Proposal for a Thesis

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Extension School

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Michael Jones

Address

City State Zip

Phone Number

Email address

Thesis Director:

Stuart Simpson, Ph.D.

Address

City State Zip

Email address

I.

Tentative Title

"A business case on the evaluation of biosimilar development candidates"

## II.

## Research Problem

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 have taken advantage of these advances and are using them to create life-changing therapeutics 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, and patients). While most traditional pharmaceuticals cost approximately $730 per year (Emerton, 2013), 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 biologic drugs, also known as *biosimilars*, are not yet available in the US market. However, this is expected to change over the next ten years as several of the first biologics to enter the market are experiencing 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 industry as biosimilar deals between drug companies and Contract Manufacturing Organizations (CMOs) have continued to increase since 2000

(Bourgoin, 2011). With a notion that a branded biologic with large sales can result in large revenue gains for a counterpart biosimilar, many drug companies have already begun to develop biosimilars for some of the top-selling biologics. Some of these biologics include Humira, Remicade, Enbrel, Rituxan, Herceptin and Avastin, which already have 16, 9, 21, 34, 30 and 16 biosimilars respectively, in development (Thayer, 2013).

While the US biosimilar market exhibits tremendous potential as an investment, not every generic to a reference biologic will be a worthy investment. Since the development of a biosimilar requires significant capital, a drug company interested in the biosimilar venture will need to have a strategy in place when selecting the biosimilar(s) it would like to develop and advance to the US market. While the trend appears to favor biosimilar candidates for those reference biologics experiencing high sales (Rader, 2013), this case study will explore the investment opportunity of biosimilars by evaluating two biosimilar candidates with contrasting market profiles. Rather than relying on evaluations centered on general sales as a projection of future value, such as the Nickisch and Bode-Greuel (2013) study, this case study will expand the Nickisch and Bode-Greuel evaluation to include a more thorough and individualized analysis of the biosimilar market. By applying this model, I believe this approach will provide a more conclusive measure of value for a biosimilar candidate in the current market than the evaluation made by Nickisch and Bode-Greuel. Furthermore, it is my hypothesis that a biosimilar candidate for a reference biologic with fewer sales but a promising market outlook will be a better

investment opportunity than a biosimilar for reference biologic experiencing blockbuster sales.

One of the most important elements in the evaluation of an investment is determining value creation. Although there are various methods to assess value, when evaluating a product, it is common to determine value creation by analyzing future cash flows (revenue and cost) through quantitative models, such as a net present value (NPV) model (Brealey, Myers, & Allen, 2008; Higgins, 2009; Harris, 1997). Since the development of a drug is contingent on many factors, the NPV model can be adjusted to specifically evaluate the potential of a drug development candidate (Nickisch & Bode-Greuel, 2013; Bode-Greuel & Greuel, 2005). By tailoring the NPV to reflect the biosimilar business model and the market of each biosimilar candidate, the value of each candidate can be determined and compared. Using this approach, the hypothesis will be tested by comparing the outcome of the following two scenarios: (1) the value of a biosimilar monoclonal antibody candidate for a top-selling biologic and (2) the value of a biosimilar monoclonal antibody candidate for a biologic with both fewer sales and a more favorable market outlook than the biologic presented in scenario 1. Some prospective biologics with fewer sales (under $2 billion worldwide in 2013) include Tysabri, Synagis, Xolair, and Soliris (GlobalData, 2014).

While the biosimilar business is believed to be a profitable business for top-selling biologics, this case study will question this notion by challenging the Nickisch and Bode-Greuel study. Rather than relying on peak sales of the reference biologic to measure the value of a biosimilar candidate, as done by Nickisch and Bode-

Greuel, this case study will implement a more robust evaluation approach that will take into account both the current biosimilar landscape and market profile of the two biosimilar candidates of interest. In addition to providing a compelling business argument in the evaluation of a biosimilar candidate, this case study will introduce and explain the business model of biosimilars for those interested in pursuing the biosimilar business.

## III.

## Definition of Terms

"Biologics": a class of drugs derived from living organisms that are composed of biological entities such as proteins, peptides, nucleic acids, or cells (Wang & Singh, 2014).

"Biologics Price Competition and Innovation (BPCI) Act": Passed as part of the Patient Protection and Affordable Care (PPAC) Act to allow the FDA to create a regulatory pathway for the approval of biosimilars (Wang & Singh, 2014).

