EVALUATION OF THE FINANCIAL IMPACT OF CONTINUOUS CHROMATOGRAPHY IN THE PRODUCTION OF BIOLOGICS

by

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Submitted to the MIT Sloan School of Management and the Engineering Systems Division in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration
AND
Master of Science in Engineering Systems

In conjunction with the Leaders for Global Operations Program at the
Massachusetts Institute of Technology

June 2011

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Evaluation of the Financial Impact of Continuous Chromatography in the Production of Biologics

By: Bayan Takizawa

Submitted to the MIT Sloan School of Management and the Department of Engineering Systems
on May 6, 2011 in Partial Fulfillment of the
Requirements for the Degrees of Master of Business Administration and
Master of Science in Engineering Systems

ABSTRACT

The primary goal of this internship is to explore the financial impact of changing one or more of the downstream chromatography steps involved in the purification of a complex biologic molecule from a batch process to a continuous one. This is particularly relevant, as biologics represent the fastest growing segment of the human therapeutics market, and, consequently, have become a major component of most large pharmaceutical companies, such as Novartis.[1]

Specifically, I examined the Multicolumn Countercurrent Solvent Gradient Purification (MCSGP) system, a continuous chromatography unit produced by ChromaCon, in the first part of the internship.[2] By collecting and analyzing data from previous experiments done with this technology, I was able to estimate the potential benefits in the production process of Biologic X. Then, after evaluating the current cost structure of this molecule, I determined the reduction in COGS associated with the successful implementation of MCSGP.

In the second part of the internship, I examined the downstream purification of another, more complicated molecule. I studied each individual step, and then modeled each one as if it were continuous. For the chromatography steps, I applied either the MCSGP, or another continuous technology developed by Novasep, the BioSC process. Other key steps, such as the specific enzymatic reactions that are currently done in large batch reactors, were also modeled as continuous processes.

I was able to show that with the MCSGP technology, the COGS of the drug substance (DS) of Biologic X could be decreased by 25%, with a resulting eNPV of savings of >$25M. Furthermore, I determined that: 1) MCSGP has a significant developmental risk, but it has considerable cost savings because it can increase product yields, and 2) BioSC has less developmental risk, and it can significantly decrease costs of high throughput products that require large amounts of expensive resins and buffers.

There are clearly significant benefits to be gained from continuous chromatography technologies. One must weigh the developmental risks with the financial benefits, keeping in consideration the regulatory implications of changing manufacturing methods. The end result of this work will hopefully translate into higher margins and profits for Sandoz Biopharmaceuticals.

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ACKNOWLEDGEMENTS

I would like to thank the following people:

Sandoz:
Andreas Premstaller
Klaus Graumann
Sascha Keller
Thomas Stangler
Bernhard Widner
Bjorn Philipps
Jens Demand
Martin Ludwicek
Norbert Palma
Britta Deutel
Richard Hoelzl
Angela Gruber
Harald Pilser
Johannes Reiter
Martina Messner
Christina Klingler
Sabine Mitterer
Valentin Resinger
Dirk Kreder

Novartis:
Thibaud Stoll
Marc Reifferscheid
Bernd Kalbfuss

MIT:
Charles Cooney
Roy Welsch
Donovan Collins
Asvin Srinivasan

External:
Gerhard Winter
Rainer Hahn
Frank Hanakm
Harald Stahl

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BACKGROUND

1 Background

1.1 Sandoz and Novartis

In 1996, Sandoz and Ciba-Geigy merged to form the large pharmaceutical giant known today as Novartis. The two predecessor companies were themselves well diversified before the merger:

- Ciba-Geigy was involved in many different industries, including pharmaceuticals, chemicals, and materials.
- Sandoz also had a very diverse portfolio of products, including pharmaceuticals, chemicals, agricultural products, and consumables such as baby food.

After the merger between Sandoz and Ciba-Geigy, the pharmaceutical branches of these two companies combined efforts, and many of the other divisions were spun-off into different business entities. The two companies joined their generic drug divisions and named that separate branch Sandoz. So, whereas the Sandoz company that was known before the merger was a multi-faceted corporation, after the unification it became the generics company of Novartis.

Sandoz is one of the many different segments of Novartis, which also includes the following:

- Pharma (pharmaceuticals)
- Generics (Sandoz)
- Consumer Health
- Vaccines/Diagnostics
- Alcon (recently acquired ophthalmology-focused pharmaceutical)

Of the $44.3B revenue that Novartis achieved in 2009, $7.5B was derived from Sandoz products. Of the 100,000 employees that serve Novartis companies, 23,000 are Sandoz employees. Clearly, Sandoz does represent a significant portion of Novartis' business. In addition, as the patents of many biologic molecules (complex therapeutic molecules that are

made from microorganisms or human cells that are genetically engineered to produce these molecules; the complexity of these therapeutics does not allow for their chemical synthesis) expire in the coming years, and the biosimilar (the generic version of biologic molecules) registration pathway becomes more clear-cut in the United States, Novartis will rely on Sandoz to lead those efforts. The market for biosimilars is estimated to be $19.4B by 2014.[3] Sandoz is already the world leader in biosimilars, with three approved drugs on the market: Binocrit (a generic version of Procrit, a biologic that increases red blood cell production), Omnitrope (a generic version of growth hormone), and Zarzio (a generic version of filgrastim – a granulocyte colony-stimulating factor, or G-CSF, used to increase white blood cell production).

1.2 Continuous Manufacturing and MIT

The pharmaceutical industry, due to cost pressures from increased global competition and reduced reimbursement rates, has had to focus its attention on operational processes. Whereas before these companies were able to enjoy the most profitable returns of any industry, allowing them to forgo operational excellence, their margins are now decreasing and the optimization of their manufacturing processes has become paramount.[4]

The industry has traditionally used batch processes for the production of pharmaceutical agents. This is because of the ease of segregating products into lots; the relatively smaller amount of product manufactured compared to other industries, such as chemicals; and the batch-nature of the biomedical laboratories from which these chemicals are first synthesized.[5] However, recently, there has been a significant effort to create continuous processes that allow for decreased inventory and increased process control.[6] In fact, MIT has recently entered into a multi-million dollar collaboration with Novartis to establish a continuous manufacturing process for pharmaceuticals.[7] More specifically, the 65 million dollar investment will span over ten years, and is officially titled the "Novartis-MIT Center for Continuous Manufacturing." This collaboration will aim to improve the supply and quality of drug products, as well as reduce the environmental impact of drug development and production. Ten MIT faculty members, as well as numerous students, Ph.D. candidates, postdoctoral fellows, and staff scientists are working side-by-side with their Novartis counterparts.

This collaboration, however, involves the manufacturing of small molecule drugs, not biologics. This is because small molecules (pharmaceutical agents like acetaminophen, which

are synthesized from chemical processes) have been in production for a longer time than most biologics, like monoclonal antibodies and cytokines, allowing their manufacturing processes to be better understood and refined. With the first biologic, Eli Lilly's recombinant insulin product Humulin, approved in 1982, these larger molecules have a much younger history.[8] Similarly, continuous manufacturing of biologic molecules is still in its infancy.

