Financial Analysis of Biosimilar Development Candidates: A Case Study on the US Biosimilar Business

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Abstract

This case study investigates the US biosimilar business and the approach that should be implemented when financially analyzing biosimilar development candidates. To challenge the theory that the biosimilar business will be best suited for biologics experiencing the largest sales figures, this case study applied a financial analysis towards two biosimilar development candidates with contrasting sales. Using Soliris (eculizumab) and Remicade (infliximab) biosimilars as a test case, this case study hypothesized that a Soliris biosimilar has the opportunity to create more value over time—despite Soliris® having less sales than Remicade®—due to its favorable market outlook.

Over the next few years, the US biosimilar landscape is expected to evolve into a profitable business venture as the first wave of biologics, particularly monoclonal antibodies, begin to lose patent protection. With some biologics experiencing more than $5 billion in annual sales, many analysts believe biosimilars to these biologics will generate more value than a biosimilar to a reference biologic making under $5 billion in sales. However, based on the findings from this case study, the opposite was true. Using a product- and market-driven net present value (NPV) evaluation, this case study uncovered that a Soliris biosimilar candidate has the potential to generate more value than a Remicade biosimilar. Demonstrating that the reference biologic's sales did not translate to a greater valuation for the Remicade biosimilar, this case was able to substantiate the importance in financially analyzing biosimilar development candidates

beyond the sales of a reference biologic. In addition, this case study was able to demonstrate the utility in using a product- and market-driven valuation approach in the value determination of biosimilar development candidates.

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Chapter I

Introduction

This chapter introduces the thesis. Using a case study approach, this chapter describes the problem of interest, the hypothesis, and the objectives of the study. This chapter also presents the organizational format of the thesis.

Problem Statement

Over the past three decades, significant strides have been made in the area of drug development, particularly in the development of biologics. With advances in genetics and biotechnology improving the development of biological drugs, many drug companies are using this progress to create life-changing therapies for the treatment of various diseases. However, despite their effective ability to treat disease, these biologics come with a significant cost burden to the payer (e.g., healthcare system, insurance companies, patients, and taxpayers). While most traditional pharmaceuticals cost approximately $730 per year (Emerton, 2013), on average, biologics can cost anywhere between $15,000 and $150,000 per year (Epstein, Ehrenpreis, & Kulkarni, 2014). With the use of biologics increasing in the clinic and cost of treatment reaching an all-time high, there is a considerable demand for low-cost alternatives that can provide the same efficacy and safety as these biologics.

Unlike small-molecule drugs, generic versions of biologics, properly known as biosimilars, are just entering the US market; in March of 2015, the FDA approved the first biosimilar product, Zarxio (filgrastim-sndz). Opening the doors to biosimilars, the US biosimilar market is expected to change over the next ten years as several major biologics (e.g., monoclonal antibodies) from the 1990s are approaching patent expirations. With more than $60 billion worth of biologic sales losing patent protection (Emerton, 2013), many analysts predict biosimilars to be a profitable business venture. This sentiment of optimism has been echoed in the pharmaceutical/biotechnology industry as biosimilar deals between drug companies and contract manufacturing organizations have continued to increase since 2000 (Bourgoin, 2011). The notion that a reference biologic with billion dollar sales can result in large revenue gains for its biosimilar, has resulted in many drug companies developing biosimilars to some of the top-selling biologics, such as Humira®, Remicade®, Enbrel®, Rituxan®, Herceptin®, and Avastin® (Thayer, 2013).

Of the companies currently involved in the development of biosimilars in the US, the majority are developing biosimilars for those monoclonal antibodies experiencing sales in the billions of dollars (Rader, 2013). While the US biosimilar market exhibits tremendous potential as an investment, not every biosimilar to a reference biologic with billion-dollar sales will be a fruitful investment. With the development of a biosimilar requiring a significant investment up front, a drug company interested in the biosimilar venture will need to make strategic decisions when selecting the biosimilar(s) it would like to develop and advance to the US market.

This case study will explore this concept in depth by evaluating two biosimilar candidates with contrasting sales and market profiles. Rather than rely on biosimilar financial assessments that are centered on the sales of a reference biologic as a determinant of future value, such as the Nickisch and Bode-Greuel (2013) study, this case study will analyze each biosimilar development candidate individually and apply a net present value (NPV) evaluation that is both product- and market-driven.

Hypothesis

Many companies involved in the biosimilar venture believe that a biosimilar's value will be driven by the sales of its reference product. While studies, such as Nickisch and Bode-Greuel (2013) support this theory, this case study will challenge its validity by financially analyzing two biosimilar development candidates with the following contrasting characteristics:

1. A biosimilar monoclonal antibody candidate for which the reference biologic generates more than $5 billion in sales (based on 2013 worldwide sales) but has an unfavorable market outlook after patent expiration.
2. A biosimilar monoclonal antibody candidate for which the reference biologic generates less than $2.5 billion in sales (based on 2013 worldwide sales) but has a favorable market outlook after patent expiration.

By implementing a more market-driven valuation that takes into account the biosimilar landscape of each candidate of interest, this case study will demonstrate that not all biosimilars to top-selling biologics will produce greater value in the long-term

investment. Although the Nickisch and Bode-Greuel study suggests the biosimilar opportunity is greater for those reference biologics generating more than $5 billion in sales, this case study hypothesizes that a biosimilar candidate for which the reference biologic has less sales but a favorable market outlook, may result in a better valuation.

Thesis Objectives and Organization

The objective of this thesis is to introduce the concept of biosimilars, explain the biosimilar business, and present a compelling case study in the financial evaluation of biosimilar development candidates. Focusing specifically on the US market, this case study will undertake the following:

- Introduce and explain biosimilars and their business model.
- Explore and challenge biosimilar valuations that utilize the sales of the reference biologic as a determinant of value for a biosimilar candidate, such as the valuation conducted in the Nickisch and Bode-Greuel (2013) study.
- Provide an alternative and more accurate approach toward the financial evaluation of biosimilars by comparing two biosimilar candidates for which the reference biologics have contrasting sales and market outlooks.
- Demonstrate the potential for a low-profile biosimilar (a biosimilar for which the reference biologic captures less than $2.5 billion in sales world-wide) to provide greater long-term value than a high-profile biosimilar (a biosimilar for which the reference biologic captures more than $5 billion in sales world-wide) via an NPV analysis.

- Highlight the importance of a product- and market-driven valuation in the selection of a biosimilar development candidate.

To present the arguments above, this case study is organized into six chapters. Chapter I, Introduction, describes the problem statement, the hypothesis, the objectives, and the organization format utilized in the case study. Chapter II, Literature Review, introduces and provides background on the main themes of the case study. Chapter III, Methods and Analysis, elaborates on the methodology and analyses used to screen, select, and financially evaluate biosimilar development candidates. Chapter IV, Results, reveals the findings from the biosimilar NPV evaluation. Chapter V, Discussion, examines the results and its applicability in the valuation of other biosimilar development candidates. In addition, this chapter discusses some of the challenges and limitations of the case study and introduces other considerations in the valuation of biosimilars. Lastly, Chapter VI, Conclusion, provides a summary on the scope and findings of the case study.

Chapter II

Literature Review

The objective of this chapter is to introduce and provide background on the various scientific and business themes covered throughout this case study. Scientifically, this chapter will explain the characteristics and development processes observed for both biologics and biosimilars entering the US market. On the financial end, this chapter will elaborate on the US biosimilar business and the value determination approach for drug products, specifically biosimilars.

Biologics Background

This section provides scientific context on biological drug products, exclusively monoclonal antibodies and their differences compared to typical drug products, such as small-molecules. In addition, this section provides background on the development pipeline normally observed for biologics entering the US market.

Biologics and Monoclonal Antibodies

Biologics are therapeutics manufactured through living organisms using biotechnology methods. Composed of a biological entity, biologics are made up of peptides, proteins, nucleic acids, or cells (Wang & Singh, 2014). First developed in the

early 1980s, biologics are well known in the clinic for their ability to diagnose, prevent, and treat human diseases. Drastically different than traditional pharmaceutical drugs (i.e., small-molecules), biologics are larger in size, heterogeneous, and difficult to characterize (Table 1) (Chow, 2014).

Table 1. Small-molecules compared to biologics.

Small-molecule		Biologic
Chemically synthesized	**Production**	Living organism
Defined	**Composition**	Complex/Heterogeneous
Low	**Molecular Weight**	High
Low complexity	**Characterization**	High complexity
Low	**Immunogenicity**	High
High	**Stability**	Low
Low	**Manufacturing Difficulty**	High
Low to medium	**Cost (To Payer)**	High to very high
Oral	**Administration**	Injection

Note. Major differences between small-molecule drugs and biological therapeutics. Product differences adapted from Chow (2014).

As a result, the development of a biologic is more complex and costly as it is involves intensive engineering and manufacturing. Despite these hurdles, biologics are considered some of the most effective and preferred therapeutics for the treatment of severe diseases, such as cancer, rheumatoid arthritis, multiple sclerosis, and hepatitis. According to Wang and Singh, there are over 200 different types of biologics in today's market and an additional one-third of pharmaceutical pipelines consist of a biologic.

Presently, one of the most successful and largest growing classes of biologics are monoclonal antibodies. Produced from living organisms (usually mammalian cells) through elaborate manufacturing processes, these antibodies function similarity to those found in the human body. The only difference lies in the ability of an engineered antibody to target and/or block an antigen of interest (e.g., the antigen specific to the disease) (Ansar & Ghosh, 2013). Compared to small-molecules, monoclonal antibodies provide less off-target effects and strong binding capabilities resulting in a more effective treatment of disease. In addition to their therapeutic application, the U.S. Food and Drug Administration (FDA) has approved the use of monoclonal antibodies towards other applications, including diagnosis and bioterrorism (Ansar & Ghosh, 2013).

Developing Monoclonal Antibodies

The development of a biologic, specifically a monoclonal antibody, can be categorized in three main stages: discovery, preclinical development, and clinical development (Wang & Singh, 2014). Prior to engineering a monoclonal antibody for the treatment of a disease, the biological entity responsible for causing the disease (i.e., drug target) must first be identified and targeted. Once a target has been identified and linked to the pathogenesis of a disease, various antibodies to that target can be engineered (Wang & Singh, 2014; Ansar & Ghosh, 2013; Hu & Hansen, 2013). These antibodies can then be optimized (i.e., engineered to have minimal immunogenicity, superior biochemical and biophysical properties, and ideal pharmacokinetic properties) and produced in mass quantities (Wang & Singh, 2014).

Prior to manufacturing, it is critical to establish the process that will be used to produce the antibody of interest. This is the objective of the preclinical development phase, to establish a manufacturing process that produces a drug product of high quality and safety (Wang & Singh, 2014). Since monoclonal antibodies are produced from living organisms, many alterations may occur throughout the production process (e.g., post-translational modification, glycosylation, protein cleavage, and yield) (Genazzani, et al., 2007). Therefore, it is important to develop a manufacturing process that is both robust and consistent, to ensure that the therapeutic provided in clinical trials (and to the general public, if approved) is consistent and of the highest quality (Wang & Singh, 2014).

The final step in the development of a monoclonal antibody is clinical development. Once the early development and pre-clinical phases demonstrate promising results for the monoclonal antibody candidate, the drug sponsor can then pursue human testing. To test human subjects in the US, it is first necessary to receive clinical trial approval from the FDA. This is initiated by filing an Investigational New Drug (IND) application to the FDA that supports the request based on data acquired from earlier development phases (Wang & Singh, 2014). Once the FDA has granted IND approval, the drug sponsor can then begin clinical trials (Phase I-III) to determine if the drug is both safe and efficacious (Umscheid, Margolis, & Grossman, 2011). Depending on the results, the drug sponsor can apply to the FDA for market approval by filling a Biologics License Application (BLA). After BLA approval, the drug sponsor can then bring the product to market in the US.