"Bioreactor": a vessel that is used to cultivate cells for the purposes of producing the drug of interest.

"Biosimilar": a biologic that is highly similar in comparison to the reference biological product (Chow, 2014).

"Biotechnology": technology based on the fundamentals of biology that use living organisms or biological systems to identify, sequence, and manipulate DNA for the purposes of producing therapeutic and medical products (Simoens, 2011).

"Cloning": The biotechnology process of introducing DNA into a cell to be used for the production of a protein of interest.

"Hatch-Waxman Act": A common reference to the Drug Price Competition and Patent Term Restoration Act of 1984, this statute allows the FDA approval of generic drugs (i.e., small-molecules) via an abbreviated pathway (Wang & Singh, 2014).

"In vivo": Studies that take place using a living organism.

“Monoclonal antibody”: An engineered therapeutic antibody used to target an antigen of interest.

“Net Present Value (NPV) model”: A forward-looking quantitative model that takes into account both cash inflows and outflows to determine the potential value generation of an investment (Bode-Greuel & Greuel, 2005).

“Process development”: The process involved in the production of a therapeutic via cloned cells.

“Reference biologic”: The branded biologic (created by the originator) for which the biosimilar is compared to.

“Small-molecule”: “a drug with a low molecular weight that is chemically synthesized.

# IV.

# Background

## What is a biologic?

Biological drug products, also referred to as 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 1980's, biologics are well known in the clinic for their ability to diagnose, prevent, and treat human diseases. Drastically different than the traditional pharmaceutical drugs (i.e., small-molecules), biologics are larger in size, heterogeneous, and difficult to characterize (Table 1) (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, hepatitis, and many others. According to Wang & Singh (2014), there are currently over 200 different types of biologics in the market with approximately one third of pharmaceutical pipelines consisting of a biologic.

| Small-molecule | Vs. | 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 Risks | High |
| Low to medium | Cost (to payer) | High to very high |
| Oral | Administration | Injection |

*Table 1*: Differences between small-molecule drugs and biological therapeutics. Source: Adapted from Chow, 2014.

## Monoclonal Antibodies: A Type of Biologic

Of all the various biologics currently in the market, one of the most successful and largest growing classes of therapeutics are monoclonal antibodies. Antibodies are proteins secreted by white blood cells that are used by the human immune system to protect the body from foreign invaders. In protecting the body, the antibody recognizes the antigen expressed by the pathogen – the body has a diverse panel of antibodies that recognize different antigens – and triggers the immune response. Like antibodies generated by the immune system, therapeutic monoclonal antibodies function in a similar fashion. Produced from living organisms (usually mammalian cells) through elaborate manufacturing processes, these antibodies are engineered to have affinity towards an antigen of interest, in this case, the biological entity causing the disease (Ansar & Ghosh, 2013). As a result of detailed engineering, therapeutic monoclonal antibodies are able to reproduce similar immune response in humans by targeting the antigen of interest. Due to their strong

binding capabilities and stability, these antibodies are able to provide less off-target effects and are a more effective treatment for disease than most small-molecule drugs (Wang & Singh, 2014). In addition to their therapeutic application, the US Food and Drug Administration (FDA) has approved the use of monoclonal antibodies towards other applications, including diagnosis and bioterrorism (Ansar & Ghosh, 2013).

## The Drug Development Process For a Monoclonal Antibody

Like small-molecule drugs, the development of a therapeutic monoclonal antibody in the US 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. Taking the form of a gene, protein, or RNA, the drug target can be identified through various scientific experimentations (e.g., genetic, *in vivo* and cellular) that test the relationship between the target and disease of interest (Hughes, Rees, Kalindjian, & Philpott, 2011). For example, in cancer, there are many cell-specific antigens involved in the pathogenesis of the disease. If one can identify an antigen linked to cancer, then a monoclonal antibody can be engineered to target that antigen and modulate the disease. This same rationale applies in the discovery phase. Once a target has been identified and linked to the pathogenesis of a disease, various monoclonal antibodies to that target can be engineered (Wang & Singh, 2014; Ansar & Ghosh, 2013; Hu & Hansen, 2013). Once a lead monoclonal antibody has been

identified and optimized (i.e., engineered to have minimal immunogenicity, superior biochemical and biophysical properties, and ideal pharmacokinetic properties), it is then passed to process development for production (Wang & Singh, 2014).