1.3 Biologics and their presence at Sandoz and Novartis

Biologics represent the fastest growing segment of the human therapeutics market, and as such has become a major component of most large pharmaceutical companies, such as Novartis.[9] Whereas before, these behemoth companies were able to focus solely on small compounds, they can no longer ignore the profitability of large molecules. Indeed, Enbrel, Remicade, and Avastin were able to gross $8B, $6.9B, and $5B in sales in 2009, respectively.[10]

Novartis has increased its presence in the biologics space by developing and licensing numerous molecules, such as ranibizumab (Lucentis, co-marketed with Roche) and omalizumab (Xolair). Similarly, Sandoz Biopharmaceuticals continues to hold a strong presence in the growing biosimilar market.

With increased attention placed on follow-on biologics, as the US government and regulatory officials carve a path for their registration and approval process, companies like Novartis and Sandoz Biopharmaceuticals are investing a significant amount of capital in technologies to improve their production processes. The increased scrutiny that will be placed on these biologically-derived compounds, coupled with the cost pressures resulting from recent healthcare legislation, will undoubtedly force companies to devise manufacturing methods that are both robust and cost-efficient. Currently, many pharmaceutical companies are creating continuous production techniques that allow for greater process control and decreased inventory.[11]

The production of a biologic molecule can be separated into two major groups of processes: upstream and downstream (see **Figure 1**).

- The upstream process is mainly involved in the actual production of the molecule. Cells, either human or microbial, are genetically engineered to produce the peptide or protein of interest. This is done by modifying the genetic material, the DNA, of these cells so certain genes are expressed. After a predetermined time or number of cellular life cycles,

the media containing the cell and protein products is then sent for downstream processing. This solution is quite impure, as it contains much cellular debris, such as DNA, cellular membrane proteins, fragmented products, aggregated products, and host cell proteins. The process of producing these proteins is usually a batch process; however, there are technologies, such as the perfusion bioreactor, that allow for the continuous production of biologics.[12]

- The downstream process is mainly involved in the purification of the upstream feed and the further processing of the product. For the former, numerous purification methods are available: specialized filters, centrifugation, and chromatography are a few popular ones. This project focuses on chromatography, a process by which a solution containing a product is passed through a column containing specialized resin beads. These beads have special properties that allow for the specific binding of the protein of interest, while the impurities flow out of the column. Then, the product is eluted, or removed, from the resin with a specific eluent fluid. There are specific chromatography technologies available in which impurities bind the resin beads, and the product of interest flows right through the column (flow-through chromatography). Other downstream processes include enzymatic and refolding reactions that ensure the biologic has the correct composition and structure – they are beyond the scope of this thesis. Once the product has been adequately purified, it is known as drug substance, which is then further processed (dried, packaged, labeled) to become the drug product that is ultimately distributed and sold.

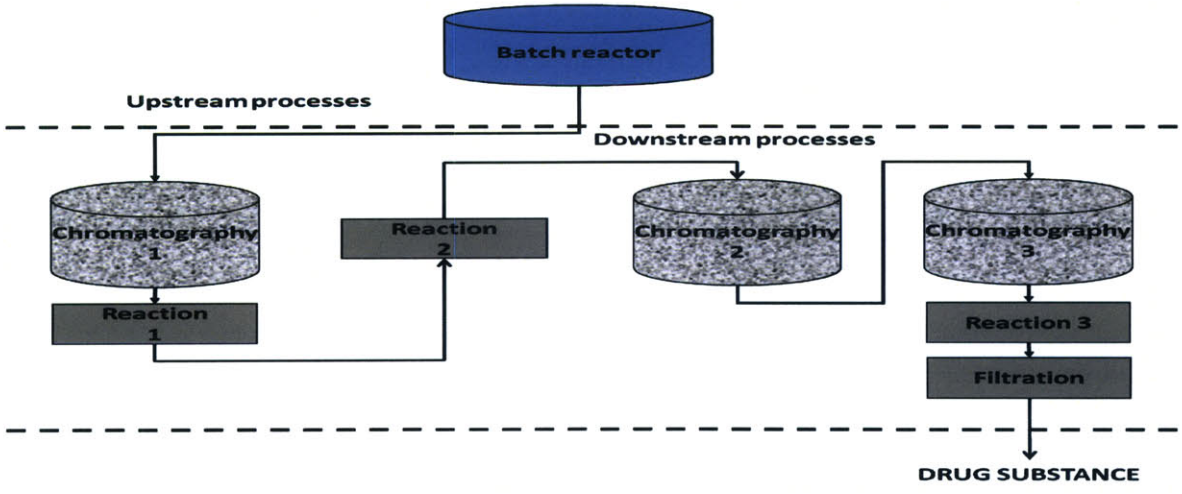

Figure 1. Typical schematic of upstream and downstream processes

As mentioned earlier, one of the key steps involved in the purification of biologics is chromatography. This has traditionally been done in a batch fashion, although there have been some technological advances that permit continuous processing.[13] Limitations of these newer methods include their difficult implementation and the binary nature of their output streams. Regarding the latter, with only two output flows, these technologies often cannot achieve the pure product extraction that traditional batch processes typically yield. However, recently a Swiss company (ChromaCon) was able to develop a system that allows for continuous chromatography and produces three output streams. This technology is called the Multicolumn Countercurrent Solvent Gradient Purification (MCSGP) system. It is very early in development, with only laboratory scale equipment available, but early data show that it can increase chromatography step yields dramatically.[14]

1.4 The Internship and Objectives

When the internship at Sandoz, specifically the Kundl plant, was proposed, the project was introduced through Novartis, as Sandoz Biopharmaceuticals had not been created. The actual proposal, though, was written by the management in Kundl, specifically Dr. Andreas Premstaller and Dr. Klaus Graumann.

- Specifically, for the first part of my project, they were interested in exploring the aforementioned MCSGP technology for a low yield step involved in the purification of Biologic X. The technology is considerably risky, as it only exists in laboratory-scale, but the initial studies are promising. Given the projected loss of product and the cost associated with the current chromatography method, Sandoz is interested in an improvement process. Thus, the first part of my internship centered around the following topic: ***Determine the financial effect and associated risks of utilizing the MCSGP technology in the downstream purification of Biologic X.*** This would require making a financial model that would translate potential increased product yields to lower production costs.
- In addition to the first goal, Sandoz is interested in exploring a fully continuous downstream purification process (they want to maintain the upstream batch processes, even though there are continuous perfusion bioreactors at different Sandoz sites). They

have a specific product, Biologic Y, which they wanted me to explore, as construction of a greenfield plant may be required to satisfy future demand. The development of this product is a collaboration between Sandoz and Novartis, so there is much interest throughout the organization. The downstream purification process of Biologic Y is much more complicated than that of Biologic X, and it requires a number of chromatography steps and enzymatic reactions, as well as a lyophilization step. The main goal of the second part of my internship was to address the following topic: ***Determine the financial impact of creating a production line for Biologic Y that has a completely continuous downstream purification process.*** To do this, I will utilize relevant parts of the model created in the first part of my internship, as well as new ones. For example, for some of the chromatography steps I will also explore other technologies, such as the BioSC process by Novasep (to be described in Chapter 3). In addition, the enzymatic reactions will be modeled as tubular reactors that could ensure a continuous flow. The lyophilization process was left in its current process, as it is beyond the scope of my project, and could be explored by another internship.

