Total	813991.6667	11				

Table 4-38: *Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for each generation.*

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 0.902802
- Degree of freedom : 2
- P-value calculated : 0.636735

The null hypothesis tested is that the duration of the regulatory approval phase for each generation is the same. As the P-value calculated is more than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference between the duration of the regulatory approval phase for the different generations. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test (refer to Table 4-38).

Results from the single factor ANOVA and Kruskal-Wallis test were confirmed with a regression analysis (refer to Figure 4-20 below). R^2 value was calculated to be 0.06, which

corresponds to an 6% of the variability in the linear model. P-value calculated using this data is 0.4431. As the P-value calculated is greater than 0.05, this indicates statistically strong evidence to accept the null hypothesis, that the duration of the regulatory approval phase does not change over generations.

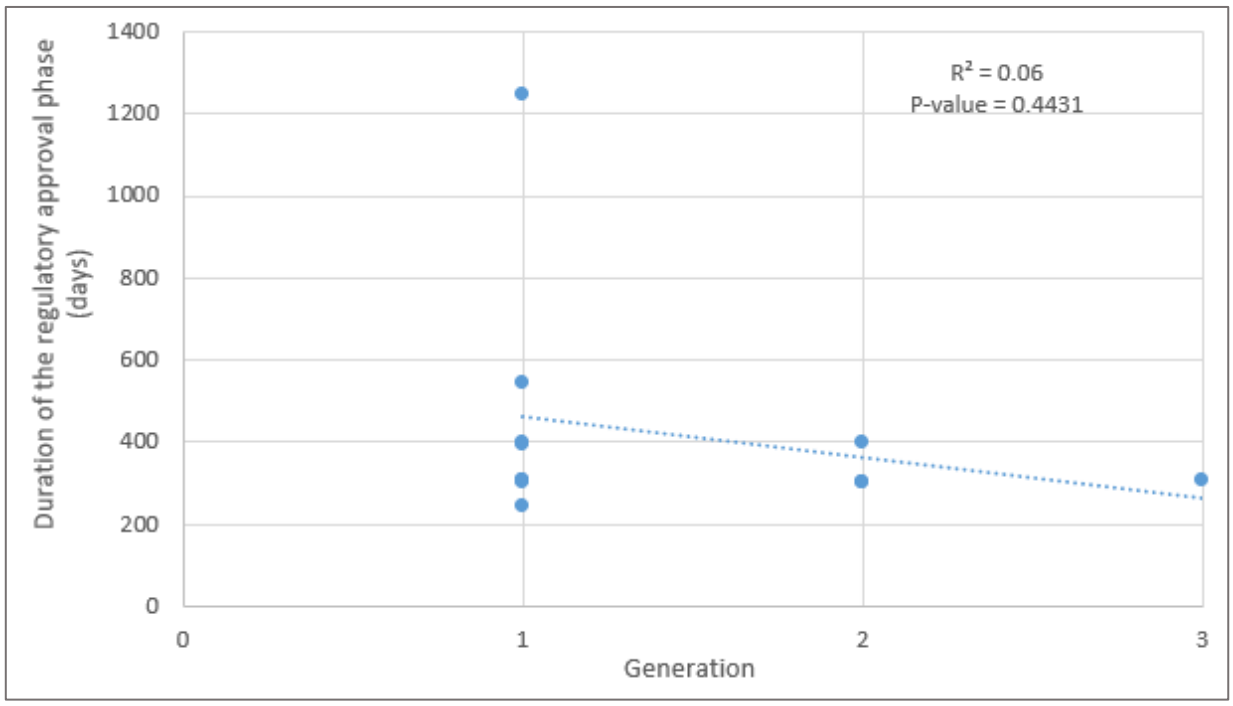


Figure 4-20: Duration of the regulatory approval phase vs. generation.

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression test assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : -0.27345
- Number of data points : 12
- P-value calculated : 0.3898

The null hypothesis tested is that the duration of the regulatory approval phase does not change with different generations. As the P-value calculated is greater than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference in the duration of the

regulatory approval phase over generations. The results from the Spearman's Rank correlation test is in congruence with the results from the regression analysis above.

4.3.3.1. Trends in Time Taken for Biosimilar Regulatory Approvals vs. Generation, without Retacrit

The data analysis was then conducted without Retacrit, as discussed in section 4.3.2.2., the delays experienced were due to the regulatory concerns at the manufacturing plant for Retacrit. It was suspected that this extreme outlier might confound the data analysis. Means, standard deviations and medians without Retacrit, for each generation were calculated (refer to Table 4-39 below) to observe whether there are variations and/or trends in the time taken for regulatory approval between the different generations. Means and standard deviations are also graphically represented in Figure 4-21 below.

Generation	Number of biosimilars	Mean (days)	Standard Deviation (days)	Median (days)
1	7	354	99.59	304
2	3	333	54.27	302
3	1	Not Applicable	Not Applicable	Not Applicable

Table 4-39: Means, standard deviations and medians calculated for each generation, without including Retacrit.

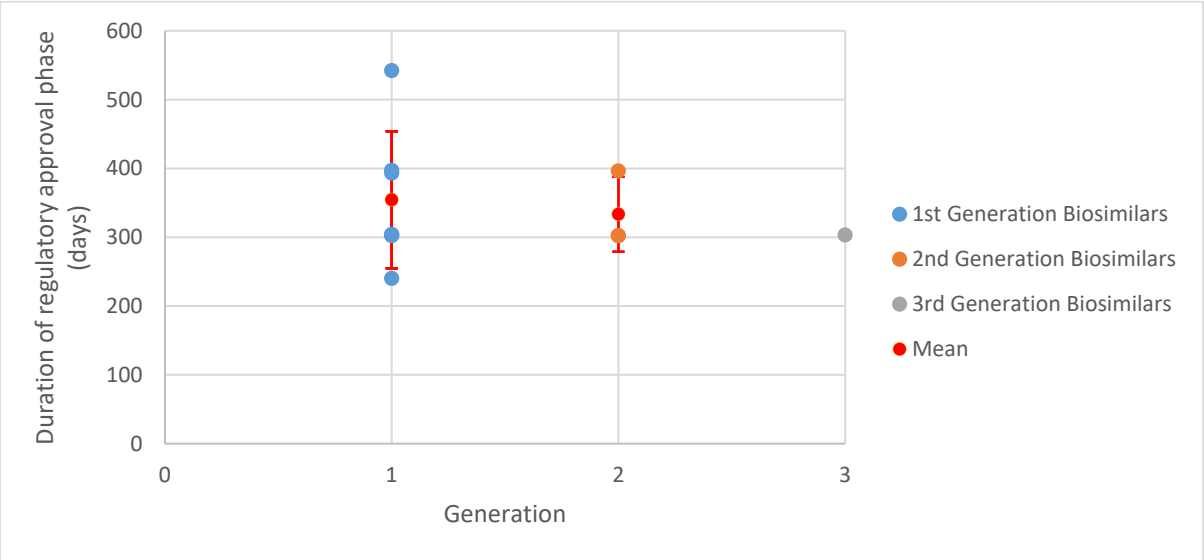


Figure 4-21: Time taken for regulatory approvals vs. generation, without Retacrit. Means and standard deviations calculated for each generation is indicated in red.

Figure 4-21 above, indicates a possible decrease in mean time taken for regulatory approval against ascending order of generations.

A single factor ANOVA was conducted to test the null hypothesis that the mean duration of the regulatory approval phase for each generation is the same. To conduct a single factor ANOVA the data was arranged as shown in Table 4-40, whereby each generation column was taken as one population. Retacrit was excluded from this data. The results show that the calculated F value 0.1702 is less than the F critical value 4.45897 (refer to Table 4-41 below). Since the F calculated is less than F critical, null hypothesis is accepted, indicating that there is no statistical difference in the duration of the regulatory approval phase and hence the time taken for regulatory approval between the different generations (P-value 0.846439). Thus, the removal of Retacrit has only slightly changed the F-calculated value from the single-factor ANOVA calculations in this scenario and has not changed the overall conclusion.

1st mover biosimilars	**2nd mover biosimilars**	**3rd mover biosimilars**
302	396	303
240	302	
397	302	
303		
393		
304		
542		

Table 4-40: Duration of the regulatory approval phase arranged by each generation, without Retacrit, to conduct a single factor ANOVA.