Prior to producing the monoclonal antibody that will be utilized in clinical trials, it is critical to establish the manufacturing process that will be used to produce the antibody of interest. This is the objective of the pre-clinical 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 the general public, if given approval) 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 testing in humans. To test human subjects in the US, it is first necessary to receive clinical trial approval from the US 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 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 then apply to the FDA for approval by filling a Biologics License Application (BLA). Once the BLA is approved, the drug sponsor can then market and sell the therapeutic monoclonal antibody in the US.

## An Introduction to Biosimilars

According to the FDA (2012), a US biosimilar is a biological product that is highly similar to an FDA-licensed biological product (the reference product) for which there are no clinically meaningful differences in terms of safety, purity, and potency of the product. While there are no biosimilars in the US market, this is believed to change over the next few years, as several reference biologics will begin to lose patent exclusivity in the US. With legislative channels in place to allow the development of generic biologics, several biosimilars are expected to enter the market over the next ten years (Blackstone & Fuhr, 2013). As a result of the demand, biosimilars to some of the best-selling biologics, such as Herceptin, Humira, Avastin and Enbrel, are expected to enter the US market by 2020 (Bourgoin, 2011).

Currently, biologics are one of the most expensive therapeutics in the US market. Ranging 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 (Bourgoin, 2011) and biosimilars already approved in the European market, the demand for biosimilars is steadily increasing in the US. As a result, Congress has passed legislation to allow biosimilars to enter the US market. With the Hatch-Waxman Act

opening the door for generic chemical drugs (Blackstone & Fuhr, 2013), Congress has recently 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 to the generic drug pathway observed by small-molecules (Bourgoin, 2011). Through this channel, drug companies can now receive regulatory guidance on the scientific issues surrounding biosimilarity (Chow, 2014).

## Challenges in the Development of Generic Drugs: Biosimilar Versus Small-Molecule

As discussed earlier, unlike small-molecule generics, the production of a biosimilar is difficult and complex. Produced via a living organism, the engineered biosimilar is exposed to several alterations that occur within the cell (e.g., glycosylation, acylation, sulfation, phosphorylation, and proteolysis) and throughout the production process (e.g., oxidation, deamination, denaturation and aggregation) (Kresse, 2009). Without knowing all the details involved in the production and manufacturing of the original biologic (some of it is usually kept as a trade secret), it may be impractical for a biosimilar to be identical to the reference biologic. As a result, regulatory guidelines regarding the assessment of similarity (e.g., structural, functional, and clinical) are not as clear and established as it is for small-molecule generics. Since there are only a handful of companies with the experience and capability to develop biosimilars, the barrier to entry is anticipated to be high (Blackstone & Fuhr, 2013).

In addition to the development challenges in the production of a biosimilar, there are challenges in the business model of biosimilars. With a limited number of experts in the area of biologics, the cost of developing a biosimilar is expected to be more costly than the development of a generic small-molecule. According to Nickisch and Bode-Greuel (2013), the cost of developing a generic small-molecule is between $1 and $3 million, while a biosimilar can range between $50 and $200 million, depending on the molecule. In addition to cost, development times are also longer for biosimilars with an average of 7 to 9 years (Nickisch & Bode-Greuel, 2013). Lastly, the development risk of a biosimilar is greater than the development of a generic small-molecule. Although the risk in developing a biosimilar is inherently less than the development of a new biologic – a biosimilar gets to bypass the high-risk drug discovery phase as well as phase II clinical trials since the reference biologic has already demonstrated efficacy in the clinic – a biosimilar only has a 50 to 75 percent probability of success compared to the 95 percent observed for a small-molecule generic (Nickisch & Bode-Greuel, 2013). This risk combined with cost, time, and the challenges in manufacturing, make the development of a biosimilar a more complicated business than the typical generic drug business.

## The European Biosimilar Experience

The European Medicines Agency (EMA) is one of the first regulatory agencies to approve biosimilars in the generic drug market. With 14 approved biosimilars, some of which include epoetins, somatropins, and filgrastims (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 European Union, 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 inequity, a sizeable uptake difference is observed between both countries, with the UK experiencing greater uptake over time compared to Germany (IMS Health, 2011). In addition to price variations, the uptake of the biosimilar filgrastim has also been influenced by sentiment, specifically the opinion of physicians. Since the effects of treatment in filgrastim are readily apparent, physicians feel more comfortable prescribing a biosimilar that can be changed quickly; rather than a biosimilar that has a longer timetable in treatment, such as somatropin (IMS Health, 2011).