Biosimilars Background

The goal of this section is to transition from biologics to biosimilars. Expanding on the scientific, regulatory, and legal areas of biosimilars, this section elaborates on the development of biosimilars in the US. To provide additional context, this section provides background on the current EU biosimilar experience.

Biosimilars

According to the FDA, a biosimilar is a biological product that is highly similar to an FDA-licensed biological product (the reference biologic) for which there are no clinically meaningful differences in terms of safety, purity, and potency of the product (Kozlowski, 2012). In layman's terms, a biosimilar is generic version of a biological drug. Currently, there is only one biosimilar approved in the US, Zarxio (filgrastim-sndz). However, this is expected to change as several biologics will begin to lose patent exclusivity in the US over the next few years. With the cost of biologics ranging on average between $15,000 and $150,000 per year (Epstein, Ehrenpreis, & Kulkarni, 2014), biologics have created a financial strain on both the US healthcare system and payers. With potential cost savings in the billion-dollar range and several biosimilars already approved in the European market, the demand for biosimilars in the US is steadily increasing (Bourgoin, 2011).

Development of Biosimilars in the US

Similar to biologics, biosimilars are engineered through biotechnology methods and produced via living organisms. However, the development pipeline for a biosimilar is

slightly different than the development of either a new biologic or a generic small-molecule (Lymphoma Coalition, 2015; Wang & Singh, 2014). For a biosimilar, the goal of development is to produce a molecule that is highly similar to the FDA-licensed reference biologic (Kozlowski, 2012). As a result, the development process is primarily focused on the preclinical and clinical phase—there is no discovery phase since the biosimilar target is the same as the reference biologic.

In the preclinical phase, engineering, manufacturing, and characterization are the main components in the development of a biosimilar. With the quality of the final product contingent on the steps taken throughout the engineering and production process, a biosimilar must undergo rigorous preclinical development to establish a product that is comparable to the reference biologic. Unlike small-molecule generics where the production process is a direct chemical synthesis of the molecule, biosimilars undergo a complex production process that requires substantial experimentation and testing. Since the manufacturing process of a reference biologic is usually undisclosed (kept as a trade secret), deep analytical characterization is critical in assessing and comparing the product attributes (e.g., structural, physiochemical, and posttranslational) of the biosimilar to its reference biologic. In addition to product attributes, the biosimilar must also demonstrate similar biological activity (e.g., binding and potency). Here, it is common for preclinical development to also include in vivo and/or ex vivo comparability studies to demonstrate safety and efficacy (Donninger, Carlsen, Estdale, Bower, & Kaiser, 2012).

In the clinical phase, both Phase I and Phase III trials may be applicable to biosimilars—Phase II clinical trials are not needed since the dosing scheme has already been defined by the reference biologic (Nickisch & Bode-Greuel, 2013; Lymphoma

Coalition, 2015). For biosimilars, Phase I may be used to demonstrate pharmacokinetic (PK) and pharmacodynamic (PD) comparability and Phase III may be used to confirm safety and efficacy comparability to the indication(s) established by the reference biologic (Lymphoma Coalition, 2015; Wang & Singh, 2014). Since the utility of a clinical trial for biosimilarity determination is still unknown, the FDA does not require a clinical component in the approval process of a biosimilar (Chow, 2014). As a result, the clinical trial study design can vary depending on the approach and development strategy of a biosimilar sponsor (Wang & Singh, 2014).

US Regulatory Framework for Biosimilars

Currently in the US, the pathway for generic approval is established under the Hatch-Waxman Act of 1984 (Wang & Singh, 2014). However, this law only applies to small-molecule generics. Since biopharmaceuticals are more complex and heterogeneous than small-molecules, the guidelines within the Hatch-Waxman Act cannot apply to biosimilars. As a result, on March 2010, Congress passed the Biologics Price Competition and Innovation Act (BPCIA) (under Subtitle VII of the Patient Protection and Affordable Care Act) to allow the FDA to create a regulatory pathway for biosimilars separate from the generic drug pathway observed by small-molecules (Bourgoin, 2011; Wang & Singh, 2014). Under this abbreviated biologic pathway, a biosimilar sponsor can apply for licensure by submitting a 351(k) BLA (U.S. Food and Drug Administration, 2015).

Challenges in the Development of a Biosimilar

While the FDA has created a regulatory pathway and guidance around biosimilars, FDA guidelines regarding the assessment of similarity (e.g., structural, functional, and clinical) are not as clearly defined as they are for small-molecule generics (Chow, 2014). As a result, the development approach for a biosimilar is open for interpretation. Since biosimilarity will be determined on a case-by-case basis and on the totality of a biosimilar package, each drug sponsor may have their own approach in demonstrating comparability between a biosimilar and its reference biologic (Wang & Singh, 2014; Chow, 2014). For example, a company sponsor with substantial experience in clinical trials but limited practice in analytical characterization, may feel comfortable addressing biosimilarity through extensive clinical trials rather than investing significant effort in preclinical development. As a result, the development of a biosimilar is expected to vary from company to company.

Biosimilars also experience a development challenge on the business end. Compared to typical small-molecule generics, the development of a biosimilar can range anywhere between $50 and $200 million compared to $1 and $3 million for a small-molecule generic (Nickisch & Bode-Greuel, 2013). Additionally, development times are longer for biosimilars with an average of seven to nine years (Nickisch & Bode-Greuel). Another challenge in the development of a biosimilar compared to a small-molecule generic is risk. While the risk in developing a biosimilar is inherently less than the development of a new drug—biosimilars bypasses the high-risk drug discovery phase—biosimilars only have a 50 to 75 percent probability of success compared to the 95 percent observed with small-molecule generics (Nickisch & Bode-Greuel, 2013). This

risk combined with cost, time, and manufacturing challenges, make the development of a biosimilar a more complicated undertaking than the typical generic drug.

The European Biosimilar Experience

The European Medicines Agency (EMA) is one of the first regulatory agencies to approve biosimilars. With several approved biosimilars, some of which include epoetins, somatropins, filgrastims, and antibodies (Epstein, Ehrenpreis, & Kulkarni, 2014), Europe accounts for 80 percent of the global spending in biosimilars (IMS Health, 2011). Currently, the greatest challenge with biosimilars in the European market is the varied uptake observed across countries and drug classes (IMS Health, 2011). Due to differences in pricing and sentiment across different countries in the EU, the uptake of a biosimilar can vary from country to country. For example, the biosimilar filgrastim (brand name: Neupogen) is priced at €149.7 in Germany, while in the UK the same biosimilar is priced at €74.1 (Rovira, Espin, Garcia, & Labry, 2011). As a result of this variance, a sizeable uptake difference is observed between both countries, with the UK experiencing greater uptake compared to Germany (IMS Health, 2011).

Despite the challenges in the uptake of a biosimilar in Europe, the European market is beginning to adapt to biosimilars. With biosimilar sales increasing from €3.3 million in 2007 to €65 million in 2009 (and the sales of respective reference biologics decreasing), the European biosimilar market is evolving into a more favorable market for payers (Rovira, Espin, Garcia, & Labry, 2011). As physicians and patients continue to gain experience with biosimilars and the policies surrounding biosimilars continue to mature, the European biosimilar market is expected to expand. This is already apparent in

the number of biosimilar applications filed to the EMA. In 2012, the EMA received an all-time high of seven biosimilar applications, compared to one biosimilar application filed in 2009 (Dalgaard, Evers, & Silva, 2013).

The US Biosimilar Business

This section provides context on the business of biosimilars. Expanding on the market of biosimilars, this section introduces and clarifies the opportunities and challenges that exist for biosimilars entering the US market.

Opportunity for the Biosimilars Market

As the patent cliff closes in on several top-selling biologics and the demand for low-cost alternatives continues to increase, the biosimilar market in the US is predicted to flourish over the next decade. Currently, the following issues are driving a favorable outlook for biosimilars: (1) US accounts for the majority of global spending in biologics (IMS Health, 2011), (2) expenditures in biologics have increased over time (Blackstone & Fuhr, 2013), and (3) over $50 billion in sales from biologics facing the loss of exclusivity (LOE) will be available for counterpart biosimilars (Grant Thornton, 2013). As a result, the US biosimilar market is projected to be one of the biggest opportunities in the generic drug industry by 2020 (IMS Health, 2011).

One of the main drivers in the market outlook for biosimilars is demand. With increasing expenditures and lofty prices observed in the biologics industry, there is a growing demand across a spectrum of stakeholders (e.g., payers, patients, physicians,

taxpayers, and healthcare policymakers) for the development of biosimilars. Although pharmaceutical drugs account for eight to ten percent of the total health care cost in major markets, the cost of biologics continues to escalate beyond the $10,000 range (Nickisch & Bode-Greuel, 2013). With the rise of cost exceeding the overall inflation rate—in 2010, biologics experienced an approximate nine percent increase over the consumer price index (Blackstone & Fuhr, 2013)—the US healthcare system is already beginning to feel the financial burden, primarily Medicare. Since Medicare covers all specialty drugs, there has been little incentive for innovator biologic companies to implement a price reduction (Blackstone & Fuhr, 2013). However, with the top six biologics consuming 43 percent of the pharmaceutical budget for Medicare Part B (Nickisch & Bode-Greuel, 2013), healthcare officials are advocating for biosimilars in hopes of reducing US healthcare costs.

One of the other factors influencing the biosimilar market is the barrier to entry. Although most generics are faced with high levels of competition, when it comes to biosimilars, the competitive landscape is expected to be less than those currently observed in the generic drug industry. With several challenges in the development of biologics, only a few drug companies will have the capabilities and fortitude to develop biosimilars. With a market in the billion-dollar range for some biologics, particularly monoclonal antibodies, the high barrier to entry will allow fewer competitors to enter the market, thus favoring those biosimilar that have penetrated the market. (Blackstone & Fuhr, 2013).

Lastly, biosimilars have a price advantage. Expected to cost 10 to 30 percent less than reference biologics (U.S. Federal Trade Commission, 2009), biosimilars have the

opportunity to capture larger profits given the minor reduction in cost. With the high barrier to entry, these margins are able to sustain for a longer period of time, especially when the biosimilar expands the access of treatment to patients who were unable to afford the therapeutic beforehand. Small-molecule generics, on the other hand, have significant price reductions (sometimes up to 85 percent) and a low barrier to entry, which results in high competition and thin margins for generic sponsors (Nickisch & Bode-Greuel, 2013).

Although biosimilar development costs are substantial, compared to new drugs, biosimilars exhibit reduced development cost, time, and risk. According to Blackstone and Fuhr (2013), the average cost of developing a new biotechnology drug is approximately $1.9 billion. This is significantly more than the average investment in the development of a biosimilar, which is estimated to be between $50 and $200 million (Nickisch & Bode-Greuel, 2013). A part of this is attributed to differences in development time, with biosimilars expecting two to six years less development than new biologics (Nickisch & Bode-Greuel, 2013; Wang & Singh, 2014). Lastly, biosimilars exhibit a greater likelihood of success than new drugs. With 95 percent of all new drugs in an R&D pipeline never making it to market (Blackstone & Fuhr, 2013), biosimilars embrace a greater chance of reaching market with a 50 to 75 percent probability of success (Nickisch & Bode-Greuel, 2013).

Uncertainties of the Biosimilars Market

One of the biggest issues of uncertainty in the biosimilar market is uptake. Given the novelty of biosimilars, the US is expected to experience a slow uptake in biosimilars

during the first few years in market. However, this is expected to change as biosimilars continue to penetrate the US market and establish a presence in the clinic. With Europe's recent increase in biosimilar uptake and their lack of issues surrounding safety (Blackstone & Fuhr, 2013), analysts believe the uptake will surge by 2020, when the US will be the leading market for biosimilars (IMS Health, 2011). However, this forecast will be contingent on pricing. If the price difference between biosimilars and reference biologics is minimal, there is a possibility that payers may not adopt biosimilars. As a result, in the US, pricing will be a determining factor in biosimilar uptake.