Source of Variation	*SS*	*df*	*MS*	*F calculated*	*P-value*	*F critical*
Between Groups	2783.619048	2	1391.81	0.170241	0.846439	4.45897
Within Groups	65404.38095	8	8175.548			
Total	68188	10				

Table 4-41: *Results from the single-factor ANOVA testing the differences in mean duration of regulatory phase for each generation.*

Furthermore, non-parametric Kruskal-Wallis test was conducted in addition to ANOVA testing. ANOVA tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of

the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Kruskal-Wallis test is as follows:

- K statistic : 0.465116
- Degree of freedom : 2
- P-value calculated : 0.792504

The null hypothesis tested is that the duration of the regulatory approval phase for each generation is the same. As the P-value calculated is more than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference between the duration of the regulatory approval phase for the different generations, without Retacrit. The results from the Kruskal-Wallis test is in congruence with the results from the ANOVA test (refer to Table 4-41).

Results from the single factor ANOVA was confirmed with a regression analysis (refer to Figure 4-22 below). R^2 value was calculated to be 0.0403, which corresponds to an 4.03% of the variability in the linear model. P-value calculated using this data is 0.5538. As the P-value calculated is greater than 0.05, this indicates statistically strong evidence to accept the null hypothesis, that the duration of the regulatory approval phase does not change over generations.

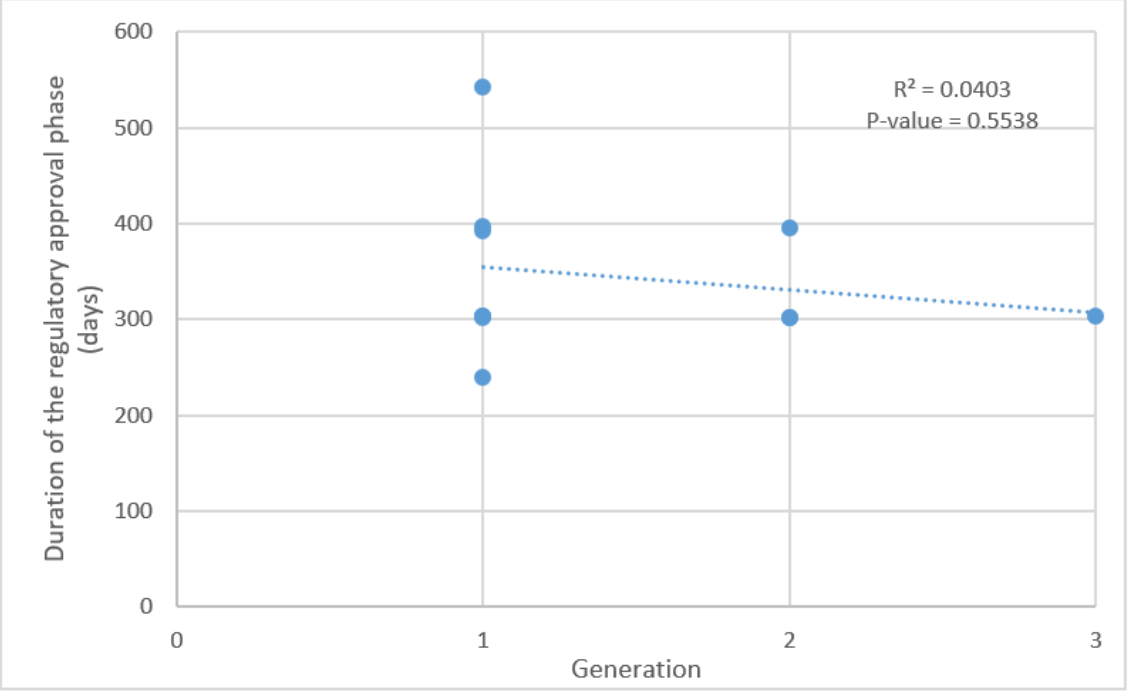


Figure 4-22: Duration of the regulatory approval phase, without Retacrit vs. generation.

Furthermore, non-parametric Spearman's Rank correlation coefficient was calculated in addition to regression testing. Regression tests assume that the data are normally distributed. In comparison, non-parametric tests do not have assumptions related any underlying distribution. This increases the robustness of the statistical model used in this thesis, especially considering that the population of data analyzed is small. The results from the Spearman's Rank correlation coefficient calculation is as follows:

- Spearman's rank correlation coefficient : -0.19949
- Number of data points : 11
- P-value calculated : 0.55647

The null hypothesis tested is that the duration of the regulatory approval phase does not change with different generations, without Retacrit. As the P-value calculated is greater than 0.05, the null hypothesis is accepted. This indicates that there is no statistically significant difference in the duration of the regulatory approval phase over generations, without Retacrit. The results from the Spearman's Rank correlation test is in congruence with the results from the regression analysis above.

4.3.4. Trends in Time Taken for Biosimilar Regulatory Approvals for each Reference Originator

This section details the findings from the data analysis conducted to investigate whether the molecular nature or class of drug affects the duration of the regulatory approval phase of biosimilars. To identify whether the molecular nature or class of drugs had any effect on the regulatory approval duration, biosimilar approvals were grouped against their reference originator. Table 4-42 shows unique biosimilar approvals against their reference originator. Table 4-42 also shows that as of 31st July 2018 there have been biosimilar applications and subsequent regulatory approvals for biosimilars referencing 8 different originator biopharmaceuticals. Out of these 8 reference originators:

- 1 reference originator has three generations of biosimilars (highlighted in yellow),
- 2 reference originators have two generations of biosimilars (highlighted in grey),

- 5 reference originators have only one generation of biosimilars (highlighted in green).

#	Originator	1st Generation	2nd Generation	3rd Generation
1	Neupogen	Zarxio	Nivestim	
2	Remicade	Inflectra	Renflexis	Ixifi
3	Epogen/Procrit	Retacrit		
4	Enbrel	Erelzi		
5	Humira	Amjevita	Cyletzo	
6	Avastin	Mvasi		
7	Herceptin	Ogivri		
8	Neulasta	Fulphila		

Table 4-42: Summary of reference originators and the corresponding generations of biosimilars.

The duration of the regulatory approval phase for each generation of biosimilars referencing the different originators was graphically represented to identify any trends (refer to Figure 4-23 below). Figure 4-23 shows that for the data available, except for the Epogen/Procrit biosimilar (Retacrit), the number of days for regulatory approval remains consistent across the generations, for three different reference originators. However, the data set is of limited size, so this conclusion must be regarded as provisional at this stage. No further statistical analysis was conducted due to limited availability of data.