Despite the challenges in the uptake of a biosimilar in Europe, the European market is beginning to adapt to the presence of 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 applications filed to the EMA. In 2012, the EMA received an all-time high of seven

biosimilar applications, compared to the one biosimilar application filed in 2009 (Dalgaard, Evers, & Silva, 2013).

## The Market Outlook for Biosimilars in the US

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 expected to develop 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 which are losing patent protection will be available for counterpart biosimilars (Grant Thornton, 2013). As a result, the US biosimilar market is forecasted to be the biggest opportunity 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 biologic industry, there is a growing demand across the spectrum of stakeholders (including Congress, payers, etc.) for the development of biosimilars. Although pharmaceutical drugs account for 8 to 10 percent of the total health care cost in the major markets, the cost of biologics continue 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 9 percent increase over the Consumer Price Index (Blackstone & Fuhr, 2013) – the US healthcare system is already beginning to

feel the financial burden, specifically 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 healthcare costs in the US.

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 significantly less than those seen in the generic drug industry. With several challenges in the production and manufacturing of biologics, only a few drug companies will have the capabilities to develop biosimilars. With a market in the billion-dollar range for some biologics, particularly monoclonal antibodies, the high barrier to entry will allow biosimilar companies to capture a significant portion of the reference biologic market (Blackstone & Fuhr, 2013). With biosimilars expected to cost 10 to 30 percent less than reference biologics (US Federal Trade Commission, 2009), biosimilars are expected to capture greater margins than typically seen in generics. This is will be even greater in those cases where the biosimilar expands the access of treatment to those patients who were unable to afford the therapeutic beforehand.

While biosimilar development costs are expected to be greater than small-molecule generics, 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 less 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 embracing 2 to 6 years less development than new biologics (Nickisch & Bode-Greuel, 2013; Wang & Singh, 2014). Lastly, biosimilars exhibit 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 in the US Biosimilar Market

While there are various favorable components in the investment of a biosimilar, there are also a few issues of uncertainty that can impact the US biosimilar 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 its first few years in market. However, this is expected to change as biosimilars continue to enter the US market and establish a presence in the clinic. With Europe's recent increase in biosimilar uptake and their lack of issues around 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 highly contingent on pricing. If the price difference between biosimilar and reference biologic is not significant, there is a possibility

that payers will not adopt biosimilars. As a result, pricing will be a determining factor in uptake.

The other area of uncertainty is with the FDA and its approval method. With different levels of biosimilar similarity at play, there could be 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 a biosimilar, the impact will be aimed at only a few biosimilars 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 highly similar safety and efficacy as the reference biologic.

The last major hurdle and uncertainty in the biosimilar market is the impact of clinical trials. Currently, the FDA does not have a mandate for 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 may require the implementation of clinical trials to demonstrate similarity between biosimilar and reference biologic (Chow, 2014). This uncertainty in clinical trials could play an impact on development costs for a biosimilar. Another potential challenge with clinical trials, beyond cost, is recruitment. Since biosimilars target a population of severely ill subjects, many subjects may be inclined to avoid a clinical trial in fear of getting the biosimilar drug over the established reference biologic (Blackstone &

Fuhr, 2013). This reservation could make recruiting very difficult for biosimilars, especially in those cases when more than one company is recruiting the same patient population (Blackstone & Fuhr, 2013).

## Entering the Biosimilar Market

As discussed earlier, each biosimilar candidate will need to go through development and an FDA approval process for the therapeutic to be marketed as a biosimilar in the US. While the development approach for a biosimilar candidate may differ from company to company, the development process is highly dependent on the drug company's ability to execute. However, unlike development, market outlook of a biosimilar is not entirely dependent on execution. While some aspects, such as advertising, can be manipulated, there are many external dynamics in the drug market that cannot be controlled. As a result, for a drug company to be successful in the biosimilar business, it will need to understand the external forces impacting the market of a given biosimilar and take them into account when analyzing the value of a biosimilar candidate. With significant capital needed to bring a biosimilar to market, a company will need to be prudent in deciding which biosimilar(s) to pursue.