Another area of uncertainty is the FDA and its approval method. Different levels of biosimilarity could result in a difference in market share for biosimilars approved as highly similar versus those approved as similar but not interchangeable. The lack of interchangeability could influence a patient to select a reference biologic over its biosimilar, despite the tradeoff in cost. Although the issue of interchangeability is a potential risk in the investment of biosimilars, only a few biosimilars will be impacted since physicians administer the majority of biologics directly (Blackstone & Fuhr, 2013). With substitution at the discretion of the physician rather than the pharmacy, there is an opportunity to influence physicians to side with a biosimilar, should a biosimilar exhibit comparable safety and efficacy to the reference biologic.

The last major hurdle and uncertainty in the biosimilar market is the impact of clinical trials. Currently, the FDA does not require clinical trials when comparing the safety and efficacy of a biosimilar to its reference biologic (Chow, 2014). However, in the case of interchangeability, the FDA requires clinical trials in demonstrating biosimilarity (Chow, 2014). This ambiguity in clinical trials could impact development

costs for a given biosimilar. Another potential challenge with clinical trials is recruitment. Biosimilars target a population of severely ill subjects and many may be inclined to avoid the hassle and risk of a clinical trial and pursue treatment with the reference biologic (Blackstone & Fuhr, 2013). This reservation could make patient recruitment very difficult for biosimilars, especially for those biosimilars that treat rare diseases where the patient population is already very small.

Determining the Value of Therapeutics

The goal of this section is to introduce the investment side of therapeutics. Here, the theme of value creation is presented and the methods to determine value are explained. In particular, this section focuses on the net present value (NPV) model used in the value determination of drug products.

Value Creation and Valuations

Along with providing a service or good, the ultimate goal of a business is to create value. While value can be defined in various ways, for pharmaceutical/biotechnology products, value is typically defined in terms of economic earnings—the amount of revenue that exceeds all costs associated with the product (Fuller, 2001). When cash inflows exceed cash outflows, the business is said to be generating value. This concept of value creation can also be applied towards future investments (Higgins, 2009; Bode-Greuel & Greuel, 2005; Stewart, Allison, & Johnson, 2001). For the pharmaceutical/biotechnology industry, the ability to estimate the future value of a product and/or technology is critical in the decision making process of a company. Since investments in the pharmaceutical/biotechnology sector require significant capital and

time, a company's success is dependent on its ability to provide accurate valuations of its future investments.

According to Professor Robert Higgins (2009), there are three critical components in determining the value of an investment: the determination of future cash flows, the figure of merit, and the figure of merit to an acceptance criteria. The first component, the determination of future cash flows (i.e., forecasting), is the annual revenue that is projected from a product and/or service. In the pharmaceutical/biotechnology industry, this is usually presented as the revenue expected from sales, royalty payments, and/or milestone payments (Bode-Greuel & Greuel, 2005; Stewart, Allison, & Johnson, 2001). Unlike the two components that are more direct, the determination of future cash flow is a challenging process that requires a thorough understanding of a company's product/service, market, and strategy (Higgins, 2009). One of the greatest challenges in forecasting is the need to integrate qualitative inputs into quantitative outputs. For example, in the pharmaceutical/biotechnology industry, sales is mostly driven by external factors in the market, such as competition, patient size, healthcare policies, clinical perception, price, and clinical effectiveness (Cook, 2006). As a result, in order to provide an accurate assessment of future cash flow in the pharmaceutical/biotechnology industry, the forecaster must understand both the business of drug development and the market of the drug candidate.

The second component to a valuation, the figure of merit, is the number that summarizes an investment's worth (i.e., value creation) (Higgins, 2009). While there are a variety of approaches in determining the figure of merit, one common approach used in the pharmaceutical/biotechnology industry is the NPV model (Bode-Greuel & Greuel,

2005; Stewart, Allison, & Johnson, 2001). A forward-looking financial model, the NPV takes into account all potential cash flows (in and out) throughout the life of a given investment and provides a projection of future value (Bode-Greuel & Greuel, 2005; Nickisch & Bode-Greuel, 2013; Stewart, Allison, & Johnson, 2001; Higgins, 2009).

The last component to a valuation, the figure of merit to an acceptance criteria, is the method of comparison used to determine if the output (from the financial model), warrants acceptance of an investment (Higgins, 2009). For an NPV, the acceptance criteria is straightforward. Since the output of the NPV is a monetary value, results from the NPV can be viewed as an increase or decrease in wealth accruement (Higgins, 2009). In other words, if the NPV results in a positive value ($NPV > 0$), the investment is expected to create value; however, if the NPV results in a negative value ($NPV < 0$), the investment is expected not to create value (Higgins, 2009; Bode-Greuel & Greuel, 2005; Higgins, 2009; Nickisch & Bode-Greuel, 2013). When comparing across products, the NPV with the highest value is reported as the investment with greatest value potential.

The NPV Model

The NPV model can be broken down into three major estimates: revenue, cost, and time (Stewart, Allison, & Johnson, 2001). The first estimate, revenue, goes back to the earlier concept of future cash inflow and forecasting (Bode-Greuel & Greuel, 2005; Stewart, Allison, & Johnson, 2001). In the case of a therapeutic, the goal of forecasting is to create an estimate of future cash inflow based on the annual sales that are anticipated for the drug over its lifetime (Stewart, Allison, & Johnson). This consists of all the revenues generated (from sales) both before and after LOE (Bode-Greuel & Greuel).

Revenue after LOE is commonly referred to as terminal value and is usually expected to be diminish over time given the impact of competition (e.g., generics and emerging therapeutics) and product substitution (Bode-Greuel & Greuel).

Another estimate of the NPV model, cost, is the expense of the investment. This would consist of all the costs associated in the development of a drug (Stewart, Allison, & Johnson, 2001). For new drugs, this includes discovery, preclinical, and clinical phases. In addition to the expenses of development, there are also costs in the commercialization of a drug, such as: (1) cost of goods sold (COGS) and (2) selling, general and administrative (SG&A) expenses (Bode-Greuel & Greuel, 2005). Similar to the qualitative components that go into the projection of revenue, costs must accurately reflect the environment of the market and product (Bode-Greuel & Greuel). For example, different drugs may have different commercialization needs (e.g., salesforce and marketing) depending on the target market of the drug (Bode-Greuel & Greuel). As a result, costs must be tailored to the product in order to provide credible assumptions in the NPV model.

The third estimate of an NPV model is time. Here, time is in the context of money and the present value of a future sum (Higgins, 2009). Since money in the present has greater value than money in the future, a discount rate must be applied to the NPV to reflect the monetary loss in value over time (Stewart, Allison, & Johnson, 2001). For a company that is generating revenue, the discount rate is reflective of the investment risk and rate of return observed in investments with the same risk (Higgins). For example, in the drug development business, it is customary for large pharmaceutical companies to have a lower discount rate than a startup biotechnology company, since startup ventures

have greater inherent risk than investments in well-established companies (Bode-Greuel & Greuel).

Another optional estimate that can be included in the NPV model, is the probability of success (POS) for the investment (Bode-Greuel & Greuel, 2005). In the pharmaceutical/biotechnology industry, POS is usually perceived as the risk in the development and approval of a drug. Although risk of development is not a necessary component in the calculation of an NPV, in the industry, it is regularly incorporated in the NPV model given the high-level of risk observed in the development of drugs. Here, the NPV is referred to as a risk-adjusted net present value (rNPV) (Stewart, Allison, & Johnson). When calculating the rNPV for a pharmaceutical/biotechnology product, each stage of the drug development process is evaluated in terms of a POS (Stewart, Allison, & Johnson, 2001). For a new drug, this would include the following development stages: discovery and preclinical, clinical (Phases I-III), and regulatory (Bode-Greuel & Greuel).

Financially Valuating Biosimilars

Building on the previous segment, this section applies the previous concept of value determination to biosimilars. In doing so, this section expands on the NPV model and its applicability toward the financial evaluation of biosimilar development candidates. This section also introduces and provides context on the valuation model challenged in this case study.

Applying an NPV Model towards Biosimilars

While a standardized approach in the financial assessment of biosimilars does not exist, the NPV model described earlier can be applied to financially assess biosimilar development candidates (Bode-Greuel & Greuel, 2005; Nickisch & Bode-Greuel, 2013; Stewart, Allison, & Johnson, 2001). Since biosimilars exhibit different development hurdles and risks compared to new drugs, it is critical to incorporate these differences in the NPV to accurately reflect the valuation of a biosimilar versus a new drug. Beginning with the development pipeline, biosimilars must go through a preclinical, clinical, and regulatory process (Nickisch & Bode-Greuel). Although the development pipeline is similar across all biosimilars, the approach within each stage will vary depending on the molecule and biosimilar sponsor. Since biosimilar regulatory guidelines are evolving on clinical trials, the clinical trial design is subject to these variations (Chow, 2014). Both Phase I and III clinical trials are relevant to biosimilars, however, a biosimilar sponsor may choose to conduct both trials, conduct a single trial, or forgo the entire clinical stage depending on their comparability strategy (Wang & Singh, 2014). Therefore, it will be important to understand the development and regulatory strategy of a biosimilar sponsor when calculating the NPV.

Once the sponsor's approach has been identified and defined, base case assumptions for the biosimilar NPV can be established. These base case assumptions include: (1) development time, (2) development cost, (3) POS, (4) expected revenue via forecasted sales, (5) COGS, (6) SG&A, (7) tax rate, (8) inflation rate, and (9) discount rate. While some of the base case assumptions may be applicable to all biosimilars, some assumptions can be product-specific. For example, estimates such as development cost

and revenue, can vary significantly based on the market of the biosimilar development candidate.

The Nickisch and Bode-Greuel Study

In 2013, Nickisch and Bode-Greuel published a study on the financial attractiveness of biosimilars based on sales from various reference biologics. Using an NPV model with peak sale scenarios for biosimilars, the Nickisch and Bode-Greuel valuation concluded that the value creation of a biosimilar will be driven by the sales of its reference biologic. In other words, biosimilars to reference biologics with large sales will result in a greater valuation. While this study deserves praise for being one of the few business cases to discuss the biosimilar business and the applicability of an NPV towards the financial evaluation of a biosimilar, the Nickisch and Bode-Greuel study has two major shortcomings.

As stated earlier, one of the most important components of a valuation is the determination of future cash flow (Higgins, 2009). Unlike the calculation of an NPV that requires technical execution, forecasting future cash flows requires extrapolation based on product knowledge and market insight (Higgins, 2009). This was one of the shortcomings of the Nickisch and Bode-Greuel (2013) study. Rather than applying a product-specific forecast that takes into account the market dynamics that can impact the future cash flow of a given biosimilar, the study utilized a general and static forecast (based solely on the sales of reference biologics) for all biosimilars. For example, instead of treating biosimilars individually, all biosimilars to reference biologics generating $5 billion or more in sales, were treated equally and assumed to provide equal returns.

The second shortcoming to the Nickisch and Bode-Greuel (2013) study is a direct consequence of the imprecise approach implemented above (i.e., the calculation of future cash flows). In this case, the inappropriate calculation of future cash flow resulted in a skewed financial analysis. With a valuation favoring biosimilars based on the sales generated by the reference biologic, the Nickisch and Bode-Greuel valuation created a perception that the biosimilar opportunity is best suited for those reference biologics generating the largest sales figures. Lacking an analysis to a specific biosimilar and its market, the valuation in this study misleadingly implied that a biosimilar for a reference biologic generating $5 billion in sales would be a better investment than a biosimilar for a reference biologic generating $2.5 billion in sales (Nickisch and Bode-Greuel).