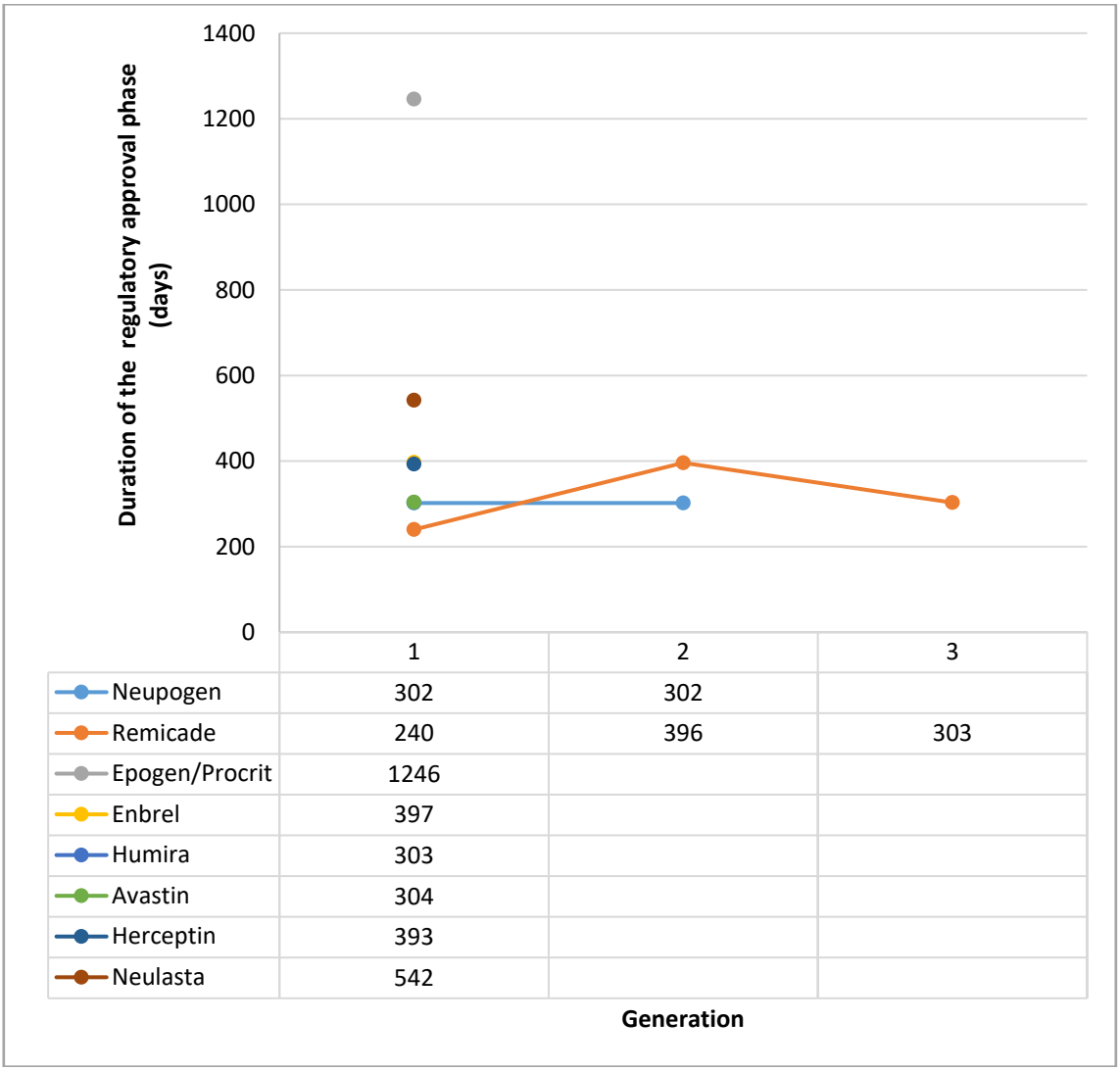


Figure 4-23: Number of days taken for regulatory approval of each generation of biosimilars developed referencing different originators.

4.3.5. 95% Confidence Interval for all Biosimilar Approvals in the United States

To further understand the distribution of time taken for biosimilar regulatory approval, 95% confidence interval was calculated for biosimilar approvals on or prior to 31st July 2018 (entire study population). Refer to Table 4-43 below for the results of this calculation.

Mean	419.1667 days
Standard Deviation	272.0280 days
Population size	12
Standard Error of the Mean	78.5277 days
Lower Limit (Mean – 1.96*Standard Error of the Mean)	265.2523
Upper Limit (Mean + 1.96*Standard Error of the Mean)	573.0810

Table 4-43: Results from 95% confidence interval calculation for biosimilar approvals in the U.S.

Results show that 95% confidence interval lies between 265 to 573 days. Looking at the time it took for biosimilar regulatory approvals in Table 4-35 above, only 2 out of the 12 biosimilars falls outside of the 95% confidence level. These two biosimilars are Retacrit and Inflectra, with time taken for regulatory approvals being 1246 days and 240 days respectively. This indicates that an expected large percentage of data points fall within the 95% confidence interval (refer to Figure 4-24 below).

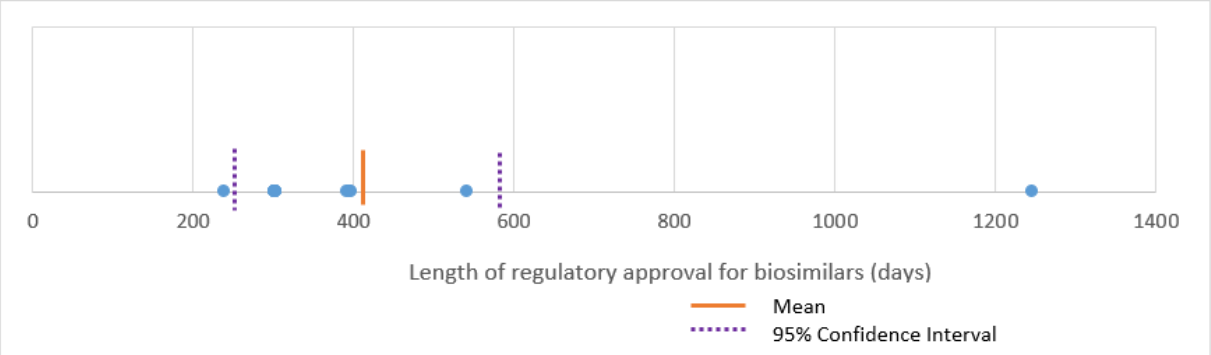


Figure 4-24: Mean and 95% confidence interval for biosimilar approvals in the U.S.

4.3.5.1. 95% Confidence Interval Calculation, without Retacrit

The 95% Confidence Interval was then calculated for biosimilar approvals in the US, without Retacrit. Refer to Table 4-44 below for the results of this calculation. Results show that 95% confidence interval lies between 295 to 392 days. As expected, the 95% confidence interval without Retacrit was much narrower than with Retracrit. Looking at the time it took for biosimilar regulatory approvals in Table 4-35 above, 4 out of the 11 biosimilars falls outside of the 95% confidence level. Of the four biosimilars, Erelzi and Renflexis fall marginally outside the 95% confidence interval with durations of regulatory approval being 295 and 392 days respectively. Inflectra (240 days) and Fulphila (540 days) are the other two biosimilars that fall outside of the 95% confidence interval. Erelzi and Renflexis marginally, 295 and 396 days respectively (refer to Figure 4-25 below).

Mean	344 days
Standard Deviation	82.5760 days
Population size	11
Standard Error of the Mean	24.8976 days
Lower Limit (Mean – 1.96*Standard Error of the Mean)	295.2006 days
Upper Limit (Mean + 1.96*Standard Error of the Mean)	392.7993 days

Table 4-44: *Results from 95% confidence interval calculation for biosimilar approvals in the U.S., without Retacrit.*

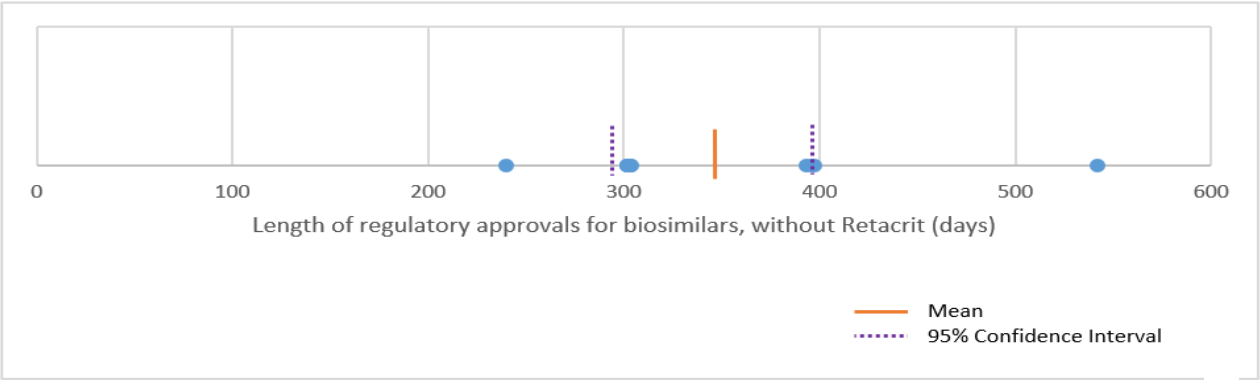


Figure 4-25: Mean and 95% confidence interval for biosimilar approvals in the U.S., without Retacrit.

4.3.6. Summary of Key Findings - Biosimilar Regulatory Approvals in the United States of America

Based on the data analysis conducted indicate the following potential trends and findings.

I. Durations of regulatory approval phase for biosimilars approved in the U.S does not vary significantly over time and, interestingly, is consistent even after the removal of more recent approvals. However, as noted above, the U.S. data set is small, so this conclusion must be regarded as provisional.