With current biosimilars in development consisting mostly of top-selling reference biologics (Rader, 2013), there appears to be a notion that high sales for a reference biologic will result in a promising business opportunity for its counterpart biosimilar. For example, Herceptin, a top-selling oncology biologic with $6.4 billion in sales has over 20 biosimilars in development (Rader, 2013). Whereas Lucentis, an

ophthalmologic biologic with approximately half the sales ($3.7 billion), has only 2 biosimilars in development (Rader, 2013). While some analysts believe a top selling biologic is a favorable proposition (Rader, 2013; Blackstone & Fuhr, 2013; Nickisch & Bode-Greuel, 2013), this case study aims to challenge this theory by implementing an evaluation approach that is founded on the individual market profile of a given biosimilar candidate rather than relying exclusively on sales as a general predictor of success.

## Evaluating a Biosimilar Development Candidate

Given the lack of biosimilars in the US market and the substantial difference between biosimilars and small-molecule generics, a standard approach to the evaluation of a biosimilar has not yet been established. As a result, each biosimilar company will need to develop its own evaluation model that will best inform the value of a biosimilar development candidate. While the lack of standards can make the evaluation process daunting, an evaluation model can be redesigned using current financial models in the drug industry. One common model used in biotechnology to determine the value of drug candidates and technology platforms is net present value (NPV) (Bode-Greuel & Greuel, 2005). A forward-looking financial model, the NPV evaluates assumptions on future cash flows (gained or lost) for a given investment and determines the overall value of a venture (Bode-Greuel & Greuel, 2005). Since the purpose of an evaluation is to determine value creation, the NPV can be used to satisfy this requirement. If the evaluation results in a positive NPV (NPV > 0), the investment is expected to create value; however, if the

evaluation results in a negative NPV (NPV < 0), the investment is expected not to create value (Bode-Greuel & Greuel, 2005; Higgins, 2009; Nickisch & Bode-Greuel, 2013).

In evaluating a biosimilar candidate, the NPV model can be used to make decisions on the selection of a biosimilar development candidate (Nickisch & Bode-Greuel, 2013). However, prior to using the NPV as decision-making tool, it will be critical to fully evaluate the current market of a biosimilar in order to make credible assumptions in the NPV regarding future costs and revenues (Bode-Greuel & Greuel, 2005). Since cash flow is influenced by the market, an evaluation that looks at the individual market landscape of a given biosimilar candidate will provide greater confidence on estimated cost and revenue. For example, a biosimilar that experiences $1 billion in sales in a given year, may experience a significant drop a few years later due to changes in the market such as, increased competition, emerging therapeutics, lifecycle management, changes in treatment algorithm, and reaction from payers (IMS Health, 2011). As a result, it will be wise for a company to make an evaluation based on the individual market profile of a given biosimilar, rather than allowing sales of a reference biologic to be the deciding factor in the selection of a biosimilar development candidate.

## The Nickisch and Bode-Greuel Study on Biosimilars

While a standardized approach to the evaluation of biosimilars does not currently exist, in 2013, Nickisch and Bode-Greuel published a study on the evaluation of biosimilar candidates via NPV analysis. In this study, the authors

analyzed the business model of biosimilars, and evaluated the attractiveness of biosimilar candidates based on peak sales of the reference biologics. Creating various scenarios for peak sales, Nickisch and Bode-Greuel determined that sales within $2-5 billion for a reference biologic would result in a "more favorable" biosimilar investment (assuming a 30% market share) (p. 30). While this study deserves praise for being one of the few business studies to discuss the biosimilar business and present an evaluation approach for biosimilars, the Nickisch and Bode-Greuel study has two major shortcomings.

The first shortcoming was the lack of an individualized market analysis. Rather than evaluating biosimilar candidates based on their unique market profile, the Nickisch and Bode-Greuel study weighted the market for all biosimilar candidates equally and assessed value predominantly on the peak sales of the reference biologic. The second shortcoming was the use of legacy data. Since the study was published in 2013, many of the data points collected to create the evaluation dated back to 2012 and earlier. Since biosimilars have not entered the US market, the biosimilar landscape is constantly evolving in the areas of legal (e.g., patents), commercial, FDA regulations, economics (e.g., reimbursement and pricing), and even sentiment. As a result, many of the assumptions presented in the Nickisch and Bode-Greuel study were outdated. To create an accurate biosimilar evaluation, the biosimilar landscape must be analyzed with data that is reflective of current issues. This case study will aim to address both these shortcomings from the Nickisch and Bode-Greuel study.