CHAPTER 2
INTRODUCTION TO CURRENT PROCESSES

2 Current Processes

2.1 General Concepts

For the purpose of this thesis, I will provide as many details as possible, so as to make this as helpful as possible. However, most of the products that Sandoz is developing are not public knowledge. This is especially true with the follow-on biologics, or biosimilars, as this market is similar to the generics market for small molecule therapies. The main reasons for not disclosing the products in development are the following:

1. *First-mover advantage among biosimilars.* Just as generics that are first to market derive an economic benefit, so too will a developer of a follow-on biologic. These benefits are:
    a. The first generic/biosimilar to the market will be the first one adopted by prescribers and payers. This will have the effect of establishing brand loyalty, as patients and doctors often become reluctant to keep switching different drug products.
    b. The first generic/biosimilar to market will enjoy a certain period of exclusivity. For small molecules, the first generics company to get its version of a drug approved typically gets 180 days of market exclusivity after the original drug patent expires.[15] During this time no other generics company can market their copy of the drug. The pathway for biosimilars is still very early, but according to the Biologics Price Competition and Innovation Act of 2009, the first biosimilar will receive *at least one year* of exclusivity, during which time other biosimilars cannot be marketed.[16]
2. *Prevention of broad interest.* Sandoz does not want other companies to know which biologics it is pursuing, and at what stages they are in. Indeed, if other companies discover what compounds Sandoz is pursuing, they might decide to pursue them as well.

The addition of more competitors would decrease the potential market share that Sandoz could enjoy.

3. *Prevention of countermeasures by the originator company.* The author believes originator companies are quite wary of the potential entrance of biosimilars. Should one of these companies become aware of a potential competitor, it would likely launch a pre-emptive publicity campaign against the proposed biosimilar. In fact, originator companies have already started warning doctors and patients that biosimilars are not the same as the original compounds, and that this difference can be harmful.

For all of these reasons, I will take guarded measures so readers of this thesis cannot infer the molecules I examined. The following sections describe very common upstream and downstream processes used in the production of biologic molecules.

2.2 Upstream Production

2.2.1 Mammalian Cell Culture

Biologics are currently produced through recombinant techniques very common in the biotech industry. More specifically, the genes can be carefully inserted into the genome (DNA, or genetic material) of Chinese Hamster Ovarian (CHO) cells (mammalian cells). **Figure 2** shows how recombinant technology is utilized to create cells that can express the protein of interest.

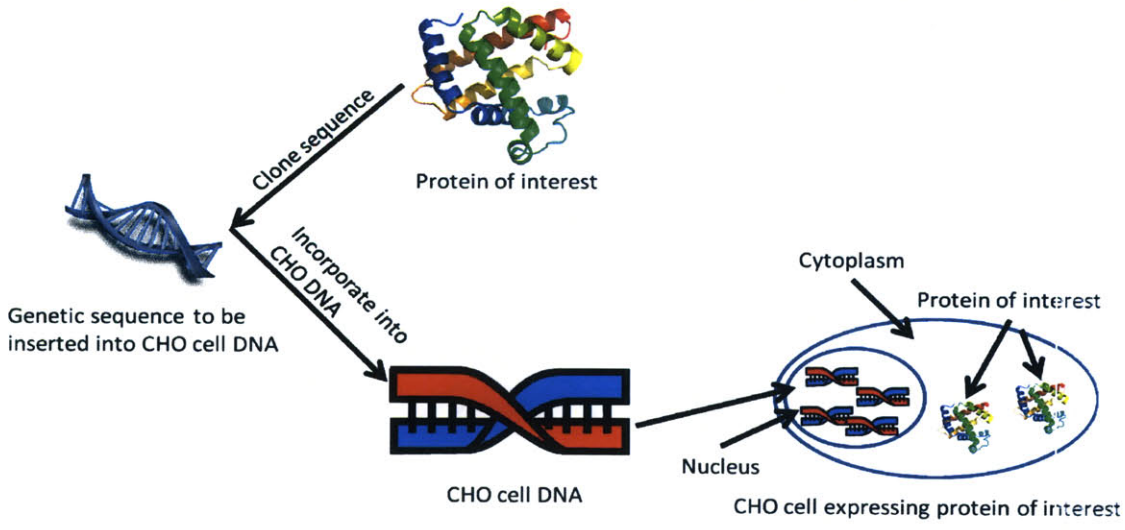

Figure 2. Recombinant technique for mammalian cells[17]

These cells are then screened to make sure the inserted gene is in the correct position, after which they are grown in specific growth media. During this time, they are constantly multiplying and producing the protein of interest through transcription in the nucleus, and subsequent translation in the cytoplasm. **Figure 3** shows how genes are transcribed from DNA to RNA in the nucleus, and then translated from RNA to proteins in the cytoplasm.

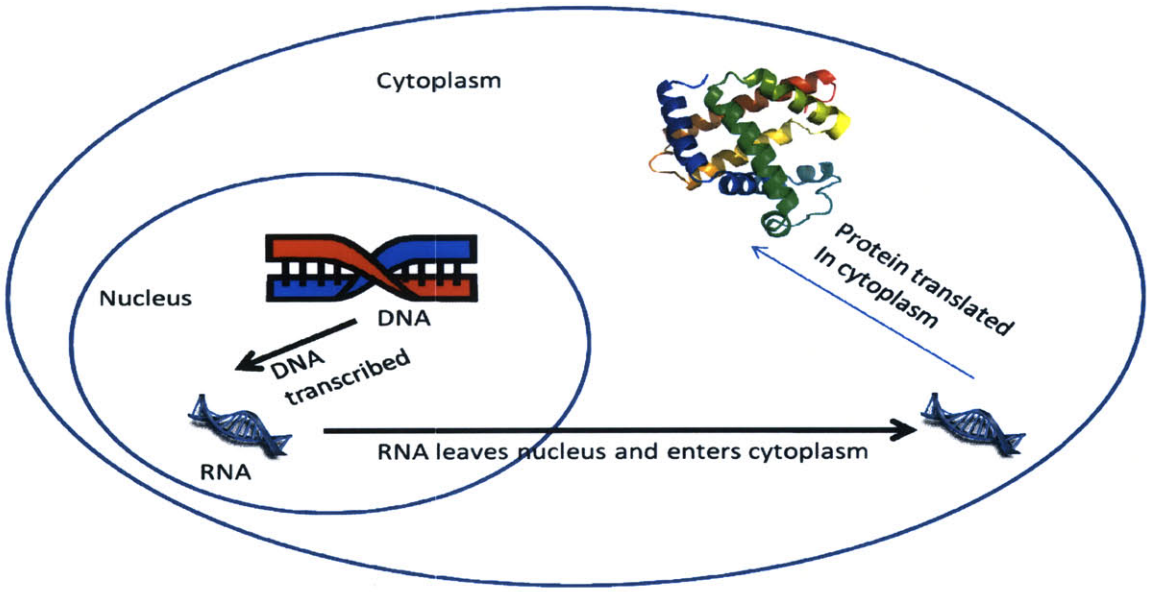

Figure 3. Transcription and translation of a gene[18]