II. Durations of regulatory approval phase for biosimilars approved in the U.S. shows no statistical difference between each subsequent generation of biosimilars, with the average duration of regulatory approval phases remaining consistent with each subsequent generation.

III. Durations of regulatory approval phase for biosimilars approved in the U.S. does not vary significantly between the different reference originators, but this requires additional research, as the data set is currently small.

IV. As most of the data points were found to be inside or marginally outside of the 95% confidence interval, it is likely that most future biosimilar applications will take between 295 to 392 days from application of aBLA to receive regulatory approval from the FDA.

Furthermore, the presence of biosimilar Retacrit appears to have a confounding effect on the analysis of the duration of regulatory phase of biosimilars over time and with the different reference originators.

When comparing the EU EMA biosimilar approvals to U.S. FDA approvals:

I. EMA has approved 41 unique biosimilars in a period of 15 years. corresponding to 2.7 applications per year. FDA has approved 12 biosimilars in a period of 6.5 years, corresponding to 1.84 applications per year.
II. The mean time taken for EMA approval of biosimilars is 440.29 days for biosimilar approvals till the 31st July 2018 and 466.50 days for biosimilar approvals till the Adjusted Cut-Off Date. In comparison the mean time taken for FDA approval of biosimilars is 419 days. However, after removing the anomaly, Retacrit, the mean duration calculated for regulatory approval in the U.S. is 344 days. This is 96 days faster than Europe.
III. Europe has up to 5 generations of biosimilars and, in comparison U.S. has up to 3 generations of biosimilars.
IV. The EMA has approved biosimilars referencing 15 originators and, in comparison the FDA has approved biosimilars referencing 8 originators.

4.4. Chapter Conclusion

The data analysis presented in this chapter investigated how passage of time, generations and reference originator have affected the duration of the pre-market regulatory approval phase of biosimilars approved in the EU and the U.S on or prior to 31st July 2018.

The findings indicate that in the EU the earlier applicants and earlier generations of biosimilar applicants had a longer duration of regulatory approval phase. The analysis shows that in the EU, the durations of the regulatory approval phase for biosimilars do not seem to have been impacted by the reference originator. The analysis also shows that in the U.S. the durations of the regulatory approval phase is consistent for all approvals and the three factors, i.e. passage of time, generations and reference originator, do not seem to have an individually impacted on the duration of regulatory

approval phase of biosimilars, although the data on reference originator must be regarded as provisional. As the available number of biosimilar approvals in the U.S. is limited, a larger extent of variation due to chance differences, and may not have had the power to detect a difference is expected. Furthermore, in this chapter the comparison between EU biosimilar approvals and the U.S. biosimilar approvals was made (refer to section 4.3.6). The next chapter of this thesis discusses the contributions of the thesis and suggests directions for further research.

CHAPTER 5: DISCUSSION AND FUTURE RESEARCH

5.1. Introduction to the Chapter

This thesis addressed the research question whether first mover advantage (FMA) exists during the regulatory approval phase for first mover biosimilars commercialized in the EU and the U.S. (refer to Chapter 2 section 2.7 Figure 2-3). Being the first to enter a new market can be costly but also can be profitable[53]. If first movers have advantages in access to information, intellectual property, and subsequent gains in product line breadth, product quality and long-term market share, they will profit from first entry [53,64] (refer to Chapter 2 section 2.3.). However, if late entrants can perform better than first movers, through a shorter regulatory approval phase, better positioning, branding, and/or superior technology, these firms could benefit more by entering after the first movers[40] (refer to Chapter 2 section 2.4.).

With lack of patent protection and lack of regulatory provisions that provide exclusivity periods for first to market biosimilars, biosimilars at present rely on market performance to recoup their investment. Hence, if there is no first mover advantage during the regulatory approval phase, it will weaken the incentives for a biosimilar developer to overcome the market entry barriers and navigate the challenging development process. Chapter 3 of this thesis identified ways to quantify and measure the duration of the regulatory approval phase for biosimilars. The trends in the time taken for regulatory approval phase for biosimilars approved by the EMA and FDA prior to 31st July 2018, were investigated. These trends were analyzed with respect to date(s) of regulatory application(s) (Chapter 4 sections 4.2.2. and 4.3.3.), different generations of biosimilars (Chapter 4 sections 4.2.3. and 4.3.3.) and reference originators (Chapter 4 sections 4.2.4. and 4.3.4.). The results of these analyzes were presented in Chapter 4 of this thesis. The current chapter discusses the implications of the research findings for first and later mover biosimilars, potential contributions of this thesis to the industry and policy as well as suggestions for future research.

5.2. Contributions of this Research

The focus of this thesis was on biosimilars that have received regulatory approvals in the EU and the U.S. This section of the thesis reflects on the findings of Chapter 4 for biosimilars that have received regulatory approval in these two jurisdictions.

5.2.1. European Union

In the EU, 50 biosimilars had received regulatory approval from the EMA by 31st July 2018. From these 50, 41 unique approvals (refer to Chapter 4 section 4.2.1.2. on unique and non-unique biosimilar applications) were investigated in this thesis. The data analysis discovered the following trends for biosimilar approvals in the EU:

I. The durations of the regulatory approval phase for biosimilars have changed significantly over time (refer to Chapter 4 section 4.2.2.).
II. The durations of regulatory approval phase show significant change with each subsequent generation of biosimilars, with the average duration of regulatory approval phase decreasing with each subsequent generation (refer to Chapter 4 section 4.2.2.).
III. The durations of regulatory approval phase do not differ significantly between biosimilars referencing different originator biologics (refer to Chapter 4 section 4.2.3.).

In addition, within the sample set of data used in this study, close to 60% of biosimilar approvals fall outside the calculated 95% confidence interval for the duration taken for biosimilar regulatory approvals (refer to Chapter 4 section 4.2.5.). Thus, it will be difficult to accurately predict the duration of the regulatory approval phase for future biosimilar applications, unless there is a stabilization of the regulatory process in the longer term. These findings are further discussed in the following sections of this chapter.

5.2.1.1. Duration of Regulatory Approval Phase Has Changed Significantly Over Time

The data analysis showed that the approval phase for biosimilars has decreased over time in the EU. This is in congruence with what might have been predicted based on the literature in relation

to both small molecule generics and originators, where maturation of the regulatory process over time was expected to result in expedition of regulatory phases for some classes of drugs[28].

5.2.1.2. Duration of Regulatory Approval Phase Decreases with each Subsequent Generation

The data analysis shows that the average duration of the regulatory approval phase for first generation biosimilars is longer than for the subsequent generations of biosimilars and that the average duration of regulatory approval phase decreased for each subsequent generation. This result provides evidence that for the early generations of biosimilars, there could in fact be a relative *disadvantage* (refer to Chapter 2 section 2.4. on first mover disadvantage).

There are two potential reasons for this finding. Firstly, once a biosimilar finishes regulatory approval by the EMA, the data submitted by the biosimilar developers and the discussions between the EMA and the biosimilar developer becomes publicly available. This information can potentially assist the subsequent generation of biosimilars as the information related to the biosimilar application of the first biosimilar applicant provides information specific to biosimilar regulatory approval that the first mover biosimilars cannot obtain via originator regulatory approval dossiers. Such biosimilar specific information that becomes publicly available via first biosimilar approval include details about reference product selection (refer to Chapter 2 section 2.6.1.3) and the type and amount of pre-clinical (refer to Chapter 2 section 2.6.1.4) and clinical data (refer to Chapter 2 section 2.6.1.5) that is deemed acceptable by the regulatory agency for regulatory approval. This disadvantage to the early generations of biosimilars, where the subsequent generations of biosimilar applicants profit from the work of a prior biosimilar applicants, is commonly known in literature as the free rider effect (refer to Chapter 2 section 2.4.1. on free rider effect).

Secondly, EMA's method of establishing molecule or International Non- proprietary Name (INN) specific guidelines usually when the first generation of biosimilars obtain regulatory approval may advantage the subsequent generations. This is because the first generation biosimilar would need to navigate a complex regulatory approval process adhering to general guidelines for biosimilars whilst the subsequent generations would have more specific guidelines often developed

by the EMA after their experience with the first-generation biosimilar applicant. In addition to free rider effects as above, the first generation navigating the regulatory framework shows the first generation of biosimilars resolving market uncertainties (refer to Chapter 2 section 2.4.3. resolution of market uncertainties by the first mover).