# V.

## Case Study Methods

Based on current biosimilar deals and the opinions of a few analysts, there appears to be notion that biosimilars for top-selling reference biologics will result in a favorable business opportunity (Rader, 2013; Nickisch & Bode-Greuel, 2013; Blackstone & Fuhr, 2013). While this may be the case in some occasions, this case study aims to counter this view by challenging the Nickisch and Bode-Greuel (2013) study. In the Nickisch and Bode-Greuel study, the authors presented a generalized evaluation for biosimilars that focused primarily on peak sales of a reference biologic. As opposed to applying a generalized model dictated by sales, this case study will expand the evaluation methodology used by Nickisch and Bode-Greuel and apply a market-specific evaluation that reflects the current landscape of a given biosimilar candidate. In doing so, this case study will analyze the following two scenarios: (1) the value of a biosimilar monoclonal antibody candidate for a top-selling biologic and (2) the value of a biosimilar monoclonal antibody candidate for a biologic with both fewer sales and a more favorable market outlook than the biologic presented in scenario 1. When selecting the two biosimilar candidates to compare, the following criteria will be implemented: (1) biosimilar reference biologic must differ in sales (using WW sales for 2013) by at least 20 percent, (2) biosimilar reference biologic must have an expiry patent date on or before 2020, (3) biosimilar reference biologic must have a preliminary market outlook that satisfies the scenarios above.

Once the biosimilar candidates have been selected, this case study will analyze and compare both candidates using an NPV model similar to the Bode-Greuel and Greuel (2005) model. In addition to the Bode-Greuel and Greuel model, this case study will use the Nickisch and Bode-Greuel evaluation model that was tailored to biosimilars. However, unlike the Nickisch and Bode-Greuel model, the evaluation in this case study will include an individualized market analysis that is reflective of the two biosimilar candidates of interest and the current biosimilar landscape. This market analysis will involve the following: (1) clinical outlook of drug (e.g., mechanism of action, therapy type, indications, presentations, placement in treatment algorithm, etc.), (2) competitive landscape, (3) disruptive therapies (e.g., new emerging drugs or biosimilars of a different reference biologic), (4) reference biologic sales and (5) annual cost of treatment. Based on this analysis, an accurate base case assumption for cost, revenue, and probability of success can be determined for each biosimilar candidate and applied to the NPV calculation. Based on the NPV results, the hypothesis can then be tested.

Note: Data needed to support the selection of the biosimilar candidates as well as the market analysis will be acquired via secondary sources, such as analysts reports, literature, and market research databases (e.g., GlobalData and EvaluatePharma).

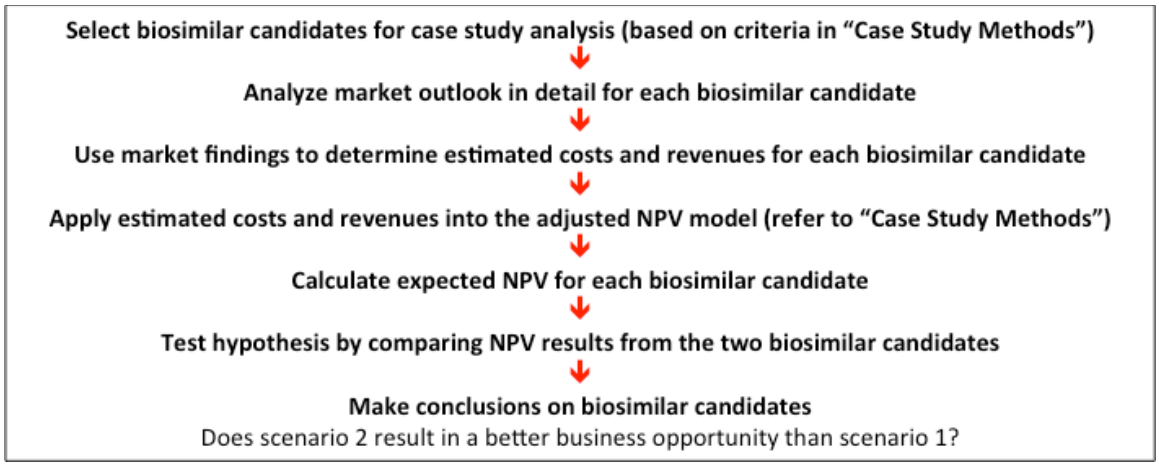


*Figure 1*: Case study experimentation workflow.