These genetically altered CHO cells are cultured into larger and larger media tanks, in which they are induced to produce more protein. The growth time is optimized so that the maximum amount of protein is extracted from this solution before there is significant cell death and degradation of the desired proteins. After this growth or harvest phase, the proteins are ready to be collected and purified – this occurs in the downstream purification process.

2.2.2 Microbial Cell Culture

Just as proteins are made in mammalian cells, they can also be produced in other cells, such as microbes. In fact, this technique is very widespread, as many biologics are produced in the common bacterium Escherichia coli (E. coli). Although methods in mammalian and bacterial cells are similar, the downstream purification processes of the latter are often complicated by the

fact that the protein products often require re-folding steps. This is because the bacterial (microbial) cells often do not have the same internal machinery that allows mammalian cells to completely process the proteins before they are released. However, growing and harvesting proteins from microbial cells can be advantageous in that they are easier and cheaper to culture, they are not as vulnerable to contamination, their growth times are much quicker, and they are able to produce higher product titers (amounts). Indeed, determining which cell type to use can be quite challenging. As each protein product has its unique set of characteristics, one must weigh the pros and cons on an individual basis, and then decide which cell line will yield the best results. The techniques for inserting the desired gene products into the microbial cell's DNA is very similar to those involved in mammalian cells (section 2.2.1).

2.3 Downstream Purification

After the proteins from the upstream production step have been collected, the protein of interest must be purified. This can be a challenging task, as there are many proteins and cellular debris in the solution, which include:

- Host cell proteins (HCPs) – these are proteins that are normally produced by CHO and microbial cells that must now be separated from protein of interest.
- Degraded products – some of the target proteins will be degraded during the process. Removing these presents a significant challenge, as they have many similar characteristics as the protein of interest.
- Aggregated product – some of the target proteins will aggregate in such a way as to become non-usable. Similar to the degraded products, they are often difficult to remove, as they too have similar characteristics as the protein of interest.
- DNA and other molecules – these also must be removed before a final drug product can be produced.

There are many methods that are utilized to purify biologics. Several key processes will be discussed below – these are general methodologies that are meant to help the reader understand the rest of the thesis. The list is not comprehensive, as there are other techniques, such as centrifugation, precipitation, and crystallization, which are commonly used as well. However, the following processes will be most helpful when reading chapters 3-5:

- **Filtration**: There are numerous types of filters that are utilized in the separation process of biologics. The step yields (their significance to be described later in Chapter 4) are generally pretty high at >90% (less than 10% of the product is usually lost). Common methods of filtration are the following:
    - *Ultrafiltration*: This process is used to remove large molecules/impurities. The solution is forced through a semi-permeable membrane (filter) which collects large impurities, allowing the protein of interest to pass through.
    - *Diafiltration*: This process is used to remove small molecules, such as exchange salts (used in chromatography), from the solution of interest. Solvent is typically added to the solution, which is then passed tangentially across a filter which collects/traps the small impurities as they go by the semi-permeable membrane, allowing the larger protein molecules to pass. This is done several times to achieve a desired purity. This type of filtration is also known as tangential flow filtration.
    - There are other common filtration methods, such as nanofiltration and microfiltration, but they are similar to the ones described above.
- **pH adjustment**: During the course of the downstream purification process, the pH of the solution is often adjusted. By adding either acidic compounds, such as hydrochloric acid (HCl) or sulfuric acid (H_2SO_4), or basic compounds, such as sodium hydroxide (NaOH) or potassium hydroxide (KOH), the pH of the solution can be adjusted accordingly. This is important, as certain chromatography steps require the solution to be within a certain pH range. In addition, proper protein folding is also dependent on the pH of the solution. Finally, changing the pH can help kill off any potential viral contaminants.
- **Chromatography**: This is a very common separation process that is used in many different industries. Small resin beads, typically agarose or polyacrylamide, contain surface properties that allow for the binding of specific molecules. These can either be the molecules of interest, or the impurities that need to be removed. In the case of the former, a solution containing the protein of interest is pumped through the resin, resulting in the protein binding to the resin. There are very specific conditions, such as the pH and polarity of the solution, that allow this interaction to take place. Then, after the impurities have washed through the resin column, another solvent, the eluent, is used to

remove the proteins off of the resin. Again, solution properties, such as the pH, are critical to allow for the dissociation of the protein from the resin. This common motif is known as a "bind and elute" mechanism, and is shown in **Figure 4**. Specific chromatography processes include the following:

- *Ion exchange chromatography*. Ion exchange chromatography is a very common chromatographic technique.[19] It takes advantage of the different charges of the molecules to be separated. This method is divided into two main categories:
  - Cation exchange chromatography. In this method, the resins contain negative charges, and so positively charged molecules are attracted to them. As the positively charged molecules attach to the resins, the more negatively charged molecules continue to flow through the column. It is conventional for the protein of interest to be bound to the resin, while impurities pass through.
  - Anion exchange chromatography. In contrast to cation exchanges, the resins in this method are positively charged. Thus, they attract anionic (negatively charged) molecules, allowing the positive ones to pass freely.
- *Flow through chromatography*. This is a variation of chromatography in which the molecule of interest is allowed to pass through the column while the impurity that is being isolated binds to the resin. In this way, the initial flow stream is the product stream, and the eluent removes the impurities from the resin.
- *Affinity chromatography.* Affinity chromatography takes advantage of how strongly certain molecules are attracted to each other.[20] This can be the result of the complex interaction of an antibody and its antigen, or a receptor and its ligand.[21]
  - *Protein A chromatography*: This is a chromatographic method that is mainly used when purifying monoclonal antibodies. In this case, the resin beads have many particles of Protein A attached to them. Protein A is unique in that it is able to bind mainly to the Fc (fragment, crystallizable) portion of the monoclonal antibody with great specificity and potency. So, when a solution containing monoclonal antibodies is passed through a column with Protein A resin, the antibodies bind to the resin, while the

impurities pass through. Resins that contain Protein A are very expensive, but they are very effective as well.