5.2.1.3. Duration of Regulatory Approval does not Vary Significantly Between Biosimilars Referencing Different Originator Biologics

This finding provides evidence that, to date, the duration of the regulatory approval process is independent of the originator. Based on table 5-1 below, there are several different types of molecules that forms 15 originators referenced by biosimilars approved in the EU, investigated in this study. These types of molecules vary greatly in terms of molecular nature and complexity. It is known that more complex biologics increase the time taken for pre-clinical and clinical development of biosimilars[28].

#	Originator	INN	Type of Molecule
1	Humatrope	**Somatropin**	**Peptide hormone**
2	Genotropin	**Somatropin**	**Peptide hormone**
3	Eprex/Erypo	**Epoetin alfa**	**Glycoprotein**
4	Neupogen	**Filgrastim**	**Haematopoietic growth factors**
5	Remicade	**Infliximab**	**Monoclonal antibody (mAb)**
6	Gonal-f	**Follitropin alfa**	**Peptide hormone**
7	Lantus	**Insulin glargine**	**Peptide hormone**
8	Enbrel	**Etarnacept**	**Fusion protein**
9	Clexane	**Enoxaparin sodium**	**Low molecular weight heparin**
10	Forsteo	**Teriparatide**	**Peptide hormone**
11	MabThera	**Rituximab**	**Monoclonal antibody (mAb)**
12	Humira	**Adalimumab**	**Monoclonal antibody (mAb)**
13	Herceptin	**Trastuzmab**	**Monoclonal antibody (mAb)**
14	Humalog	**Insulin lispro**	**Peptide hormone**
15	Avastin	**Bevacizumab**	**Monoclonal antibody (mAb)**

Table 5-1: Summary of originators referenced by biosimilars in the EU and the respective type of molecules

In contrast, this finding shows that the complexity of the molecule may not be a contributor in determining the duration of the regulatory approval phase for biosimilars in the EU. This result also provides evidence that the nature and complexity of molecules does not influence whether there is first mover advantage during the regulatory approval phase for biosimilar applicants in the EU.

5.2.2. United States of America

The FDA had approved 12 biosimilar applications till 31st July 2018. In Chapter 4 of this thesis the duration of the regulatory approval phase for these biosimilar approvals was investigated. The data analysis conducted found the following trends for biosimilar approvals in the U.S.:

I. The durations of regulatory approval phase for biosimilars approvals in the U.S do not change significantly over time (refer to Chapter 4 section 4.3.2.). Furthermore, with the removal of the very recent approvals the time taken for regulatory approval seem to be "flattening out" (refer to Figures 4-13 and 4-14 in Chapter 4).

II. The durations of regulatory approval phase for biosimilars approved in the U.S. show no change with each subsequent generation of biosimilars, with the average duration of regulatory approval phases remaining consistent with each subsequent generation (refer to Chapter 4 section 4.3.3.).

III. The durations of regulatory approval phase for biosimilars approved in the U.S. do not change significantly with the different reference originators (refer to Chapter 4 section 4.3.4.).

In addition, as most of the data points were found to be inside or marginally outside of the 95% confidence interval of 295 to 392 days, it is likely that for most future biosimilar applications to the FDA, the regulatory approval phase will take between 295 to 392 days (refer to Chapter 4 Section 4.3.5). These findings are discussed in the next section of the chapter.

However, as the sample size of number of biosimilar approvals in the U.S. is limited, a larger extent of variation due to chance differences, and may not have had the power to detect a difference is expected. Hence, it must be remembered that these finding must be regarded as provisional and could change in the next few years.

5.2.2.1. The Duration of Regulatory Approval Phase has not Changed Significantly Over Time

This finding shows that the time at which a biosimilar application was filed to the FDA had not significantly changed the length of the regulatory approval phase. This result hence provides evidence that the time at which a biosimilar application is filed does not influence whether there is a first mover advantage during the biosimilar regulatory approval phase. This is in contrary to the findings observed for biosimilar approvals in the EU (refer to Chapter 5 section 5.2.1.1) and the expectations based on current literature[28].

5.2.2.2. The Duration of Regulatory Approval Phase has not Changed with Subsequent Generations

The data analysis shows that the average duration of the regulatory approval phase does not change significantly with each subsequent generation of sampled biosimilar applications from the U.S. This contrasts with the findings from the EU. The EMA developed biosimilar guidelines prior to the FDA, establishing the first biosimilar guideline in 2005. More than six years later, FDA issued three biosimilar guidelines in February 2012, which paved the pathway for biosimilar applications and subsequent approvals[147]. Since the FDA guidelines were established later than the EMA, 9 out of the 12 FDA biosimilars approvals included in this study received FDA approvals after the EMA approval[151]. The ability for these biosimilar developers to use both pre-market and post-market clinical in the EU as part of the abbreviated Biologics License Application (aBLA) to the FDA, may counter the first mover disadvantage seen in the EU. However, two of the more recent biosimilars approvals, Cyletzo and Hyrimoz received FDA approval prior to the EMA approval. Whether applications to the FDA first would affect the regulatory approval phase can be a research consideration in the future.

This result provides evidence that generation to which a biosimilar application belongs to does not influence whether an advantage exists during the biosimilar regulatory approval phase. Europe has up to 5 generations of biosimilars and in comparison, the U.S. has up to 3 generations of biosimilars. There are only 12 biosimilar approvals in the U.S. during this study period and only three generations of biosimilars with the number of biosimilars in each generation is small. Whether

these findings would change with more biosimilar approvals by the FDA in the U.S. can be investigated in future research.

5.2.2.3. The Duration of Regulatory Approval does not Vary Significantly Between Biosimilars Referencing Different Originator Molecules

The data analysis demonstrated that the duration of the regulatory approval process is independent of the reference originators. This is similar to the findings in the EU. Based on table 5-2 below, there are several different types of molecules that forms 8 originators referenced by biosimilars approved in the U.S., investigated in this study. These types of molecules vary greatly in terms of molecular nature and complexity. It is known that more complex biologics increase the time taken for pre-clinical and clinical development of biosimilars[28]. As such this result also provides evidence that the nature and complexity of molecules does not influence whether there is a first mover advantage during the biosimilar regulatory approval phase.

#	Originator	INN	Type of Molecule
1	Neupogen	**Filgrastim**	**Haematopoietic growth factors**
2	Remicade	**Infliximab**	**Monoclonal antibody (mAb)**
3	Epogen/Procrit	**Epoetin alfa**	**Glycoprotein**
4	Enbrel	**Etarnacept**	**Fusion protein**
5	Humira	**Adalimumab**	**Monoclonal antibody (mAb)**
6	Avastin	**Bevacizumab**	**Monoclonal antibody (mAb)**
7	Herceptin	**Trastuzmab**	**Monoclonal antibody (mAb)**
8	Neulasta	**Pegfilgrastim**	**Haematopoietic growth factors**

Table 5-2: *Summary of originator biologics referenced by biosimilars in the U.S. and the respective type of molecule*

5.2.3. Comparison of EU EMA Biosimilar Regulatory Approvals to the U.S. FDA Approvals

5.2.3.1. Number of Biosimilar Regulatory Approvals and Rate of Approvals

The EMA established biosimilar approval pathway 16.5 years ago (see Figure 2-3 in Chapter 2, Section 2.7.). The EMA has since approved 41 unique biosimilars in a period of 16.5 years. This corresponds to 2.48 applications per year. In comparison, the FDA established biosimilar regulatory approval pathway 6.5 years ago (see Figure 2-3 in Chapter 2, Section 2.7.). FDA has since approved 12 biosimilars in a period of 6.5 years, that is, 1.84 applications per year. The EMA has approved biosimilars referencing 15 originators and the FDA has approved biosimilars referencing 8

originators. Figure 5-1 shows biosimilar approvals for each year since biosimilar regulations were established in the EU and the U.S respectively. At present, the U.S. is behind the EMA in the total number of biosimilar approvals and the rate of biosimilars approvals per year.