# VI.

## Case Study Limitations

One of the limitations of an evaluation based on future assumptions, such as a net present value (NPV) model, is the need to predict future cash flows. While calculated projections can be made on future cash flows, these forecasts are contingent on current knowledge – they do not take into account the uncertainties of the future. As a result, the NPV model is subject to change. While these changes can impact the final evaluation, the impact a given change has on an evaluation can be mitigated by establishing credible assumptions (Bode-Greuel & Greuel, 2005). This is one of the main efforts of this case study. Rather than relying heavily on the current sales of a reference biologic as a predictor of future cash flows for the counterpart biosimilar, this case study will analyze the current market outlook of each biosimilar candidate and will take into account potential uncertainties that can impact the future value of a biosimilar candidate.

VII.

## Tentative Schedule

Submission of proposal to research advisor……...December 15, 2014

Proposal returned for revision……..….January 2, 2015

Submission of final proposal……..…January 15, 2015

Proposal accepted by research advisor……...…....February 1, 2015

Thesis director agrees to serve……..….February 2, 2015

First draft returned by thesis director……...……..….June 15, 2015

Revised draft completed…….……July 1, 2015

Revised draft returned by thesis director……..……..……..July 15, 2015

Final text submitted to thesis director and research advisor……...…….August 1, 2015

Final text approved…….……..…September 1, 2015

Final approved thesis uploaded to ETD…….……...….October 15, 2015

Graduation……...November, 2015

VIII.

# Bibliography

## Works Annotated


Ansar, W., & Ghosh, S. (2013). Monoclonal antibodies: A tool in clinical research. *Indian Journal of Clinical Medicine , 4*, 9-21.

- Technical review on monoclonal antibodies and their use in the clinic.
- Review provides a breakdown of current marketed monoclonal antibodies and their indications.

Berkowitz, S. A., Engen, J. R., Mazzeo, J. R., & Jones, G. B. (2013). Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. *Nature Reviews Drug Discovery , 11* (7), 527-540.

- An analysis (based on FDA guidance) on the analytical assessment of biosimilars.
- There are no exact criteria in assessing biosimilarity; rather biosimilarity will be contingent on the totality of the package from the biosimilar sponsor.

Blackstone, E. A., & Fuhr, J. P. (2013). The economics of biosimilars. *American Health & Drug Benefits , 6* (8), 469-477.

- Examines the financial potential for biosimilars in the US by evaluating the US biologic market and the EU experience with biosimilars.
- Lists various confounding factors that can affect the biosimilar business.

Bode-Greuel, K. M., & Greuel, J. M. (2005). Determining the value of drug development candidates and technology platforms. *Journal of Commercial Biotechnology , 11* (2), 155-170.

- A comprehensive financial analysis on the evaluation of drug development candidates.
- Applies an augmented NPV model to determine value creation.

Bourgoin, A. F. (2011). *What you need to know about the follow-on biologic market in the US: Implications, strategies, and impact.* Boston: Thomson Reuters.

- Brief outlook on regulatory needs, patents, and market strategies impacting the emergence of biosimilars in the US.
- Strategy in the selection of a biosimilar will influence success.

Chow, S.-C. (2014). *Biosimilars: Design and analysis of follow-on biologics.* Boca Raton, FL: CRC Press.

- Comprehensive review on the scientific and practical issues surrounding the design and analysis of biosimilar studies.

Dalgaard, K., Evers, M., & Silva, J. S. (2013). *Biosimilars seven years on: Where are we and what's next?* Boston: McKinsey & Company.

- Summary on the biosimilar movement across the globe and current sentiment.
- Highlights biosimilar sentiment across three main stakeholders: generic companies with marketed biosimilars, smaller entrants with no market biosimilars, and originators.

Emerton, D. A. (2013). Profitability in the Biosimilars Market. *BioProcess International , 11* (6), 6-14, 23.

- An assessment (based on pricing) on the potential profitability of an FDA approved biosimilar.
- While the biosimilar market remains attractive, there are various factors, such as pricing, that can impact the return of investment.

Epstein, M. S., Ehrenpreis, E. D., & Kulkarni, P. M. (2014). Biosimilars: The need, the challenge, the future: The FDA perspective. (doi:10.1038/ajg.2014.151, Ed.) *Am J Gastroenterol* , 1-4.

- Summary on the financial and future prospective of biosimilars based on a regulatory outlook.
- Success observed in biologics will translate to biosimilars.