- *Hydrophobic interaction chromatography*: This chromatographic method, otherwise known as HIC, takes advantage of the hydrophobic surface properties of the molecule of interest. The HIC resin beads contain hydrophobic surface areas that allow binding of these hydrophobic facets. For this to be successful, the correct conditions, such as the pH and salt concentrations, must be carefully applied.[22]

- *Size exclusion chromatography*. Size exclusion chromatography, also known as SEC, is another broad category of chromatography that is commonly used. In this method, the resin is very porous, and smaller molecules traveling down the column spend much time in these porous structures. Larger molecules, conversely, cannot enter these pores, causing them to flow down the column at a faster rate. In this way, larger molecules are able to be separate first from the smaller molecules that follow after them.[23]

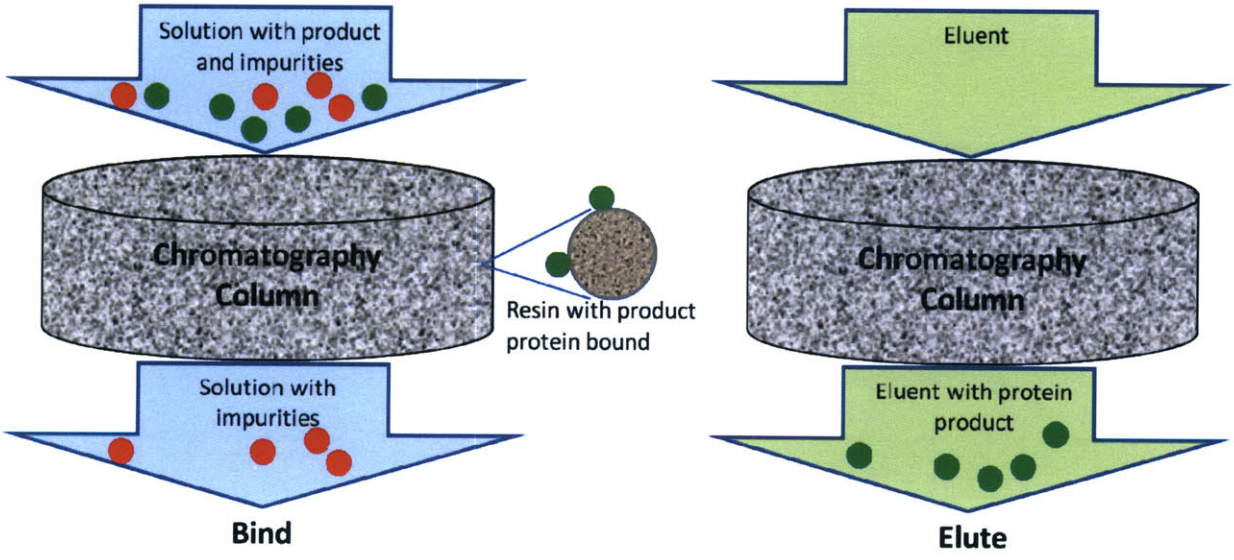

Figure 4. Typical bind and elute chromatography

- **Enzymatic reactions**. As mentioned previously, there are certain post-translational steps that are performed in mammalian cells that are not done in microbial cells. These could include re-folding (to ensure the protein will have the correct shape so it can perform its

required actions) reactions, or the addition of certain groups (such as a methyl group). The particular reactions are not described in this document, and are not pertinent to the objective of this thesis. It is only required to know that these reactions are necessary for the production of the drug substance.

- **Lyophilization**. Lyophilization, also known as freeze drying, is a very costly and time-consuming process in which proteins in a liquid solution are basically dried to form a powdery drug substance.[24] This is a complicated process, as biologics are not stable, and are very sensitive to high temperatures – they degrade very quickly. The basic steps of freeze drying include the following:
    - The solution is cooled/frozen in a low pressure environment (this facilitates the evaporation of solvent at lower temperatures).
    - The frozen bed of solution is then heated in this low pressure environment in such a way as to allow for the sublimation (phase change from solid to gas) of the solvent. The low pressure environment allows for the sublimation process at low temperatures, preserving the proteins.

This thesis does not focus on the lyophilization and technologies that model it as a continuous process (spray-drying), as they are very complicated, and merit their own separate investigations.

CHAPTER 3
CONTINUOUS PROCESSES

3 Continuous Processes

3.1 Introduction

This chapter will focus on three general groups of continuous processes: continuous chromatography technologies, tubular reactors, and spray drying. Although there are other different continuous technologies being implemented in downstream purification, these are the ones I focused on during my internship. In addition, although perfusion reactors, which permit continuous harvesting of protein products in the upstream process, are interesting, they will not be discussed in detail. The current batch process has its advantages (tested, reliable, familiarity, and less vulnerable to contamination), but I believe that recent advancements in perfusion reactors may make this new technology more viable. Indeed, new perfusion reactors are now achieving titers similar to that of their batch counterparts.

3.2 Continuous Chromatography

3.2.1 MCSGP

The Swiss company ChromaCon has developed a novel technology that allows for continuous chromatographic separations.[25] This technique is called the Multicolumn Countercurrent Solvent Gradient Purification (MCSGP) system. It is unique in that it is able to generate three output streams, whereas other continuous systems typically have only two. In addition, by generating these three streams, it is able to increase the overall yield of the process. This can be extremely beneficial for low yield processes that lose much expensive product.

The actual mathematical description of this process is beyond the scope of this thesis, which focuses on the financial impact of the technology. Furthermore, these mathematical models have not been very useful in predicting the actual performance of the MCSGP on certain processes. Rather, to more accurately determine the yield improvement achievable with this

process, empirical data is required through experimentation. For these reasons, only a general description of the process will be included, which should be sufficient to understand how it functions. The basic set up consists of three chromatography columns in series connected by a complicated network of tubes and pumps. These allow for the two basic configurations that the process alternates between, which allows for this separation advantage. Specifically, the steps include the following:

1. During the first phase (see **Figure 5**), there are three feeds, one to each of the columns that are labeled 1, 2, and 3. There are also three corresponding outputs. Light binding impurities are colored blue, product streams are colored red, strong binding impurities are colored green, feeds are colored brown, and the eluent streams are colored gray.
    a. In column 1, the input represents the feed. When the feed enters this column, which already contains strong binding impurities, product, and light binding impurities, the light binding impurities are eluted out. The feed that enters the column arranges itself in a gradient according to the binding properties of its components: the light binding impurities travel furthest down the column, as they are not slowed by interactions with the resins, while the strong binding impurities travel the least down the column, as they are strongly attracted to the resin. The actual desired protein product situates between these two extremes.
    b. Simultaneously, in column 2, eluent is fed in, while the protein product is expelled from the column and collected for further processing. Real-time chromatographs (displays which show the composition of the outlet stream) confirm the identity and purity of this stream.
    c. Concurrently, in column 3, eluent is fed in while the strong binding impurities are removed from the output stream.
    d. Once a pre-determined amount of product is collected from column 2 (based on content feed and real-time chromatographs), the three columns are rotated in a direction counter to the input flows. Column 1 occupies column 2's position, column 2 occupies column 3's position, and column 3 goes to column 1's position. Now the set up is ready for the second phase.