EMA established guidelines for approval of biosimilars in June 2003, whilst FDA established similar guidelines in February 2012 (refer to Figure 3-2 in Chapter 3, Section 3.2). Literature identifies this time difference in establishing regulatory frameworks as a factor for the U.S. biosimilar approvals to be lagging behind the E.U.[28]. Whether the biosimilar approvals in the U.S. will reach the same numbers or rate of approvals as the EU are questions that can only be answered by future research.

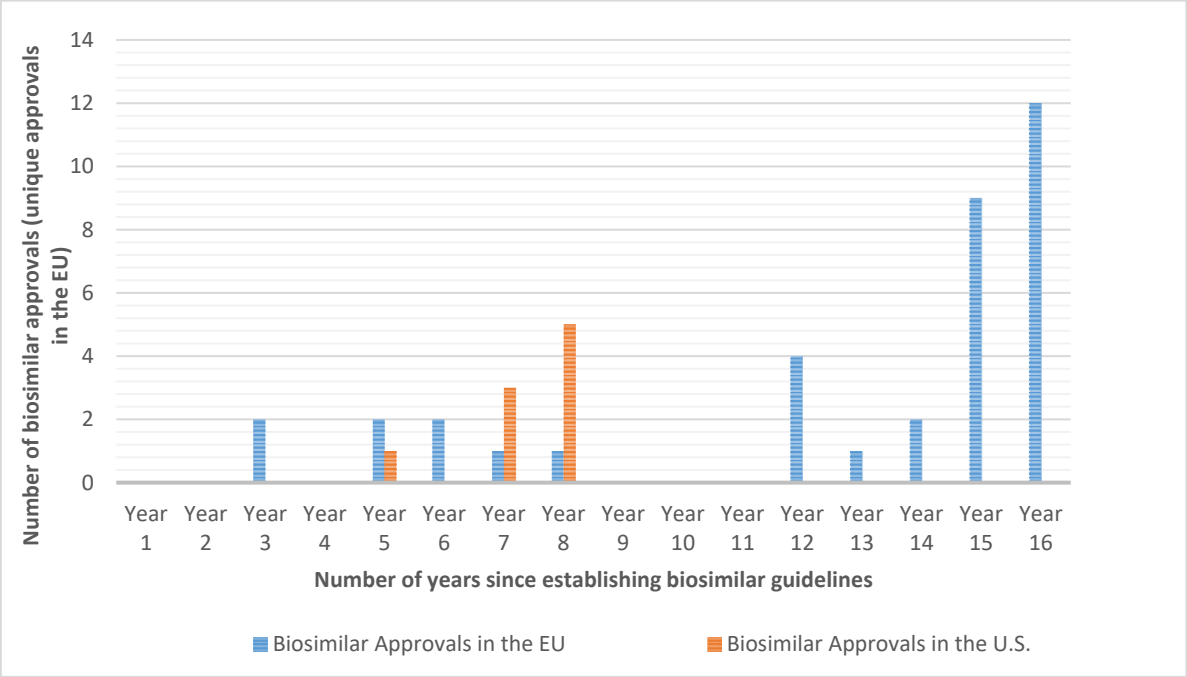


Figure 5-1: Number of drug approvals for each year since biosimilar regulations were established in the EU and the U.S. Year 1 represents the first year after the respective regulation were passed into law: 2004 for the EU (biosimilar regulation was formally introduced in June 2003 under Directive 2003/63/EC[152]) and 2010 for the Biologics Price Competition and Innovation Act of 2009 (BPCIA)[115].

5.2.3.1. Time taken for Regulatory Approvals

For the sampled data, the average time taken for regulatory approval was 96 days faster for U.S. biosimilar applications than for EU biosimilar applications (refer to Chapter 4 Section 4.3.5). It was discovered that 9 out of the 12 U.S. biosimilars approvals included in this study received FDA

approvals after the EMA approval[151]. The prior approvals in the EU allows biosimilar applicants to provide both pre-market and post-market clinical data from the EU to the FDA. In addition, both the FDA and the biosimilar developers can learn from the regulatory approval process taken by the EMA for prior biosimilar approvals in the EU. These two factors may have contributed to the observed difference in average time taken for regulatory approvals, as well as the consistency observed in the time taken for regulatory approvals (see Figures 4-13 and 4-14 in Chapter 4) and the narrow 95% confidence interval observed for the sample of biosimilar applications in the U.S. that was investigated in this study.

5.3. Recommendations

It is evident that in the case of biopharmaceuticals and their biosimilars, where the high technical complexity exacerbates time and cost, the balance between public good and private reward is not simple to achieve. The need to achieve this balance continues to influence the current policy and regulatory levers. Ongoing policy initiatives regarding regulation, development, approval and reimbursement of biosimilars will assist in surmounting the high barriers to market entry (see Chapter 2, section 2.6.1., on Biosimilar Commercialization Challenges in the U.S. and the EU). Such policy initiatives are likely to influence whether the first mover biosimilar has an advantage during the commercialization phase, and will, in turn, influence the development of a competitive market.

The next section of this chapter discusses three potential policy interventions that could accelerate the availability of biosimilars to the public and could have a favorable impact price. This discussion around recommendations on potential policy interventions aims to address the findings from the data analysis conducted.

5.3.1. Staggered Incentive Structure to Counter Potential 1st Generation Disadvantage

The biosimilar industry, specifically the biosimilar industry in the U.S. has often been compared to the small molecular generics industry. The Drug Price Competition and Patent Term Restoration Act of 1984[153], commonly known as Hatch Waxman Act (HWA) is considered a pivotal

policy intervention which assisted in accelerating the growth of the generics industry in the U.S[154,155]. HWA simultaneously drove industry growth and price reduction, lowered barriers to market entry and opened up the small molecule chemical drug market to generics, improving accessibility and affordability of these drugs for millions of people[154]. Figure 5-2 shows the impact of HWA on the prescription drug market; in 1983 generic drugs accounted for only 3.4% of the total prescription drug market, but by 1984 their market share increased to 8% and continued to steadily increase in the ensuing years[156] A key provision of the HWA was a 180-day market exclusivity period for the first generic that met certain set criteria[117].

The challenges faced by biosimilars detailed in Chapter 2 Section 2.7.1., shows that biosimilars face many developmental hurdles prior to market entry. Furthermore, in particular the first mover biosimilar applicant is likely have to navigate interpreting evolving regulatory requirements related to adequacy of clinical or non-clinical data in a submission, reference product selection as well as IP challenges posed by originator biologic companies[28]. A major relevant issue is that the first mover biosimilar is more likely to be subject to legal challenges by the originator firm, in order to delay biosimilar competition, whereas such costly legal challenges (refer to Chapter 2 section 2.6.1.8) are less likely for later entrants per first mover disadvantage theory on free riders (refer to Chapter 2 section 2.4.1.) . The results from Chapter 4 of this thesis indicate that currently a first mover advantage does not exist during the regulatory approval phase for biosimilars. In addition, in Europe the data analysis showed that there is first mover *disadvantage* to the early generations of biosimilar regulatory applicants in the EU. An incentive structure for biosimilars similar to the 180-day market exclusivity period for generics provided by the HWA could potentially counter the absence of a first mover advantage (indeed the existence of a generational first mover disadvantage).

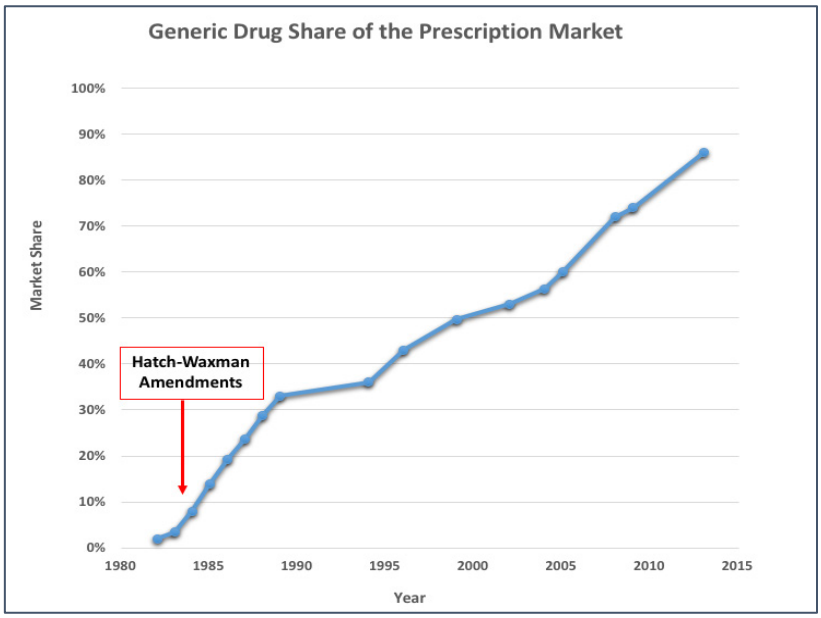


Figure 5-2: Generic Share of the Prescription Market in the years prior to and post the Hatch-Waxman Act[156, 157-159]. The slow growth in generic drug share in prescription market in the early 1990s is largely attributable to the generic drug scandal that occurred in 1989, which negatively impacted consumers' perception & uptake of generic drugs[155].