Genazzani, A. A., Biggio, G., Caputi, A. P., Tacca, M. D., Drago, F., Fantozzi, R., et al. (2007). Biosimilar drugs. *Biodrugs , 21* (6), 351-356.

- A summary on the differences between biosimilars and reference biologics and the challenges facing biosimilars.
- Guidelines will need to be established to manage biosimilars in the healthcare arena.

GlobalData. (2014). *Pharma eTrack: Sales Analytics*. Retrieved December 16, 2014, from GlobalData: http://www.pharmaetrack.com

- Sales figures for reference biologics (from date of launch to present).

Grant Thornton. (2013). *Bio-dynamism: Insights into the biosimilars market: An overall perspective.* New Delhi: Grant Thornton India LLP.

- Overview on various market dynamics that may impact biosimilars both in the US and globally.
- Biosimilar success is contingent on market strategy.

Hughes, J., Rees, S., Kalindjian, S., & Philpott, K. (2011). Principles of early drug discovery. *British Journal of Pharmacology , 162*, 1239-1249.

- Review on the development process for new drugs.
- Highlights statistics (years, cost, etc.) relevant to new drug development.

IMS Health. (2011). *Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape.* Report, London.

- Report on the market landscape for biosimilars both in the US and in emerging markets.
- Outlines several factors that may influence the market for biosimilars across various stakeholders.

Kozlowski, S. (2012, August 8). *Biosimilars - An update focused on quality considerations.* Retrieved December 17, 2014, from US Food and Drug Administration: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf

- A presentation by the FDA that discusses guidelines specific to the assessment of biosimilarity.
- Outlines consideration that should be made when seeking FDA approval for a biosimilar.

Kresse, G.-B. (2009). Biosimilars - Science, status, and strategic perspective. *European Journal of Pharmaceuticals and Biopharmaceuticals , 72*, 479-486.

- Overview on the regulatory and market framework for biosimilars as well as the scientific considerations that may impact biosimilars.
- Findings are relevant to US market and emerging markets.

Nickisch, K., & Bode-Greuel, K. M. (2013). NPV modeling for the selection of value-creating biosimilar development candidates. *Journal of Commercial Biotechnology , 19* (1), 24-32.

- A financial assessment (via NPV) on the financial attractiveness of biosimilars based on peak sales from the reference biologic.

- Emphasis on sales of reference biologic as a key determinant of value creation for a counterpart biosimilar.

Rader, R. A. (2013). An analysis of the US biosimilars development pipeline and likely evolution. *BioProcess International , 11* (6), 16-23.

- A global analysis on the development of biosimilars and their evolution in the marketplace.
- Outlines top-selling reference biologics for which a counterpart biosimilar is currently in development.

Rovira, J., Espin, J., Garcia, L., & Labry, A. O. (2011). *The impact of biosimilars' entry in the EU market.* Granada: Andalusian School of Public Health.

- Comprehensive analysis on the development and progress of biosimilars in the EU market.
- Highlights key issues that were experienced in the EU biosimilar market that may impact the US biosimilar market.

Simoens, S. (2011). Biosimilar medicines and cost-effectiveness. *ClinicoEconomics and Outcomes Research , 3*, 29-36.

- An analysis on the pricing economics of biosimilars.
- The degree of similarity between a biosimilar and reference biologic will be critical in determining the cost-effectiveness of the biosimilar (i.e., the price at which one would select one over the other).

Thayer, A. M. (2013). The new copycats. *Chemical and Engineering News , 91* (40), 15-23.

- Report on the companies involved in developing biosimilars.
- Highlights biosimilar deals and reference biologics that are facing biosimilar competition.

Umscheid, C., Margolis, D., & Grossman, C. (2011). Key concepts of clinical trials: A narrative review. *Postgrad Med , 125* (3), 194-204.

- Comprehensive review of the US clinical trial system.
- Outlines the main components involved in preclinical and clinical phases (I-III).

US Federal Trade Commission. (2009). *Emerging health care issues: Follow-on biologic drug competition.* Federal Trade Commission. Washington DC: Federal Trade Commission.

- A comprehensive report on the impact of biosimilars in the US market.

- Outlines various areas of impact, specifically, competition between reference biologics and their counterpart biosimilars.

Wang, W., & Singh, M. (2014). *Biological Drug Products.* Hoboken, NJ: John Wiley & Sons.

- A comprehensive review on the development of biologics.
- Outlines technical, regulatory, legal, and clinical aspects involved in the development and approval of biologics in the US.