Chapter III

Methods and Analysis

As stated by Yin (2014), the main goal of a case study is to gather insight in real-world context. One method that can provide this kind of resolution is a case study with a quantitative outcome analysis (Yin, 2014). To test the hypothesis of this case study, various biosimilar development candidates were screened, selected, and quantitatively evaluated. In conducting this analysis, many procedures were implemented to uncover the findings from this case study. To explain these procedures in detail, this chapter highlights two approaches: selection and valuation. The selection section explains the screening approach utilized in the collection of biosimilar development candidates and the valuation section explains the quantitative model implemented in the financial evaluation of the biosimilar development candidates selected.

Selection of Biosimilar Development Candidates

Using data triangulation as a method for data collection (Yin, 2014), various sources of evidence were used to screen biosimilar candidates. To select the biosimilar candidates, the data collected from each candidate was applied towards a weighted metric analysis that analyzed their commercial attractiveness on nine market dynamics. Based on this analysis and the requirements set forth in the hypothesis, two biosimilar

candidates were ultimately selected for financial evaluation. This section will elaborate more on the screening and selection approach applied in this case study.

Screening Biosimilar Candidates

Prior to analyzing the commercial attractiveness of a biosimilar development candidate, a preliminary screen was implemented to reduce the number of biosimilar candidates and to identify the candidates that were most appropriate in testing the hypothesis. In this preliminary screen, three filters were applied in the following order: molecule type, expected biosimilar launch date, and sales (Figure 1).

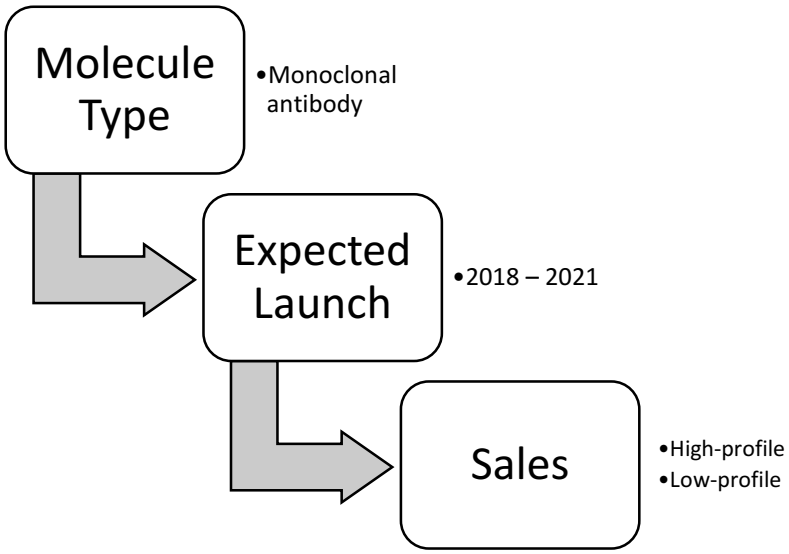

Figure 1. Screening process for preliminary selection of biosimilar candidates. This illustration captures the screening process starting with molecule type, expected launch date, and sales.

For the first filter, molecule type, only biosimilar monoclonal antibodies were explored. Since the case study revolves around the theme of sales, particularly sales greater than $1 billion, monoclonal antibodies were selected due to their ability to generate sales in this range. In addition, monoclonal antibodies share similar development costs and risk compared to other biologics. This allows for antibody-based products to be compared across a common benchmark.

The second filter implemented in the preliminary screen was expected biosimilar launch date. Regarded as the year in which the biosimilar will enter the market, this date is contingent on the LOE of the reference biologic. Since launch date can impact a valuation, it is critical to select a year that can be compared across all biosimilar candidates and that is within a reasonable range for forecasting (late LOEs could result in less accurate projections). As a result, only biosimilars for reference biologics with LOEs between 2018 and 2021 were evaluated. This range was selected for the following reasons:

1. Allows the valuation to implement assumptions based on current data (e.g., market dynamics and regulatory policies).
2. The three year gap in patent expiry allows biosimilar valuations to be compared across each other—most external environments are expected to maintain the same within this three year timeframe.
3. Reflects expected entrance of biosimilars in the US market. Since preliminary FDA guidance on biosimilars was released in 2012 (Blackstone & Fuhr, 2013), a biosimilar development start date around this time would result in an approximate launch year between 2018 and 2021.

The last and most relevant filter applied was sales. Using 2013 worldwide sales figures from the reference biologic as a base case, biosimilar candidates were separated into two categories. Biosimilars for which the reference biologic generates more than $5 billion in sales were labeled as high-profile biosimilars; biosimilars for which the reference biologic generates less than $2.5 billion in sales were labeled as low-profile biosimilars. By binning biosimilar candidates as high-profile or low-profile, candidates from each group were compared on the basis of sales and used to challenge the findings from the Nickisch and Bode-Greuel (2013) study.

Commercial Assessment for Biosimilar Candidates of Interest

Based on the preliminary screening above, four biosimilar candidates—two from each sales category, high-profile and low-profile—were selected for commercial analysis. Focusing primarily on the external factors that may influence biosimilar sales, a commercial assessment was conducted based on nine key market dynamics (Appendix A). Using a metric score from 1 to 5, biosimilar candidates were graded on each market dynamic; 5 representing a favorable outlook and 1 representing an unfavorable outlook.

In addition to an individual score, a weight was applied to each market dynamic. Since market dynamics have varying degrees of impact and cannot be considered equal, a degree of impact was assigned to each market dynamic. With low, medium, and high degrees of impact, each degree was assigned a weight of 1x, 2x, or 3x, respectively. Based on the degree of impact, the original score was then weighted to determine the aggregate score. For example, if a biosimilar candidate scored a 5 in population size

capture, a final score of 10 was recorded for that market dynamic since population size capture exhibits a medium impact (i.e., 2x).

Once all scores and weights were totaled, a percent commercial attractiveness (out of 100 points) was calculated for each biosimilar candidate. This percent denoted the overall commercial attractiveness of the biosimilar candidate—with a score of 100 percent representing an ideal commercial candidate. Based on this commercial attractiveness score, two biosimilar candidates were selected (in accordance with the requirements set forth in the hypothesis) for financial evaluation.

Financial Evaluation of Selected Biosimilar Development Candidates

With the two biosimilar candidates selected from the previous section, a quantitative NPV model (tailored to biosimilars) was applied to each candidate for value determination. To execute the NPV analysis, various inputs and assumptions were applied to the model to accurately access and compare the value of each biosimilar candidate. This section will elaborate on the inputs and assumptions used as well as the calculation of the NPV in the biosimilar valuation.

NPV Inputs and Assumptions

As explained in Chapter II, an NPV model can be applied in the valuation of therapeutics. In this case study, the NPV model was augmented to allow biosimilars to be assessed based on their corresponding development and regulatory pathways for market entrance in the US. Prior to the calculation of the NPV, various inputs and assumptions

specific to each biosimilar candidate were applied to the model. The following section will explain each input and assumption.

Future cash flow. In the NPV, future cash flow (i.e., revenue) was determined based on the forecasted US sales of the biosimilar development candidate over a ten year span. In forecasting annual sales for each biosimilar candidate, three components were analyzed: biosimilar market share, biosimilar price, and biosimilar demand. While the calculation approach is identical for each biosimilar candidate, it is important to note that the sales forecast for each biosimilar candidate differed since each candidate had a different share, price, and demand due to its individual market outlook.

In calculating annual biosimilar market share, the commercial assessment from the previous section was taken into consideration. With an anticipated biosimilar market share between 10 and 30 percent in the US (U.S. Federal Trade Commission, 2009), the annual market share for each biosimilar candidate was calculated within this range. Since uptake is expected to increase every year the product is marketed, market share for each candidate was slightly increased every year to reflect this occurrence.

According to the US Federal Trade Commission (2009), biosimilars are expected to undergo a 10 to 30 percent pricing discount relative to the reference product. Based on this prediction, the sales price of each biosimilar was determine by taking a 25 percent discount to the reference product's average sales price (ASP). This amount reflects the bottom line price after all deductions (e.g., rebates and discounts).

To calculate biosimilar demand, the demand of the reference biologic was first determined—this was accomplished by taking the reference product's ratio of annual

sales to ASP. Using this demand, the annual demand change for the reference biologic was then calculated for each year. Based on this calculation, demand change after LOE was extrapolated based on trend and market outlook. For example, if the demand for a reference biologic was trending down one or two percentage points annually and the market outlook appeared unfavorable, then a downward trend was assumed for years after LOE. Once the demand change was determined for ten years after LOE, the annual biosimilar demand was then conversely calculated based on the annual market share expected for each biosimilar candidate.

Using the values obtained from above, both biosimilar demand and price were utilized to forecast the annual sales of each biosimilar candidate. Extending ten years from launch, annual sales were used as the measure of future cash flow.

Development time. The average development time expected for biosimilars is eight to ten years (U.S. Federal Trade Commission, 2009). Based on this average, this case study applied an eight year development timeline for biosimilars. This eight year timeline was applied towards the NPV of each biosimilar candidate based on the LOE of the reference biologic. For example, if a reference biologic had an LOE of 2021, development for the counterpart biosimilar was initiated on 2013 (8 years before LOE).

Within the eight year development period, each stage of development was assigned a specific development time. Similar to the Nickisch and Bode-Greuel (2013) study, biosimilar development time for each stage was defined as follows:

- Preclinical: 3 years
- Phase I (clinical): 1 year

- Phase III (clinical): 3 years
- Regulatory: 1 year

Cost. According to the U.S. Federal Trade Commission (2009) report on biosimilars, the total development cost for a biosimilar candidate is expected to average between $100 and $200 million. Using this range as a criterion, the biosimilar development cost for the valuation in this study fell within mid-range of the expected cost, approximately $154 million. The $154 million reflects all development costs (including regulatory) expected in bringing a biosimilar development candidate to market in the US (Table 2).

Table 2. Biosimilar development pipeline and cost.

Development stage	Average length of time (years)	Average cost (million)
Preclinical	3	$90
Clinical (Phase I)	1	$8
Clinical (Phase III)	3	$54
Regulatory	1	$2
Total	**8**	**$154**

Note. Anticipated development stages, timing, and costs for biosimilars to reach the US market. Development cost and timing adapted from Nickisch and Bode-Greuel (2013).

Probability of success. While the calculation of a standard NPV does not require a measure of risk, the rNPV requires risk. Since this case study presented both NPV and rNPV values, risk was determined based on the POS of each stage in the development

and approval of a biosimilar—this was adapted based on data from the Nickisch and Bode-Greuel (2013) study. For biosimilars, this included: preclinical, Phase I (clinical), Phase II (clinical), and regulatory approval. Based on the POS of each stage, a decision tree was created to determine the various scenarios (e.g., pass or fail) that could occur in bringing a biosimilar candidate to market. Since each scenario builds from the previous outcome, an aggregate POS was calculated for each scenario and applied to the NPV model. Figure 2 illustrates the decision tree and the POS for both stage and aggregate scenarios.

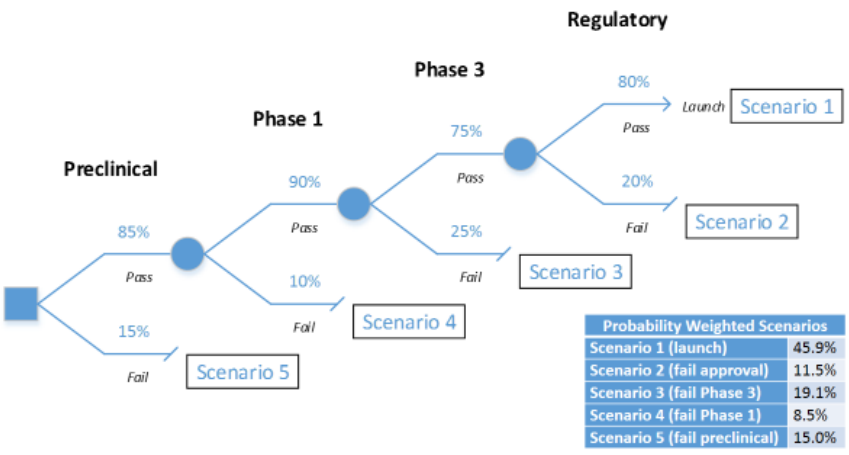

Figure 2. Development probability of success for biosimilars in the US. This figure illustrate the risk in the development of a biosimilar candidate through a stage-based POS metric scheme. Based on the development pipeline for biosimilars, this case study acknowledged five possible scenarios, each with a probability-weighted success rate. POS for each development stage adapted from Nickisch and Bode-Greuel (2013).