However, the generics industry in the U.S has also shown that such an incentive scheme that only applies to the first mover, can provide excessive leverage to the first-to-market product and can lead to anti-competitive behaviour[160]. To overcome such possible outcomes, a staggered incentive structure that benefits first as well as subsequent early generations of biosimilars might be the solution. Such a staggered incentive structure might reduce the market dominance of one product, accelerate the market entry of subsequent products, increase competition and lead to sustainable cost savings. In addition, the increased competition is likely to reduce the cost of biopharmaceuticals to the public.

Another potential positive outcome of a staggered incentive structure is the minimization of possible market distortions by of *"authorized-biosimilars"*. In the generics market, authorized-generics[35] are generic drugs produced by originator companies, often distributed through a third party, and priced to compete with generics[161]. They keep prices artificially high, distorting the market and making it difficult for true generics to gain market share[35]. The Federal Trade Commission in the U.S. also reports that some originator companies use agreements not to launch authorized-generics

as a way to compensate would-be generic competitors, in order to delay market entry[162]. Whilst, there are currently no examples of originator companies marketing biosimilar versions of their own originator biologics, originators are actively involved in the biosimilar space and there is potential for *"authorized-biosimilars"*. Increased complexity and high cost related to biopharmaceutical development and manufacturing means that originator companies venturing into biosimilar space will have a considerable advantage over new entrants. Originator companies such as Biogen Idec, Merck and Teva Pharmaceuticals have commenced biosimilar development programs. Further, Pfizer's acquisition of Hospira, a spin off from Abbott Laboratories and one of the largest biosimilar and generic companies in the world [163], is an indication of the interest originator companies have in the biosimilar market. Furthermore, given the higher cost of entry (compared to small molecule generics), the biosimilar market will be likely to have fewer competitors than generics. Any policy changes will need to take account of the possibility of *"authorized-biosimilars"*, and a staggered incentive structure could ensure that there are incentives for both first and subsequent biosimilars to enter the market, with a view to maintaining the socio-economic benefits of biosimilars.

5.3.2. Reimbursement

Another policy intervention with potential to improve biosimilar uptake by the market, which in turn provides incentive for biosimilars developers, is to improve the flexibility in the current reimbursement structure.

In the EU, reimbursement for biosimilars is determined by each individual member country. For example in Spain, France and Italy biosimilar reimbursement is set at a fixed percentage less than the originator pricing[164]. In the U.S., the reimbursement for biosimilars is governed by the Physician Fee Schedule (PFS) Guideline by the Centres of Medicare and Medicaid Services[165]. The PFS provides Medicare Part B payment guidance for biosimilars[165]. According to the original guideline, all biosimilars referencing an originator is given a Healthcare Common Procedure Coding System (HCPCS) code. Reimbursement for biosimilars is then to be carried out at the average sales

price of all biosimilars marketed in the U.S. referencing a particular originator (or one HCPCS code), plus an additional 6% of the average sales price of the reference originator product[166]. When a first generation biosimilar enters the market and average sales price for the biosimilar is not yet established, the guideline stipulates the use of the wholesale acquisition cost to calculate the Medicare reimbursement in place of the average sales price[166]. However, in 2018 the CMS requested comments on the current PFS rule on biosimilar reimbursement to understand how the reimbursement structure has impacted market experience of biosimilars in the U.S. Based on strong response from a wide range of stakeholders, the CMS has decided to implement a guideline where each biosimilar (regardless of the reference originator) is provided with a unique HCPCS code and hence reimbursement structure specific to that biosimilar[166]. This detailed guideline is yet to be published[166]. Till such guideline is published, the current biosimilar reimbursement structure in the U.S. remains as before and is determined by two factors; average sales price of biosimilars referencing an originator and the average sales price of the reference biologic.

For biosimilar developers, one potential disincentive that stems from the determination of reimbursement based on the price of the originator is where originator companies reduce their pricing to be equal to, or less than, the cost price of a biosimilar. Such behaviour has already been evident in the EU where originator pricing of erythropoietin was lowered even prior to patent expiry in anticipation of biosimilar competition[31]. Such competition and price reduction can initially be advantageous to public health, as it reduces the cost of biopharmaceuticals. However, in the long term it can be disadvantageous, as undue decrease in price of originators will affect reimbursement and may deter and reduce the number of biosimilar market entrants. The generics industry has shown that an increase in the number of market entrants has reduced the cost of these drugs[160]. For example, a study conducted by the FDA on the small molecular generics industry found that, on average, the price of the first generic is only slightly less than the originator, however the presence

of second generic product in the market reduces the average price to nearly half the originator price[81].

A reimbursement system commensurate with the differences between generics and biosimilars, and with the variations in complexity of the regulatory approval process for each product may be necessary for biosimilars to achieve systemic benefits. Furthermore, an appropriate reimbursement structure for biosimilars will play an integral role in reducing the cost of biologics by encouraging price competition among originator biologics and biosimilars and improving market uptake.

5.3.3. Promoting Uptake

The uptake of biosimilars in Europe has shown bimodal characteristics, with initial adoption for new patients, followed by substitution with interchangeable biosimilars in existing patients once the interchangeability has been formally allowed[31]. Based on the European experience, it has been asserted that the biosimilar market in the U.S. is likely to be bimodal as well[31]. However, there is increasing resistance from physicians to change their prescribing practice in relation to biosimilars, especially in the U.S.[33]. Medical practitioners will resist substitution of biosimilars if they are not confident that the biosimilars will be as efficacious or if there is a concern that the biosimilar might have different pharmacokinetics or side-effects. Such resistance could persist even after interchangeability has been formally sanctioned by regulatory bodies such as the FDA and the EMA. This resistance from physicians is not a surprise, given that they are risk averse and guided by the precept "*primum non nocere"*. Given the resistance from physicians to prescribe biosimilars, it is expected that biosimilars will be treated as therapeutic alternatives rather than therapeutic equivalents[17].

To improve biosimilar uptake by the market and to incentivize biosimilars developers, policy interventions to improve the flexibility of the current reimbursement structure must be looked at. A reimbursement system that accounts for the differences between the variations in complexity of the regulatory approval process for each class of biosimilar product would be necessary for biosimilars

to achieve the anticipated systemic benefits. An appropriate reimbursement structure for biosimilars could play an integral role in reducing the cost of biologics by encouraging price competition among biopharmaceuticals and improving market uptake. For example, Germany has established a reference price system and budget ceilings and practice specific prescription targets for physicians to encourage uptake of less expensive "follow-on" drugs[167]. As per the reference price system, patients in Germany have to bear a certain percentage of the difference in cost between the drug they opt for and the reference price[167]. In addition, if the physicians exceed their prescribing target and budget they are notified, with repayment of excess enforceable[167]. These measures have led to improved biosimilar uptake and price competition in Germany, as seen in the case of Sandoz increasing the discount of its Epoetin biosimilar *Binocrit* from 15% to 33%, through which it captured 30% market share[119]. Even in the generics market in the U.S. subsequent to the Hatch Waxman Act, the uptake of generics was attributed to state specific legislation that made it mandatory for pharmacists to switch prescriptions to the lowest priced interchangeable alternatives[159].