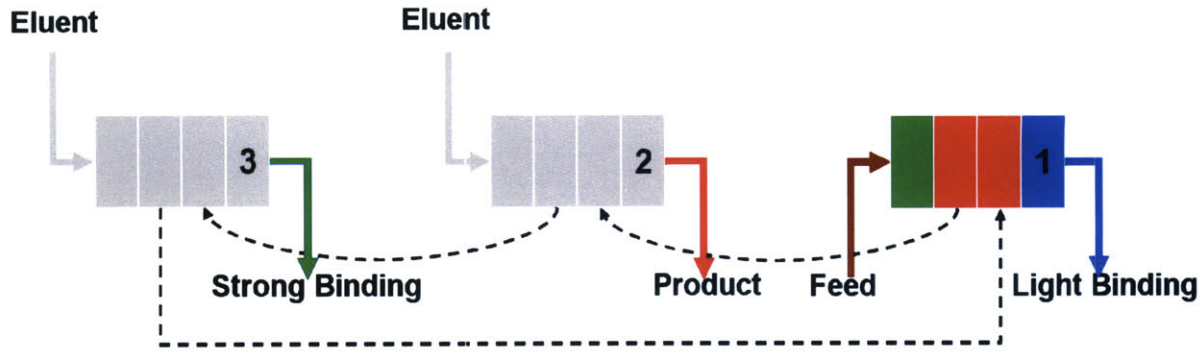

Figure 5. Phase I of the MCSGP, three inputs and three outputs

2. With the three columns in their new positions, the tubing is switched so that there is only one input and one output (see **Figure 6**).
    a. Eluent is fed into column 2, which causes any protein product to be pushed into column 1. Some of the strong binding product may leave column 2 and enter column 1, but most of it should stay in column 2.
    b. As the protein product enters column 1, the light binding impurities are forced out, into column 3. Some protein product may leave column 1 and enter column 3, but the process is calibrated so that most of the protein remains in column 1. However, all, if not most, of the light binding impurities must be forced to exit column 1, because if much is left behind, the product stream during the next phase will have low purity.
    c. As the light binding impurities and some protein product enter column 3, more light binding impurities exit this column

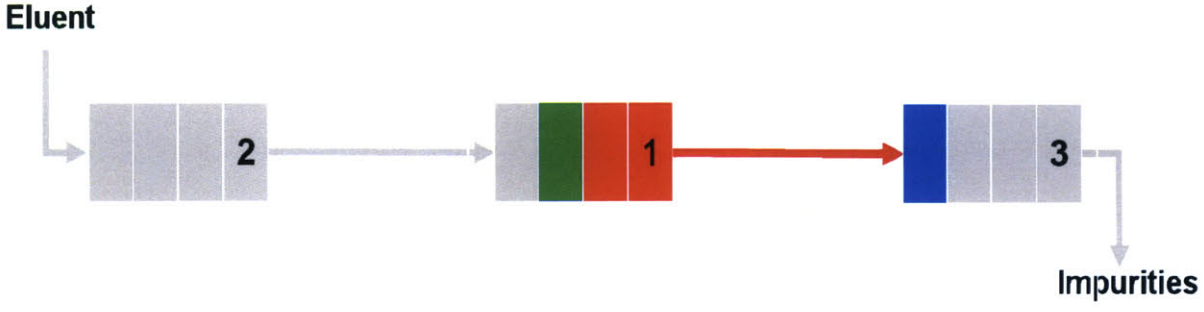

Figure 6. Phase 2 of the MCSGP, one input and one output

3. The first phase is repeated, and the tubing is changed so that there are three inputs and three outputs again (see **Figure 7**).
    a. In column 3, the input represents the feed (similar to column 1 during the first cycle). When the feed enters this column, more light binding impurities are removed.
    b. At the same time, in column 1, eluent is fed in, while the protein product is expelled from the column and collected for further processing.
    c. Concurrently, in column 2, eluent is fed in while the strong binding impurities are removed in the output stream.
    d. Once a pre-determined amount of product is collected from column 1 (based on content feed and real-time chromatographs), the three columns are rotated in a direction counter to the input flows. Column 1 occupies column 2's position, column 2 occupies column 3's position, and column 3 goes to column 1's position. Now the set up is ready for the second phase of the second cycle. This continues to repeat itself, and during the process, pure product is collected, while light binding and strong binding impurities are removed.

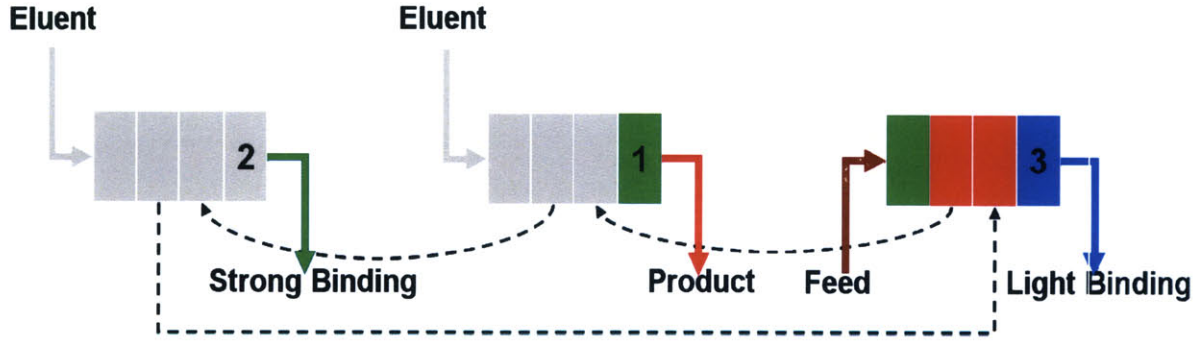

Figure 7. First phase, repeated

4. As these phases repeat, the overall effect is that the side-streams that are normally discarded during a batch chromatographic step, are recycled in such a way as to extract as much protein product as possible. The side-streams are comprised of the mixtures where the product is mixed with the light binding product or the strong binding product. One can imagine that there is a mass of protein product that is increased and decreased in size as feed is introduced and product is collected, respectively. On the tips of this mass are

areas where the protein is not pure; that is, it is contaminated by light binding or strong binding impurities (see **Figure 8**). Thus, it is clear that by optimizing and then repeating this process, the MCSGP process is able to extract more protein product and increase yields significantly.

Figure 8. Simple representation of protein product and impurities in MCSGP system

The MCSGP technology has an added benefit of requiring less buffer than conventional chromatography columns. This aspect of the technology will be discussed in Chapter 5, as I will not include the calculations in the first part of my thesis (to be discussed later).

3.2.2 BioSC

During the second part of my internship, there was more flexibility to study continuous chromatography technologies other than the MCSGP. Whereas the MCSGP has the great advantage of potentially increasing yields, it involves a significant developmental risk, as alluded to earlier. In addition, there are current batch processes that already have very high yields (>90%), for which the marginal benefit of this technology would be minimal. Thus, to model other chromatography steps as continuous, I examined more technologies. More specifically, I studied the BioSC Process that has been developed by Novasep.[26] It is more advanced than the MCSGP process – there are already large pilot-scaled projects that are able to run at rates of up to 150 L/hour.