Cost of goods sold. COGS are the total costs absorbed in the production of a product. In manufacturing a biosimilar, there are various costs involved in the production,

formulation, and packaging of the product. Since the most expensive component is the production of drug substance (i.e., the active ingredient of the drug), the COGS for this case study reflect the cost of manufacturing drug substance. Using the reference biologic as a benchmark (Appendix B), COGS for each biosimilar candidate were extrapolated based on the reference product's estimated cost in manufacturing drug substance and the individual market outlook of each biosimilar candidate (Appendix C).

The COGS calculated in this case study reflect similar estimates to the BioProcess Technology Consultants (2012) report and are less than 10 percent—a reasonable standard for biologics (Schnarr & King, 2010).

Selling, general and administrative expenses. Similar to COGS, SG&A expenses are the costs incurred in bringing a product to market. However, unlike COGS, SG&A is not dependent on product manufacturing. Rather, it is the cost of selling the product that involves all general and administrative expenses (e.g., marketing, salesforce, and overhead). Using 20 percent SG&A as a baseline for biosimilars (Nickisch & Bode-Greuel, 2013), the SG&A for each biosimilar candidate was determined based on its individual market outlook. If the biosimilar candidate had various indications in different therapeutic areas, than a higher SG&A was assigned since the product would require additional marketing and salesforce. Subsequently, if the biosimilar candidate had only one indication, then a lower SG&A was assigned.

Tax rate. Since there are various tax codes in the pharmaceutical/biotechnology sector and tax rates vary from company to company, for the purposes of this case study, a fixed tax rate of 20 percent was applied to the NPV model. This rate was established based on

the approximate average tax rate (from 2012) for various large pharmaceutical companies, such as, Amgen, Lilly, Merck, and Biogen Idec (Rockoff, 2013).

Inflation rate. According to US banking standards, the annual inflation rate is approximately two percent (Appelbaum, 2015). Based on this norm and the assumption of a two percent inflation rate implemented in other valuations, such as those conducted by Bode-Greuel and Greuel (2005) and Nickisch and Bode-Greuel (2013), this case study also implemented a two percent inflation rate in the NPV model.

Discount rate and factor. In the pharmaceutical/biotechnology industry, the discount rate fluctuates between 10 and 30 percent (Bode-Greuel & Greuel, 2005). For large established pharmaceutical companies, the average discount rate applied in an evaluation is around 10 percent. A smaller biotech company on the other hand, usually experiences a higher discount rate closer to 30 percent. For purposes of this case study, based on the discount rates applied in previous pharmaceutical/biotechnology valuations, such as Bode-Greuel and Greuel (2005) and Nickisch and Bode-Greuel (2013), a fixed 10 percent discount rate was applied in the NPV model.

Using a 10 percent discount rate, the annual discount factor for the biosimilar NPV was subsequently determined. Assuming a mid-year cash flow from the start of development, the discount factor for the entire NPV model (8 years of development and 10 years of sales after LOE) was calculated. This was computed using the following equation, similar to Elmerraji (2007):

$$Discount\ Factor = \frac{1}{(1 + Discount\ Rate)^{Period\ of\ Time\ in\ Years}}$$

Terminal value. While biosimilar sales are expected to erode after ten years (due to competition and substitution), this case study assumes that biosimilars will have terminal value after ten years of market capture—while sales may be significantly less, these sales still account for future cash flow. To determine this value, the terminal growth rate was first determined for each biosimilar candidate based on their individual biosimilar demand. Since biosimilar demand decreases after 10 years (according to the forecast in this case study), the terminal growth rate for each biosimilar candidate resulted in a negative value—the exact value was calculated based on the demand trend towards the end of the ten year forecast.

Once terminal growth rate was determined, terminal value was then calculated using both the sales from the last year of forecast and the discount rate. Applying the approach from Lacovides (2013), the following equation was used to determine terminal value:

$$Terminal\ Value = \frac{Discounted\ Cash\ Flow \times\ (1 + Terminal\ Growth\ Rate)}{Discount\ Rate - Terminal\ Growth\ Rate}$$

NPV Calculation

For this case study, two types of NPVs were calculated for each biosimilar development candidate, a standard NPV and an rNPV. While both NPV models result in a different output, the input and assumptions determined in the earlier sections apply to both models—the only difference is the inclusion of risk for the rNPV calculation.

Based on the input and assumptions from this case study, the NPV was calculated according to the difference between cash inflows (e.g., sales revenue) and cash outflows

(e.g., costs) (Higgins, 2009). Using both the discount factor and the net cash flow (with the inclusion of terminal value), the NPV was calculated for each biosimilar candidate via the following formula, augmented from the Stewart, Allison, and Johnson (2001) equation:

$$NPV = Net\ Cash\ Flow \times Discount\ Factor$$

In addition to the NPV output, the rNPV was computed. Using the POS from the previous section as the component of risk, the NPV was calculated for each POS scenario. Based on the NPV of each scenario, an aggregate NPV score was determined for each biosimilar candidate. This aggregate score was defined as the rNPV.

Case Study Research and Tools

Using data triangulation, both primary and secondary research was used to support the selection and evaluation of biosimilar development candidates (Appendix D). To quantitatively evaluate biosimilar development candidates, an analytical spreadsheet was utilized. Using Microsoft Excel (version 2013), two quantitative models (commercial assessment and NPV) were created for the purposes of this case study. All calculations were computed via this tool.

Chapter IV

Results

To test the hypothesis, this case study was broken down into two analyses. First, the selection of two biosimilar development candidates. Then, the NPV evaluation of the two biosimilar candidates selected. The next two sections reveal the findings from each analysis.

Biosimilar Candidates Selected for Financial Evaluation

In order to fulfill the requirements set forth in the hypothesis, four biosimilar development candidates were screened and selected for commercial assessment. These candidates included: (1) two high-profile biosimilars, Herceptin (trastuzumab) biosimilar and Remicade (infliximab) biosimilar and (2) two low-profile biosimilars, Soliris biosimilar (eculizumab) and Xolair (omalizumab) biosimilar. For product information on each biosimilar development candidate, refer to Appendices E-H.

Using a commercial assessment consisting of nine key market dynamics, the commercial attractiveness of the four biosimilar candidates selected were analyzed and compared (Appendix I). Of the high-profile biosimilars, Herceptin biosimilar and Remicade biosimilar scored 68 and 55 percent, respectively; whereas the low-profile biosimilars, Soliris biosimilar and Xolair biosimilar, scored 89 and 50 percent, respectively. Based on these scores and the market requirements from the hypothesis, one

biosimilar candidate from each sales category (high-profile and low-profile) was selected for financial evaluation. This consisted of a Remicade biosimilar and a Soliris biosimilar.

NPV Analysis of Biosimilar Development Candidates

Based on the development candidates selected, Remicade and Soliris biosimilars, an NPV evaluation was conducted to compare the value potential of each candidate. Using specific NPV inputs and assumptions for biosimilars, each biosimilar development candidate was valuated with the parameters established in Chapter III (Appendices J and K). For the Remicade biosimilar, the NPV model started in 2010 and was forecasted up to 2027 (assuming a 2018 LOE for the reference biologic). After inclusion of terminal value, the Remicade biosimilar resulted in a positive value for both the NPV and the rNPV, with a value of $249 million and $66 million, respectively (Table 3).

Table 3. Valuation of a Remicade biosimilar development candidate.

Standard NPV	
Total Discounted Cash Flow	$243,015,032.49
Terminal Value	$5,863,277.95
NPV	**$248,878,310.44**
Risk-adjusted NPV	
NPV - Scenario 1	$114,235,144.49
NPV - Scenario 2	-$11,916,169.97
NPV - Scenario 3	-$19,692,298.80
NPV - Scenario 4	-$6,305,606.92
NPV - Scenario 5	-$10,355,946.11
rNPV	**$65,965,122.70**

Note. This table illustrates both NPV and rNPV values for a Remicade biosimilar development candidate. For NPV, total discounted cash flow and terminal value were used in the final calculation. For rNPV, the same NPV method was implemented, however, the element of risk (i.e., POS) was included via scenarios 1-5. The combination of all scenarios resulted in the rNPV.

Similarly, a positive valuation was also observed for the low-profile biosimilar candidate, Soliris biosimilar. With the NPV model running from 2013 to 2030 (assuming a 2021 LOE for the reference biologic) and terminal value accounted for, an NPV of $551 million and an rNPV of $205 million was observed (Table 4).

Table 4. Valuation of a Soliris biosimilar development candidate.

Standard NPV	
Total Discounted Cash Flow	$517,194,408.31
Terminal Value	$33,566,901.38
NPV	**$550,761,309.70**
Risk-adjusted NPV	
NPV - Scenario 1	$252,799,441.15
NPV - Scenario 2	-$11,916,169.97
NPV - Scenario 3	-$19,692,298.80
NPV - Scenario 4	-$6,305,606.92
NPV - Scenario 5	-$10,355,946.11
rNPV	**$204,529,419.36**

Note. This table illustrates both NPV and rNPV values for a Soliris biosimilar development candidate. For NPV, total discounted cash flow and terminal value were used in the final calculation. For rNPV, the same NPV method was implemented, however, the element of risk (i.e., POS) was included via scenarios 1-5. The combination of all scenarios resulted in the rNPV.

According to the results above, both Remicade and Soliris biosimilars have the ability to generate value. With positive NPVs and rNPVs, it could be argued that either biosimilar would be a fruitful investment. However, when the two biosimilars are compared head-to-head, it is evident that a Soliris biosimilar captures greater value over time. Despite being a low-profile biosimilar, the Soliris biosimilar has a better valuation by more than 60 percent (over $100 million in value) compared to the Remicade biosimilar.

Chapter V

Discussion

Based on the findings from this case study, many inferences can be drawn that address the biosimilar business and the valuation of biosimilars. This section will discuss these outcomes in detail and will also expand on other development scenarios that are applicable to the analyses conducted in this study. This section will also present some of the challenges and limitations of the study as well as other considerations in the valuation of biosimilars, particularly socioeconomic value, which was not taken into account but is of value in future studies.

Case Study Findings

In this case study, two biosimilar development candidates with contrasting sales, Remicade biosimilar (i.e., high-profile biosimilar) and Soliris biosimilar (i.e., low-profile biosimilar), were financially evaluated and compared. Based on the findings from this study, both Remicade and Soliris biosimilars exhibited positive NPVs and rNPVs, demonstrating value capture. However, the Soliris biosimilar outperformed the high-profile Remicade biosimilar. This suggests that a Soliris biosimilar development candidate can be a better investment than a Remicade biosimilar development candidate.