5.4. Future Research Directions

The following possibilities for future research directions were identified as during this study:

- 9 of 12 biosimilar applications to the FDA in this study were biosimilars that have received prior approvals from the EMA. However, two recent applications were filed first to the FDA. There is potential to conduct future research to identify whether the trend observed in filing to the EMA first is changing and how such a change might affect the duration of regulatory approval phase for biosimilars (refer to Chapter 5 section 5.2.2.2).
- In this study, it was discovered that the first generation of biosimilars in both U.S. and EU did not benefit from a first mover advantage during the regulatory approval phase. In addition, a first mover disadvantage was discovered for the first generation of biosimilars in Europe. Europe has up to 5 generations of biosimilars for some originators. In comparison, the U.S. to date has up to 3 generations of biosimilars. There is a need for future research to investigate whether these findings will change with more biosimilar approvals in the U.S. (refer to Chapter 5 section 5.2.2.2).

- This study discovered that there is first mover disadvantage during the regulatory approval phase for biosimilars (refer to Chapter 5 section 5.2.2.2) and there is the need for policy and regulatory interventions to improve biosimilar market entry (refer to Chapter 5 section 5.3). There is an opportunity for future research to monitor whether such policy and regulatory interventions take place and to examine the effect of such interventions on the biosimilar industry.
- For this study period, in comparison to the EU the U.S. lags in number and rate of biosimilar approvals. Whether the biosimilar approvals in the U.S. eventually reach the same number as the EU is an open question. If there are increases in biosimilar uptake, it will be important to examine the legislative and other factors that are associated with this change (see Chapter 5 section 5.3).

APPENDICES

Appendix 2-1: Widely Used Definitions for First Mover

Definition
"The first appearance of a brand in a distinct new product category"[51]
"The first entrant in a new market"[43]
"First product to enter the market, earliest surviving brand"[44]
"Pioneers as producing a new product, using a new process or entering a new market"[42]
"Inventor is the firm(s) that develops patents or important technologies in a new product category. Product pioneer is the first firm to develop a working model or sample in a new product category Market pioneer is the first firm to sell in a new product category Product category is a group of close substitutes such that consumers consider the products substitutable and distinct from those in another category"[53]
"A pioneer or "first-mover" as "a firm that is among the first three firms to introduce a new product/brand into its primary served markets." [45]

Table A2-1: First mover definitions widely used in literature

Appendix 3-1: Summary of the Data Points Collected

Data Points Collected	Source	Reason for Data Collected
Europe - Overall		
1 No of biosimilars approved from the point of establishment of regulatory framework	EMA website, Company press releases	To analyze the market entry of biosimilars since regulatory intervention. Forms a basis of all other data points collected.
2 Biosimilar Applicant / Marketing Authorization Holder	EMA Website – EPAR public assessment report	Provides the name of the company applying for biosimilar approval from the EMA
3 Biosimilar Agency Product number	EMA Website	Forms a basis of all other data points collected.
4 Originator Product	EMA Website – EPAR public assessment report	Forms a basis of all other data points collected.
5 Originator Marketing Authorization Holder	EMA Website – EPAR public assessment report	Forms a basis of all other data points collected.
Europe – Regulatory Approval data		
1 Biosimilar EU Market Authorization Date	EMA Website – EPAR public assessment report	Provides the concluding date of regulatory approval Required to measure the time taken for regulatory approval
2 Biosimilar Application Date to the EMA	EMA Website – EPAR public assessment documents report	Provides the date in which the sponsor organization has applied for regulatory approval Required to measure the time taken for regulatory approval
3 Biosimilar Approved Indications – both type and number	EMA Website – EPAR public assessment report	Provides an overview to the actual uses of the biosimilars Provides information to whether all biosimilars which the same International Nonproprietary Name (INN) are approved for the same type and number of indications This also provides a measurement as to whether biosimilars apply for the same number and type of indications as the originator
4 Biosimilar Regulatory Procedure start date	EMA Website – EPAR public assessment report	Provides a measurement as to the length of time taken by the EMA to commence regulatory proceedings. This will also provide a good measurement to determine whether the time taken for regulatory approval process decreases as the regulatory framework matures; and whether this is related to increase in knowledge and capabilities within the EMA.

Data Points Collected	Source	Reason for Data Collected
5 Biosimilar Regulatory milestones as applicable: - Rapporteur's and Co-Rapporteur's first Assessment Report - First set of consolidated questions from the CHMP - Submission of responses from the applicants to the first set of questions from the CHMP - Second set of consolidated questions from the CHMP - Submission of responses from the applicants to the second set of questions from the CHMP - Third set of consolidated questions from the CHMP - Submission of responses from the applicants to the third set of questions from the CHMP - Oral presentations by the applicant - CHMP positive opinion	EMA Website – EPAR public assessment report	To map the regulatory timeline Provides an indication as to which steps took the most amount of time. Provides a measurement as to whether number of steps taken during the regulatory approval period has decreased as overtime as the regulatory framework matures
6 Originator Marketing Authorization Date	EMA Website – EPAR public assessment report	To measure the time taken for biosimilar regulatory approval
7 Originator Approved Indications – both type and number	EMA Website – EPAR public assessment report	Provides a measurement as to whether biosimilars apply for the same number and type of indications as the originator
Europe – Other Data Points		
1 Delays in Market Entry due to patent litigation	Company Press Releases, Secondary news sources	Provides a measurement as to whether there is first mover advantage or disadvantage
USA- Overall		
1 No of biosimilars approved from the point of establishment of regulatory framework	FDA website – Drugs@FDA, Company press releases	To analyze the market entry of biosimilars since regulatory intervention. Forms a basis of all other data points collected.
2 Biosimilar Applicant	FDA website – Drugs@FDA, Company press releases	Provides the name of the company applying for biosimilar approval from the EMA
3 Biologics License Application Number (BLA #)	FDA website – Drugs@FDA	Forms a basis of all other data points collected.
4 Originator Product	FDA website – Drugs@FDA	Forms a basis of all other data points collected.
5 Originator BLA #	FDA website – Drugs@FDA	Forms a basis of all other data points collected.

Data Points Collected	Source	Reason for Data Collected
4 Originator Marketing Authorization Holder	FDA website – Drugs@FDA, Company press releases, Literature	Forms a basis of all other data points collected.
USA– Regulatory Approval data		
1 Biosimilar BLA approval date	FDA website – Drugs@FDA BLA	Provides the concluding date of regulatory approval Required to measure the time taken for regulatory approval
2 Biosimilar Application Date to the FDA	FDA website – Drugs@FDA BLA	Provides the date in which the sponsor organization has applied for regulatory approval Required to measure the time taken for regulatory approval
3 Biosimilar Approved Indications – both type and number	FDA website – Drugs@FDA BLA	Provides an overview to the actual uses of the biosimilars Provides information to whether all biosimilars which the same International Nonproprietary Name (INN) are approved for the same type and number of indications This also provides a measurement as to whether biosimilars apply for the same number and type of indications as the originator
6 Originator Marketing Authorization Date	FDA website – Drugs@FDA BLA	To measure the time taken for biosimilar regulatory approval
7 Originator Approved Indications – both type and number	FDA website – Drugs@FDA BLA	Provides a measurement as to whether biosimilars apply for the same number and type of indications as the originator
USA – Other Data Points		
1 Delays in Market Entry due to patent litigation	Company Press Releases, Secondary news sources	Provides a measurement as to whether there is first mover advantage or disadvantage
2 USA generics approved via 505(b) pathway that were approved as biosimilars in the USA	FDA website – Drugs@FDA BLA, Literature	To see how alternate regulatory pathways have affected the commercialization landscape

Table A3-1: Summary of the data points collected for the current research study

Appendix 4-1: List of biosimilar application filed to the EMA prior to 31st July 2018 and not approved during this study period ending on 31st July 2018.

Biosimilar applications filed to the EMA prior to 31st July 2018, that are being reviewed and yet to receive regulatory approval[143].

Biosimilar INN	Pending Applications
Adalimumab	2
Bevacizumab	1
Etanercept	1
Pegfilgrastim	8
Rituximab	1
Trastuzumab	1
Total	**14**

Table A4-1: *List of biosimilar application filed to the EMA prior to 31st July 2018 and not approved during this study period ending on 31st July 2018.*

Note: It is important to note that whether these 14 biosimilar applications are unique or non-unique (unique and non-unique biosimilar applications are defined in Chapter 4 Section 4.2.1.2 of this thesis) is unknown.

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