The BioSC process is similar to the Simulated Moving Bed (SMB) technology that is utilized in many industries, such as the chemical industry. It has several advantages over current batch processes:

1. The BioSC process increases the utilization of resin. This is critical, as resins, especially those with Protein A, can be very costly. The mechanism by which the BioSC increases resin utilization, or binding capacity, is as follows (this can be seen visually in **Figure 9**):
    a. Instead of a single batch reactor, many reactors are arranged in series. With the BioSC process, the current limit is six reactors.
    b. As the feed goes through the first reactor, there is breakthrough of product, which then goes to the next reactor. Breakthrough occurs when even the first column is not fully "saturated" with the protein product. This is the time when typical batch reactors stop loading a column, as the protein product is very expensive. Thus, most companies would rather underutilize their resin binding capacity than lose protein product. With the BioSC process, the first column can be loaded to capacity without the risk of losing product, because it is flowing down to the other columns.
    c. Once the first reactor is fully loaded, it is eluted, washed, equilibrated, and then brought back into the series of columns.
    d. The increase in resin utilization, as reported by the company has ranged from 85%-140%. This is because there is a shift from a dynamic binding capacity (with the current batch process) to a static binding capacity that is achieved with the BioSC process. The actual increase in capacity can be predicted by studying the breakthrough curves of the products with their specific resins and existing conditions. This was not possible for this thesis, as we did not have the breakthrough curves for Biologic Y. This is not that relevant, though, as this is just an estimate, and must be followed with actual experimental data to determine the true increased resin utilization benefit.

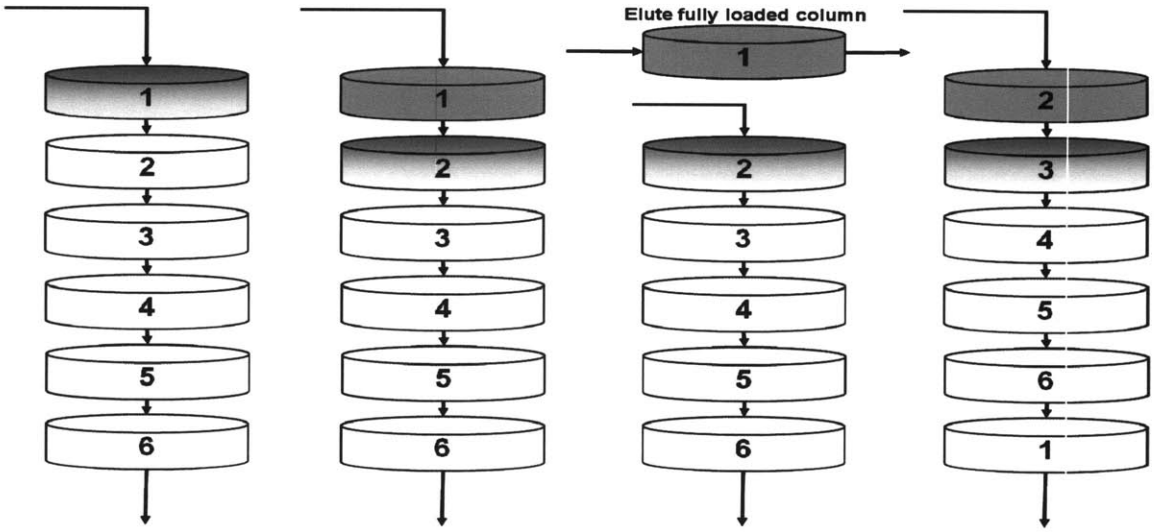

Figure 9. BioSC process

2. The BioSC process requires significantly less buffer and cleaning solutions. This is process/step dependent, but the Novasep has shown a decreased consumption of 46%-58%.[27] This is noteworthy, as some buffers, especially those that contain the expensive ingredient acetonitrile, can be costly if used in large quantities. In addition, if a company is considering building a greenfield plant, decreased required buffer storage tank space can result in significant savings.

3.3 Tubular reactors

This thesis will emphasize continuous chromatography technologies; however, as there are several enzymatic reactions involved in the downstream purification of Biologic Y, I will also examine a technology that can replace these batch reactors. More specifically, I will look at how tubular reactors can be used, and what their potential advantages and disadvantages are. There is a collaboration between Sandoz Biopharmaceuticals and Professor Rainer Hahn from the University of Natural Resources and Life Sciences in Vienna. This is part of the ongoing partnership between industry and academia called the Austrian Center of Industrial Biotechnology (ACIB). My thesis will not provide details regarding the mathematical modeling of such reactors, as I am primarily concerned with the financial impact of this technology.

Furthermore, the savings realized in my models will stem from the chromatography technologies, as will be described in Chapter 5.

Currently, several of Biologic Y's downstream purification steps involve the mixing of reactants in large tank reactors. The reactants are mixed under specific conditions, and after a pre-determined amount of time, the reaction is assumed to have run its course, and then the processed protein product is moved on to the next step. These reaction steps are fairly reliable, as they have been perfected over many years of experience. However, this is a batch reaction, and does not permit for a fully continuous downstream process.

With tubular reactors, the reactants are continuously fed into a tube-shaped reactor. They combine to form a reaction solution that flows through a pre-determined length of pipe. As the reactants flow through this pipe, they react, just as they do in the tank reactor. Finally, at the end of the tubing, the reactants have completely reacted to form the desired product. As the reactor is being continuously fed with input streams, it is also continuously releasing product in its output stream (see **Figure 10**).

Figure 10. Tubular reactor with continuous input and output

The length of tube that is required for the reaction to be completed depends on the residence time required for the reaction. This may or may not be less than what is required for a batch reactor. There may be instances where the residence time required is decreased because the reactants are in much closer proximity, and can react faster. Similarly, if the heat or pH of the solution needs to be changed, this may be accomplished in a much shorter time frame, as the cross sectional area of the tubing will be much smaller than that of a tank reactor (see **Figure 11**). However, if the reaction is a re-folding reaction, which does not depend on the proximity of reactants, then this time requirement may not be different.