Three main reasons why the valuation in this case study favored a Soliris biosimilar over a Remicade biosimilar are as follows:

1. **Soliris biosimilar is expected to generate more revenue than Remicade biosimilar.** Over the time span of ten years (from biosimilar launch), the Soliris biosimilar was estimated to generate a total of $2.8 billion in product revenue versus the $1.6 billion for the Remicade biosimilar (refer to Appendices J and K). This significant difference in revenue is a reflection of Remicade's market and its unfavorable outlook with regards to future competition and lack of lifecycle management. Soliris, on the other hand, expects minimal competition in the future and has the potential to expand the label with new indications. This label expansion could allow the biosimilar to capture additional sales in those new indications.
2. **Remicade biosimilar will require more commercial resources than Soliris biosimilar.** Remicade treats eight indications whereas Soliris treats only two indications (refer to Appendices F and G). As a result, a Remicade biosimilar is expected to need additional salesforce to support product commercialization as opposed to the Soliris biosimilar. This increase in need resulted in additional costs in the NPV model for the Remicade biosimilar with a 15 percent SG&A cost compared to the 10 percent SG&A cost for the Soliris biosimilar (refer to Appendices J and K).
3. **Remicade biosimilar is estimated to have higher manufacturing cost of goods than a Soliris biosimilar.** While the Remicade biosimilar is expected to have greater demand than the Soliris biosimilar, the price for Soliris is considerably higher. For example, per milligram, the selling price for Soliris is $15.52, while the selling price for Remicade is less than half at $6.59. As a result, the cost to

make a Soliris biosimilar is expected to be less than the cost to make a Remicade biosimilar (refer to Appendix B). This was reflected in the NPV model with the Remicade biosimilar experiencing a greater percentage in COGS than the Soliris biosimilar (refer to Appendices J and K).

Case Study Scenarios

To challenge the outcome of this case study and its applicability towards biosimilars with greater uncertainty, various development scenarios were analyzed for a Soliris biosimilar candidate. While the base case scenario for this case study can apply towards the development of most biosimilars, Soliris presents a unique situation. Given its status as an orphan drug, a Soliris biosimilar may encounter different uncertainties throughout the development process that may change the valuation of the biosimilar. In particular, risk and cost can vary. As a result, three plausible development scenarios with different risk and/or cost outcomes were analyzed for a Soliris biosimilar.

Scenario One: Increased Clinical Cost

One scenario that may be different for a Soliris biosimilar lies in development cost, specifically clinical costs. The average price of Soliris is significantly greater than most biologics, therefore, there is a possibility for a Soliris biosimilar to experience increased expenses in the clinical trial stage (in biosimilar clinical trials, the biosimilar must be compared against the reference product thus various lots of the reference product must be purchased). To take into account the increase in cost due to the acquisition of Soliris reference product, a scenario with a 50 percent increase in clinical trial costs

(compared to the case study base case) was applied toward the Soliris biosimilar valuation. Despite the increase in clinical costs (total development cost with 50 percent increase in clinical expenses was $216 million), the Soliris biosimilar was able to maintain both a positive NPV and rNPV above the Remicade biosimilar valuation (Table 5).

Table 5. Valuation for a Soliris biosimilar development candidate under scenario one assumptions.

Standard NPV	
Total Discounted Cash Flow	$483,267,780.78
Terminal Value	$33,566,901.38
NPV	**$516,834,682.17**
Risk-adjusted NPV	
NPV - Scenario 1	$237,227,119.11
NPV - Scenario 2	-$15,809,250.48
NPV - Scenario 3	-$26,180,766.32
NPV - Scenario 4	-$6,742,844.37
NPV - Scenario 5	-$10,355,946.11
rNPV	**$178,138,311.84**

Note. This table illustrates both NPV and rNPV values for a Soliris biosimilar development candidate under scenario one assumptions (increased clinical cost). For NPV, total discounted cash flow and terminal value were used in the final calculation. For rNPV, the same NPV method was implemented, however, the element of risk (i.e., POS) was included via scenarios 1-5. The combination of all scenarios resulted in the rNPV.

Scenario Two: Increased Development Risk

Another plausible scenario in the development of a Soliris biosimilar is the increase in development risk. Since a Soliris biosimilar may present development

challenges in the preclinical (Soliris is manufactured in a less commonly used cell line making it more technically challenging to replicate than most biologics) and/or clinical stage (recruitment may be a challenge due to small patient population), a higher burden of risk is conceivable. As a result, a scenario with a reduced POS was applied to account for the increase in development risk. By reducing the POS for both preclinical and clinical (Phase I and III) stages by 10 percent, the probability-weighted percentage for all scenarios decreased relative to the base case (Table 6).

Table 6. Comparison of probability weighted scenarios for a Soliris biosimilar development candidate between scenario two and base case.

Probability Weighted Scenarios	New	Old (base case)
Scenario 1 (launch)	31.2%	45.9%
Scenario 2 (stop after failure of approval)	7.8%	11.5%
Scenario 3 (stop after failure of Ph3)	21.0%	19.1%
Scenario 4 (stop after failure of Ph1)	15.0%	8.5%
Scenario 5 (stop after failure of preclinical)	25.0%	15.0%

Note. This table illustrates the component of risk in the development of a biosimilar candidate (via a stage-based POS metric scheme) between scenario two (increased development risk) and the base case.

Although the change in POS did not impact the NPV for the Soliris biosimilar, it did have a profound impact on the rNPV. Based on the POS reduction, the rNPV for the Soliris biosimilar dropped more than 40 percent (compared to the base case) with a value of $114 million (Table 7).

Table 7. Valuation for a Soliris biosimilar development candidate under scenario two assumptions.

Standard NPV	
Total Discounted Cash Flow	$517,194,408.31
Terminal Value	$33,566,901.38
NPV	**$550,761,309.70**
Risk-adjusted NPV	
NPV - Scenario 1	$171,837,528.63
NPV - Scenario 2	-$8,099,880.24
NPV - Scenario 3	-$21,622,916.33
NPV - Scenario 4	-$11,127,541.62
NPV - Scenario 5	-$17,259,910.18
rNPV	**$113,727,280.26**

Note. This table illustrates both NPV and rNPV values for a Soliris biosimilar development candidate under scenario two assumptions (increased development risk). For NPV, total discounted cash flow and terminal value were used in the final calculation. For rNPV, the same NPV method was implemented, however, the element of risk (i.e., POS) was included via scenarios 1-5. The combination of all scenarios resulted in the rNPV.

However, this rNPV evaluation for the Soliris biosimilar was still greater than the base case rNPV evaluation for the Remicade biosimilar (valued at $66 million).

Scenario Three: Increased Development Risk and Cost

As a worst case scenario, this case study evaluated a situation where both developments risk and cost experience a concurrent increase in the development of a Soliris biosimilar. Applying the same assumptions as above, 50 percent increase in clinical costs (total development cost approximately $216 million) and a reduction in POS (for both preclinical and clinical stages), both NPV and rNPV evaluations were

calculated for the Soliris biosimilar. Although the valuations were significantly lower than the base case Soliris biosimilar valuation, the worst case scenario still produced a favorable valuation (Table 8).

Table 8. Valuation for a Soliris biosimilar development candidate under scenario three assumptions.

Standard NPV	
Total Discounted Cash Flow	$483,267,780.78
Terminal Value	$33,566,901.38
NPV	**$516,834,682.17**
Risk-adjusted NPV	
NPV - Scenario 1	$161,252,420.84
NPV - Scenario 2	-$10,746,157.19
NPV - Scenario 3	-$28,747,508.11
NPV - Scenario 4	-$11,899,137.13
NPV - Scenario 5	-$17,259,910.18
rNPV	**$92,599,708.23**

Note. This table illustrates both NPV and rNPV values for a Soliris biosimilar development candidate under scenario three assumptions (increased clinical costs and development risk). For NPV, total discounted cash flow and terminal value were used in the final calculation. For rNPV, the same NPV method was implemented, however, the element of risk (i.e., POS) was included via scenarios 1-5. The combination of all scenarios resulted in the rNPV.

With an rNPV of $93 million, the worst case scenario for the Soliris biosimilar was still able to achieve a greater valuation than the Remicade biosimilar. This confirms that a Soliris biosimilar with development uncertainty and challenges, can still provide greater returns in the long-term investment.

Case Study Implications

Based on the findings, it is evident that a biosimilar to a top-selling biologic will not always serve as a better investment. While the Nickisch and Bode-Greuel (2013) valuation approach may have led one to select the Remicade biosimilar as the better candidate (due to Remicade's sales volume over Soliris), this case study was able to challenge this view by applying a different approach toward the valuation of biosimilars. Using a product- and market-driven valuation approach, this case study was able to uncover the value of a Soliris biosimilar over a Remicade biosimilar, even in situations where the Soliris biosimilar encounters development challenges/uncertainty that may impact future returns.

Although the focus of this case study is on the valuation of biosimilar development candidates, the valuation model presented in this study could also be used to provide strategic insight towards the development of a biosimilar. For example, in this case study, development costs played a significant role in the valuation of both biosimilar candidates. A company interested in improving the value of a biosimilar could use this insight to create a development strategy that mitigates development cost. This could be accomplished by actively limiting expenses in the preclinical and clinical stages or by shortening the time spent in development. By understanding each variable in the financial model presented in this case study, a company interested in the biosimilar business can establish a strategic development approach that encourages the maximization of value for their biosimilar(s) of interest.

Challenges and Limitations of the Case Study

One of the challenges and limitations of a forward-looking financial model, such as the NPV, is the need to generate future assumptions. For biosimilar development candidates, one particular risky assumption is the launch date of the product. While reference biologics have an expected LOE, the launch of a biosimilar could be delayed beyond LOE due to other product-related patents. Depending on the market outlook of the biosimilar candidate, this delay in launch could impact the valuation of a biosimilar. During this time, competition (e.g., an emerging therapeutic and/or a new formulation to the reference biologic) could cause the biosimilar to experience a reduced uptake given the loss of patients to other competitors. As a result, it is critical for a company interested in the biosimilar business to conduct thorough legal due diligence before establishing a potential launch date scenario in the valuation.

Another limitation to the NPV is the need to account for costs. While most costs fall within an average range, there are stages in the development pipeline of a biosimilar that may vary. One area that is relevant is clinical costs. Since clinical trials are optional for biosimilar approval in the US, clinical development costs can differ from company to company. For those companies that look to leverage their clinical trial expertise in the submission of their biosimilar development candidate, a higher clinical development cost could be expected. As a result, in the valuation of a biosimilar candidate, it would be prudent for a biosimilar sponsor to apply clinical cost estimates that are reflective of company strategy and regulatory guidance to improve the accuracy of the valuation.

Future cash flow is another significant challenge and limitation to the NPV model. While the inaccuracy of future cash flow can be mitigated by implementing a

product-specific and market-driven biosimilar forecast (as was prepared in this case study), because the future is uncertain, the forecast is subject to change. External factors such as competition, pricing, and uptake, can significantly impact the revenue of a product and subsequently alter the valuation. For example, for pricing, it is uncertain if biosimilars will experience small pricing discounts to the reference biologic (as is currently projected) or if prices will erode rapidly as seen with small-molecule generics. Therefore, in producing an accurate forecast, it is critical to take into account all uncertainties as risk and provide up-to-date reflections of the market.

The last major challenge and limitation of this case study was development risk, specifically POS. While the POS for this case study was supported through literature, the POS implemented throughout each development stage is speculative. Since the US biosimilar market is still under development, there is not enough data to statically affirm the POS of a biosimilar. While the POS for this case study was extrapolated based on the POS observed in the development of new drugs and generic small-molecules, it's subject to change. Based on these constraints, it would be useful for a biosimilar sponsor to analyze various POS scenarios to get a better sense of risk and its impact towards the valuation.

Other Considerations: Socioeconomic Value

This case study focused solely on the value of biosimilars as an investment. However, it is important to emphasize the socioeconomic value that biosimilars bring to society. Two areas of socioeconomic value are treatment accessibility and compliance. By providing low-cost alternatives, biosimilars can improve the health of our society

through increased accessibility (patients who were unable to afford the reference biologic could now afford the biosimilar) and compliance (the more affordable the drug, the more likely a patient will not skip a dose due to financial motives). These two factors not only improve the financial outlook of biosimilars, but they also provide a socioeconomic benefit to our healthcare system and patients. This would especially be the case for a Soliris biosimilar which would reduce the burden of cost and provide treatment options in a therapeutic area that has a significant unmet need.

Chapter VI

Conclusion

One of the most common and misleading assumptions in the biosimilar business today is the sentiment that biosimilars to top-selling reference biologics will translate to greater value. While the US biosimilar market exhibits tremendous potential as an investment, not every biosimilar to a top-selling biologic will yield large favorable returns. This led to the question postulated in this case study: Do sales of a reference biologic determine the value potential of a counterpart biosimilar? Furthermore, is a biosimilar to a reference biologic generating more than $5 billion in sales, a better investment than a biosimilar for a reference biologic generating less than $2.5 billion in sales? Based on a previous study by Nickisch and Bode-Greuel (2013) this would have led one to say yes to both questions. However, this case study proved otherwise.

Using a modified valuation approach to the Nickisch and Bode-Greuel (2013) study, this case study aimed to financially evaluate two types of biosimilars, a high-profile and a low-profile biosimilar. Applying a screening and selection method focused on commercial attractiveness, two biosimilars (out of four candidates) were selected for financial evaluation. With a Remicade biosimilar representing the high-profile biosimilar and a Soliris biosimilar representing the low-profile biosimilar, both biosimilar candidates were valuated via an NPV analysis. Using a product-specific and market-driven approach, the NPV and rNPV for both biosimilar candidates resulted in a

favorable valuation. However, the Soliris biosimilar candidate yielded greater value capture than the Remicade biosimilar (by more than 60 percent in the base case scenario). To further validate these findings, this case study applied a separate scenario analysis for the Soliris biosimilar that took into account uncertainly via increased development costs and risks. Despite these unfavorable changes, the Soliris biosimilar still prevailed over the Remicade biosimilar, with a valuation greater than 20 percent. This validated the selection of a Soliris biosimilar as the better investment candidate.

With minimal literature, guidance, and data on the financial analysis of biosimilars, there is a need for a case study that explains both the biosimilar business and the valuation of biosimilar development candidates. While the goal of this case study was to fulfill this void, it was also written to encourage a biosimilar valuation approach that went beyond the sales of a reference biologic. By applying a product-specific and market-driven valuation towards two biosimilar development candidates, this case study was able provide a result that would not have been possible via the Nickisch and Bode-Greuel (2013) valuation. Demonstrating that a Soliris biosimilar has greater long-term value than a Remicade biosimilar, this case was able to substantiate the value of a product- and market-driven approach towards the valuation of biosimilar development candidates.

Appendix A

Market Dynamics in the Commercial Assessment of a Biosimilar Development Candidate

Below are the definitions and metrics of the nine market dynamics evaluated in this case study.

1) **Lifecycle management**

   Likelihood for label expansion in a new indication, thus allowing the product to capture additional market share.

   a. Favorable: New indications in clinical trials with strong potential for approval.
   b. Unfavorable: No additional indications in clinical trials.

2) **Pricing: Cost of therapy**

   The average cost of the reference biologic over a year of treatment.

   a. Favorable: Cost is equal or greater than $200,000 per year.
   b. Unfavorable: Cost is equal or less than $1,000 per year.

3) **Payer: Restricted access due to payer management**

   Restriction to the therapeutic due to reimbursement-related issues, such as insurance or Medicaid/Medicare coverage.

a. Favorable: Coverage is broad, therefore patient access to therapeutic is vast.
b. Unfavorable: Coverage is limited, therefore patient access to therapeutic is minimal.

4) Patient size capture

Total patient size capture of the therapeutic for approved indication(s).

a. Favorable: Therapeutic covers a large patient population.
b. Unfavorable: Therapeutic covers a small patient population (similar to that of an orphan drug).

5) Clinical attractiveness

Performance of the therapeutic in terms of safety and effectiveness.

a. Favorable: Therapeutic has established usage in the clinic and is considered to be both efficacious and safe.
b. Unfavorable: Therapeutic has significant safety concerns.

6) Manufacturing costs for therapeutic

The percent cost of goods expected in manufacturing the therapeutic (details and calculation in Appendix C).

a. Favorable: Estimated cost of goods is less than or equal to one percent.
b. Unfavorable: Estimated cost of goods is greater than or equal to five percent.

7) **Commercial/marketing needs**

Resource needs, such as salesforce and advertising, required for commercialization and marketing of the therapeutic.

a. Favorable: Therapeutic covers one indication requiring limited commercial/marketing resources.
b. Unfavorable: Therapeutic covers five or more indications resulting in a considerable need for commercial/marketing resources.

8) **Novel product competition at LOE**

Anticipated competition from novel disruptive therapeutics during the reference biologic's loss of exclusivity (LOE).

a. Favorable: Insignificant to no disruptive therapeutics expected resulting in minimal threat of competition at LOE.
b. Unfavorable: Several disruptive therapeutics expected resulting in significant threat of competition at LOE.

9) **Future biosimilar competition**

Both indirect and direct competition from other biosimilars

a. Favorable: No other biosimilars for the same reference biologic and/or biosimilars in the same therapeutic area.
b. Unfavorable: Presence of other biosimilars for the same reference biologic and/or presence of biosimilars in the same therapeutic area.

Appendix B

COGS-Related Information on Reference Products

Product	Herceptin	Remicade	Soliris	Xolair
Drug amount (mg)	440	100	300	150
2013 US sales (billion)[a]	$2.2	$3.9	$0.6	$0.9
2013 US price (ASP)[b]	$3,200	$659	$155	$720
Price/mg	$7.27	$6.59	$15.52	$4.80
Demand (kg)	296	590	36	178

Note. This table highlights the drug amount (mg), US sales (2013), US price (2013), price per amount (mg) of product, and product demand for Herceptin, Remicade, Soliris, and Xolair reference products.

[a]2013 US sales adapted from EvaluatePharma (2015). [b]2013 US price adapted from Red Book Online (2015).

Appendix C

Estimated Manufacturing Costs for Biosimilar Development Candidates

Herceptin Biosimilar										
Titer (g/L)	**Scale (L)**	**# of Runs**	**Yield**	**Throughput (kg)**	**Total Product (kg)**	**Variable cost (million)**	**Fixed cost (million)**	**Total cost (million)**	**Cost/g**	**COGS[a]**
2	10,000	28	0.6	336	302	$56.0	$3.0	$59.0	$195.11	~ 3%
Remicade Biosimilar										
Titer (g/L)	**Scale (L)**	**# of Runs**	**Yield**	**Throughput (kg)**	**Total Product (kg)**	**Variable cost (million)**	**Fixed cost (million)**	**Total cost (million)**	**Cost/g**	**COGS[a]**
2	10,000	55	0.6	660	594	$110.0	$3.0	$113.0	$190.24	~ 3%
Soliris Biosimilar										
Titer (g/L)	**Scale (L)**	**# of Runs**	**Yield**	**Throughput (kg)**	**Total Product (kg)**	**Variable cost (million)**	**Fixed cost (million)**	**Total cost (million)**	**Cost/g**	**COGS[a]**
2	10,000	4	0.6	48	43	$8.0	$3.0	$11.0	$254.63	~ 2%
Xolair Biosimilar										
Titer (g/L)	**Scale (L)**	**# of Runs**	**Yield**	**Throughput (kg)**	**Total Product (kg)**	**Variable cost (million)**	**Fixed cost (million)**	**Total cost (million)**	**Cost/g**	**COGS[a]**
2	10,000	17	0.6	204	184	$34.0	$3.0	$37.0	$201.53	~ 4%

Note. This table represents the various components needed in determining the cost of manufacturing drug substance for Herceptin, Remicade, Soliris, and Xolair biosimilar development candidates. Here, COGS were presented relative to drug substance manufacturing.

[a]Assumptions in the COGS calculation include: (1) Production of 2 grams per liter at a bioreactor scale of 10,000 liters, (2) Variable cost of $2 million per run, (3) Annual fixed cost of $3 million, (4) Yield of 60 percent, and (5) 90 percent manufacturing success rate.

Definition of Terms:

- Titer: amount of product (in kilograms) produced in culture.

- Scale: scale (in liters) at which material is being produced.
- Yield: percent of drug substance after purification.
- Throughput: total amount of drug substance after purification (with 60 percent yield).
- Total product: total amount of drug substance produced (with 90 percent success rate).
- Variable cost: expenses dependent on the amount of product produced (supplies, raw materials, labor, etc.).
- Fixed cost: expenses independent of the amount of product produced (rent, equipment, etc.).
- Cost/g: cost of product per gram of material.
- COGS: ratio of production cost to price of product.

Appendix D

Primary and Secondary Research

Primary Source	Secondary Source
Personal experience • Drug development in biologics	**Publications** • Textbooks • Periodicals • Reports
Clinical trials • ClinicalTrials.gov	**Pharmaceutical databases** • DataMonitor© • EvaluatePharma© • GlobalData© • Red Book Online©
Case studies • Nickisch & Bode-Greuel (2013)	
Product labels • FDA	

Appendix E

General Product Information for Herceptin Reference Product

Generic name[a]	Trastuzumab
Mechanism of action[a]	HER2 receptor antagonist
Route of administration[a]	Intravenous infusion
Dosage[a]	440mg multi-dose vial
Indication(s) [a]	Adjuvant treatment of HER2-overexpressing breast cancer Metastatic HER2-overexpressing breast cancer Metastatic HER2-overexpressing gastric cancer
Therapy area(s) [a]	Oncology
Sales (2013 WW)[b]	$6.6 billion
Expected LOE (year)[b]	2019

Note. This table highlights general information relative to clinical, sales, and product exclusivity for the Herceptin reference product.

[a]Generic name, mechanism of action, route of administration, dosage, indication, and therapy area adapted from Genentech, Inc. (2014). [b]Sales and expected LOE are adapted from EvaluatePharma (2015).

Appendix F

General Product Information for Remicade Reference Product.

Generic name[a]	Infliximab
Mechanism of action[a]	Anti-TNF-alpha
Route of administration[a]	Intravenous infusion
Dosage[a]	100mg/20ml vial
Indication(s) [a]	Crohn's Disease Pediatric Crohn's Disease Ulcerative Colitis Pediatric Ulcerative Colitis Rheumatoid Arthritis Ankylosing Spondylitis Psoriatic Arthritis Plaque Psoriasis
Therapy area(s) [a]	Gastrointestinal Rheumatology Dermatology
Sales (2013 WW)[b]	$5.3 billion
Expected LOE (year)[b]	2018

Note. This table highlights general information relative to clinical, sales, and product exclusivity for the Remicade reference product.

[a]Generic name, mechanism of action, route of administration, dosage, indication, and therapy area adapted from Janssen Biotech, Inc. (2015). [b]Sales and expected LOE are adapted from EvaluatePharma (2015).

Appendix G

General Product Information for Soliris Reference Product

Generic name[a]	Eculizumab
Mechanism of action[a]	Anti-(human complement C5a and C5b)
Route of administration[a]	Intravenous infusion
Dosage[a]	300mg single-use vial
Indication(s) [a]	Paroxysmal Nocturnal Hemoglobinuria (PNH) Atypical Hemolytic Uremic Syndrome (aHUS)
Therapy area(s) [a]	Hematology Nephrology
Sales (2013 WW)[b]	$1.6 billion
Expected LOE (year)[b]	2021

Note. This table highlights general information relative to clinical, sales, and product exclusivity for the Soliris reference product.

[a]Generic name, mechanism of action, route of administration, dosage, indication, and therapy area adapted from Alexion Pharmaceuticals, Inc. (2014). [b]Sales and expected LOE are adapted from EvaluatePharma (2015).

Appendix H

General Product Information for Xolair Reference Product

Generic name[a]	Omalizumab
Mechanism of action[a]	IgE inhibitor
Route of administration[a]	Subcutaneous injection
Dosage[a]	150mg single-use vial
Indication(s) [a]	Asthma Chronic idiopathic urticaria
Therapy area(s) [a]	Respiratory Dermatology
Sales (2013 WW)[b]	$1.5 billion
Expected LOE (year)[b]	2018

Note. This table highlights general information relative to clinical, sales, and product exclusivity for the Soliris reference product.

[a]Generic name, mechanism of action, route of administration, dosage, indication, and therapy area adapted from Novartis AG (2014). [b]Sales and expected LOE are adapted from EvaluatePharma (2015).

Appendix I

Market Assessment for Biosimilar Development Candidates

Market Dynamics	Level of Impact	Biosimilar	Score					Total
			1	2	3	4	5	
Lifecycle Management 1 = No additional indications in development 5 = Promising indications in clinical trials	**Medium (2x)**	**Herceptin**			x			**6**
		Remicade	x					**2**
		Soliris					x	**10**
		Xolair		x				**4**
Pricing: Cost of Therapy 1 = Low (≤$1,000/yr) 5 = High(≥$200,000/yr)	**High (3x)**	**Herceptin**			x			**9**
		Remicade		x				**6**
		Soliris					x	**15**
		Xolair		x				**6**
Payer: Restricted Access Due To Payer Management 1 = High (payer reimbursement is limited) 5 = Low (payer reimbursement is broad)	**High (3x)**	**Herceptin**					x	**15**
		Remicade					x	**15**
		Soliris					x	**15**
		Xolair		x				**6**
Patient Size Capture 1 = Limited patient population 5 = Large patient population	**Medium (2x)**	**Herceptin**		x				**4**
		Remicade					x	**10**
		Soliris	x					**2**
		Xolair			x			**6**
Clinical Attractiveness 1 = Strong safety concerns 5 = Established usage in clinic and is both safe and effective	**High (3x)**	**Herceptin**					x	**15**
		Remicade			x			**9**
		Soliris					x	**15**
		Xolair		x				**6**
Manufacturing Costs for Therapeutic 1 = Estimated COG≥ 5% (Appendix C) 5 = Estimated COG≤ 1% (Appendix C)	**Medium (2x)**	**Herceptin**			x			**6**
		Remicade			x			**6**
		Soliris				x		**8**
		Xolair		x				**4**
Commercial/Marketing Needs 1 = Large (≥5 indications in different therapeutic areas) 5 = Small (indications in same therapy area)	**Low (1x)**	**Herceptin**					x	**5**
		Remicade			x			**3**
		Soliris				x		**4**
		Xolair				x		**4**
Novel Product Competition at LOE 1 = Presence of several disruptive therapies 5 = No potential threat	**Medium (2x)**	**Herceptin**			x			**6**
		Remicade	x					**2**
		Soliris					x	**10**
		Xolair			x			**6**
Future Biosimilar Competition 1 = Biosimilars to brand of interest and/or other competitors in same therapy area 5 = No potential threat	**Medium (2x)**	**Herceptin**	x					**2**
		Remicade	x					**2**
		Soliris					x	**10**
		Xolair				x		**8**
Commercial Attractiveness Out of 100 total possible points		**Herceptin**						**68%**
		Remicade						**55%**
		Soliris						**89%**
		Xolair						**50%**

Note. This table illustrates the results of the weighted commercial assessment for Herceptin, Remicade, Soliris, and Xolair biosimilar development candidates.

Appendix J

Valuation of a Remicade Biosimilar

Table J1. NPV/rNPV future cash flow model before launch for a Remicade biosimilar development candidate.

Future Cash Flow Model (Before Launch)								
	2010 (Preclinical)	2011 (Preclinical)	2012 (Preclinical)	2013 (Phase 1)	2014 (Phase 3)	2015 (Phase 3)	2016 (Phase 3)	2017 (Regulatory)
Forecasted Sales	-$30,000,000.00	-$30,000,000.00	-$30,000,000.00	-$8,000,000.00	-$18,000,000.00	-$18,000,000.00	-$18,000,000.00	-$2,000,000.00
Operating Profit Model								
COGS								
Adjusted Cash Flow								
SG&A								
Adjusted Cash Flow								
Net Cash Flows								
Inflation Model								
Inflation Rate	2%	2%	2%	2%	2%	2%	2%	2%
Net Cash Flows	-$30,600,000.00	-$30,600,000.00	-$30,600,000.00	-$8,160,000.00	-$18,360,000.00	-$18,360,000.00	-$18,360,000.00	-$2,040,000.00
Tax Model								
Tax Rate	20%	20%	20%	20%	20%	20%	20%	20%
Net Cash Flows	-$24,480,000.00	-$24,480,000.00	-$24,480,000.00	-$6,528,000.00	-$14,688,000.00	-$14,688,000.00	-$14,688,000.00	-$1,632,000.00
Discount Model								
Discount Factor	1.00	0.95	0.87	0.79	0.72	0.65	0.59	0.54
Discounted Cash Flows	-$24,480,000.00	-$23,340,764.18	-$21,218,876.53	-$5,143,970.07	-$10,521,756.96	-$9,565,233.60	-$8,695,666.91	-$878,350.19

Table J2. NPV/rNPV future cash flow model after launch for a Remicade biosimilar development candidate.

Future Cash Flow Model (After Launch)										
	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
Forecasted Sales	$ 133,442,766.37	$ 216,177,281.51	$ 225,105,403.24	$ 217,295,977.33	$ 191,730,381.27	$ 160,133,214.44	$ 132,205,981.84	$ 122,629,311.03	$ 99,918,362.63	$ 81,273,596.16
Operating Profit Model										
COGS	8%	8%	8%	8%	8%	8%	8%	8%	8%	8%
Adjusted Cash Flow	$ (10,675,421.31)	$ (17,294,182.52)	$ (18,008,432.26)	$ (17,383,678.19)	$ (15,338,430.50)	$ (12,810,657.16)	$ (10,576,478.55)	$ (9,810,344.88)	$ (7,993,469.01)	$ (6,501,887.69)
SG&A	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Adjusted Cash Flow	$ (20,016,414.95)	$ (32,426,592.23)	$ (33,765,810.49)	$ (32,594,396.60)	$ (28,759,557.19)	$ (24,019,982.17)	$ (19,830,897.28)	$ (18,394,396.65)	$ (14,987,754.39)	$ (12,191,039.42)
Net Cash Flows	$ 102,750,930.10	$ 166,456,506.76	$ 173,331,160.49	$ 167,317,902.54	$ 147,632,393.58	$ 123,302,575.12	$ 101,798,606.02	$ 94,424,569.49	$ 76,937,139.22	$ 62,580,669.04
Inflation Model										
Inflation Rate	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Net Cash Flows	$ 104,805,948.70	$ 169,785,636.90	$ 176,797,783.70	$ 170,664,260.59	$ 150,585,041.45	$ 125,768,626.62	$ 103,834,578.14	$ 96,313,060.88	$ 78,475,882.01	$ 63,832,282.43
Tax Model										
Tax Rate	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Net Cash Flows	$ 83,844,758.96	$ 135,828,509.52	$ 141,438,226.96	$ 136,531,408.47	$ 120,468,033.16	$ 100,614,901.30	$ 83,067,662.51	$ 77,050,448.71	$ 62,780,705.61	$ 51,065,825.94
Discount Model										
Discount Factor	0.49	0.44	0.40	0.37	0.33	0.30	0.28	0.25	0.23	0.21
Discounted Cash Flows	$41,023,317.84	$60,416,159.00	$57,192,133.06	$50,189,096.35	$40,258,347.15	$30,567,065.04	$22,941,971.72	$19,345,556.95	$14,329,781.64	$10,596,222.17

Appendix K

Valuation of a Soliris Biosimilar

Table K1. NPV/rNPV future cash flow model before launch for a Soliris biosimilar development candidate.

Future Cash Flow Model (Before Launch)								
	2013 (Preclinical)	2014 (Preclinical)	2015 (Preclinical)	2016 (Phase 1)	2017 (Phase 3)	2018 (Phase 3)	2019 (Phase 3)	2020 (Regulatory)
Forecasted Sales	-$30,000,000.00	-$30,000,000.00	-$30,000,000.00	-$8,000,000.00	-$18,000,000.00	-$18,000,000.00	-$18,000,000.00	-$2,000,000.00
Operating Profit Model								
COGS								
Adjusted Cash Flow								
SG&A								
Adjusted Cash Flow								
Net Cash Flows								
Inflation Model								
Inflation Rate	2%	2%	2%	2%	2%	2%	2%	2%
Net Cash Flows	-$30,600,000.00	-$30,600,000.00	-$30,600,000.00	-$8,160,000.00	-$18,360,000.00	-$18,360,000.00	-$18,360,000.00	-$2,040,000.00
Tax Model								
Tax Rate	20%	20%	20%	20%	20%	20%	20%	20%
Net Cash Flows	-$24,480,000.00	-$24,480,000.00	-$24,480,000.00	-$6,528,000.00	-$14,688,000.00	-$14,688,000.00	-$14,688,000.00	-$1,632,000.00
Discount Model								
Discount Factor	1.00	0.95	0.87	0.79	0.72	0.65	0.59	0.54
Discounted Cash Flows	-$24,480,000.00	-$23,340,764.18	-$21,218,876.53	-$5,143,970.07	-$10,521,756.96	-$9,565,233.60	-$8,695,666.91	-$878,350.19

Table K2. NPV/rNPV future cash flow model after launch for a Remicade biosimilar development candidate.

Future Cash Flow Model (After Launch)										
	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Forecasted Sales	$ 159,677,723.39	$ 319,323,511.24	$ 326,580,863.77	$ 306,986,011.95	$ 297,108,430.03	$ 279,519,610.97	$ 280,310,866.48	$ 263,744,494.27	$ 265,882,708.57	$ 252,748,102.76
Operating Profit Model										
COGS	6%	6%	6%	6%	6%	6%	6%	6%	6%	6%
Adjusted Cash Flow	$ (9,580,663.40)	$ (19,159,410.67)	$ (19,594,851.83)	$ (18,419,160.72)	$ (17,826,505.80)	$ (16,771,176.66)	$ (16,818,651.99)	$ (15,824,669.66)	$ (15,952,962.51)	$ (15,164,886.17)
SG&A	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Adjusted Cash Flow	$ (15,967,772.34)	$ (31,932,351.12)	$ (32,658,086.38)	$ (30,698,601.19)	$ (29,710,843.00)	$ (27,951,961.10)	$ (28,031,086.65)	$ (26,374,449.43)	$ (26,588,270.86)	$ (25,274,810.28)
Net Cash Flows	$ 134,129,287.65	$ 268,231,749.45	$ 274,327,925.57	$ 257,868,250.03	$ 249,571,081.22	$ 234,796,473.21	$ 235,461,127.85	$ 221,545,375.19	$ 223,341,475.20	$ 212,308,406.32
Inflation Model										
Inflation Rate	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Net Cash Flows	$ 136,811,873.40	$ 273,596,384.43	$ 279,814,484.08	$ 263,025,615.04	$ 254,562,502.85	$ 239,492,402.68	$ 240,170,350.40	$ 225,976,282.69	$ 227,808,304.70	$ 216,554,574.45
Tax Model										
Tax Rate	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Net Cash Flows	$ 109,449,498.72	$ 218,877,107.55	$ 223,851,587.26	$ 210,420,492.03	$ 203,650,002.28	$ 191,593,922.14	$ 192,136,280.32	$ 180,781,026.15	$ 182,246,643.76	$ 173,243,659.56
Discount Model										
Discount Factor	0.49	0.44	0.40	0.37	0.33	0.30	0.28	0.25	0.23	0.21
Discounted Cash Flows	$53,551,129.84	$97,355,954.05	$90,516,899.43	$77,350,804.96	$68,056,332.24	$58,206,724.88	$53,064,995.17	$45,389,867.23	$41,598,044.88	$35,948,274.06

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