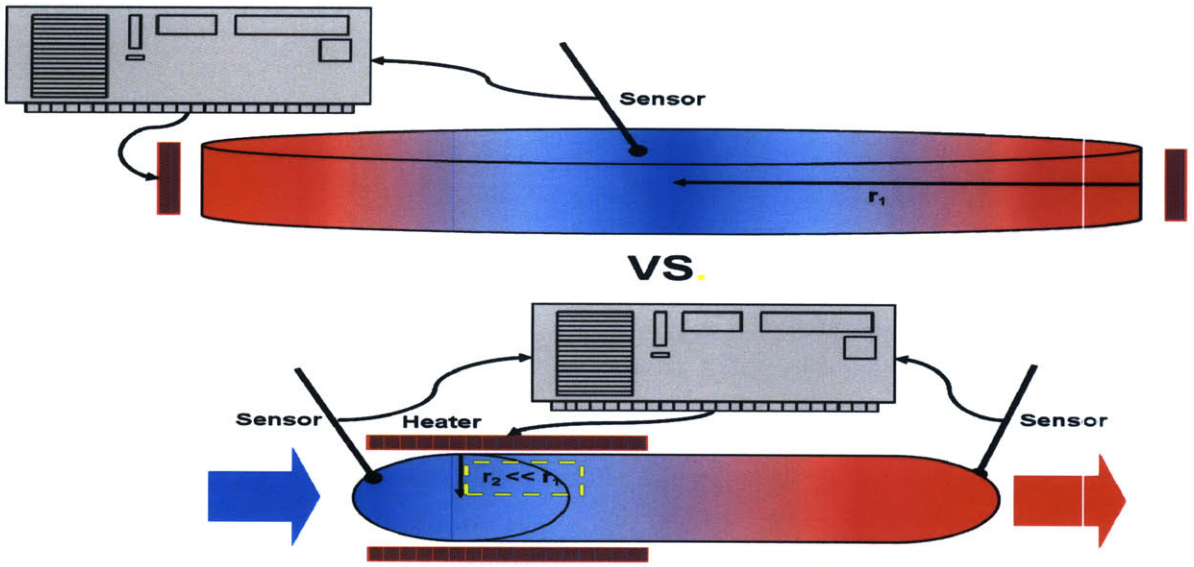

Figure 11. Advantage of tubular reactor – decreased cross sectional area

To calculate the amount of tubing required for a particular reaction, we need to know the residence time required (to be determined empirically with the particular tube specifications), the tube diameter (this can be given by the type of tubing available), and the flow rate (this is determined by the overall rate determining step of the process). Then, as per discussions with Professor Rainer, we need to make sure that the fluid flow is laminar by ensuring that the Reynolds number is less than 2,300. Turbulent flow can expose the proteins to undue stress and strain. For example, the following hypothetical case will illustrate how to determine the length of tubing:

- Inflow rate of protein solution = 5 L/min
- Inflow rate of reactant = 5 L/min
- Total flow rate = 10 L/min
- Residence time required = 60 min (pre-determined based on tube diameter)
- Volume of tubular reactor = 10 L/min * 60 min = 600L = 600,000 mL
- Tube diameter = 4 cm
- Tube area = $4*\pi$ cm^2
- Tube length = 600,000 mL/4π cm^2 = 47,771 cm = 478 m

Now, to calculate the Reynolds number, one just needs to use the fluid's density and viscosity, as well as the tube diameter and the linear flow rate:

$$Reynolds\ number = Re = \frac{\rho v D}{\mu},$$

$$where\ \rho = density\ (\frac{kg}{m^3}), v = flow\ velocity\ \left(\frac{m}{sec}\right),$$

$$D = diameter(m), and\ \mu = viscosity\ (\frac{kg}{m * sec})$$

Finally, another advantage of tubular reactors is that mixers can easily be installed throughout the tubing, accelerating the reaction even more.

3.4 Spray-drying

The last step of the downstream purification of Biologic Y is the freeze drying, or lyophilization process. This is a rather complex, time-consuming, and expensive process (described in the previous chapter). Spray-drying offers an alternative method of achieving the same goal of removing the liquid content to create a powdery protein product.[28] The basic mode of action is that the solution is rapidly sprayed out of a nozzle. The nozzle utilizes atomizers to disperse the product containing fluid into very small droplets. A hot drying gas is then applied either co-currently or counter-currently, causing the fluid from these droplets to evaporate. As the liquid evaporates, small particles of protein product, with minimal moisture, are deposited within the drum of the spray-dryer, while the hot gas containing the evaporated fluid is quickly removed. This can be complicated with protein mixtures, as they are often heat sensitive, and can degrade quickly. Sandoz has had limited success using spray-drying with other biologics, as the yields have been lower than those achieved with lyophilization. However, after discussing this technology with Professor Gerhard Winter at the Ludwig Maximilian University in Munich, I believe this process can still be viable with biologics.

A thorough investigation of the application of spray-drying to biologics is beyond the scope of this thesis. It is a very complicated process, and deserves an independent investigation. Adam Youngman, LGO 2009, wrote a thesis on the economics of spray-drying with small molecules, and this can be used as a reference.[29] However, the stability of biologics makes the application of this technology particularly challenging.

CHAPTER 4
PROCESS DATA AND MODEL FOR BIOLOGIC X

4 Process Data and Model for Biologic X

4.1 Sources of data

I was able to supplement my literature review with a tour of this facility, as well as in-depth discussions with the scientists and engineers involved in this effort. After familiarizing myself with the overall downstream purification process, I determined that there were certain parameters and data that would be required for my model:

- Yield of each step
- Time spent in each step
- Cost of raw materials
- Cost of overhead for running the line that will produce Biologic X

For the first two items listed, I was able to obtain the required information from Dr. Richard Hoelzl, who runs the line that currently produces Biologic X. For the last two items, Angela Gruber, who also works in the Schafetnau plant (finance department), was able to help me obtain the necessary data. This data will not be disclosed in this thesis – I will use fictitious numbers; however, the results should convey the same basic message as my real data.

4.2 Model of current batch chromatography processes

4.2.1 Assumptions

After I collected the data, I determined which were the most accurate and representative campaigns (with the help of my supervisor and Richard Hoelzl), and then averaged the data from those runs. This gave me the following data that would be used in my model:

- Volume and yield of product in the upstream process
- Yield at each downstream process step
- Overall yield of downstream processes

Thus, for the model that I submitted to the company, I assumed that the average of the last several campaigns could accurately predict the product yields in future runs. However, as more data is collected, and the runs become more efficient, the company must update the model.

4.2.1.1 Yield data

Yield data is an important metric in my model, as it determines how much product will be left at the end of one process, and available for the next step. The basic equation for my model is as follows:

- $Step\ i$: $input_i(grams\ per\ batch) \times yield_i = output\ _i(grams\ per\ batch)$
- $input_{i+1} = output_i$
- $Step\ i+1$: $input_{i+1} \times yield_{i+1} = output_{i+1}$

By combining all of this data, we could determine the overall yield of the process. This is simply: $process\ input\ from\ upstream\ process \times (\prod_{i=1}^{n} yield_i) = overall\ yield.$

Thus, by using data from the previous runs, we can predict what product output we could expect with a given input. Similarly, we can also predict that changing the yield of a specific step can change the overall yield. This has two implications:

- If the yield of a step has increased, then all downstream steps will now process more product – this will result in increased consumption of raw material. My model assumes that the percentage yield of these downstream steps will remain constant.
    - For example (data all fictitious), if we had the following step yields:

Step 1	60%
Step 2	60%
Step 3	60%

    - The overall yield of these processes would be: $60\% \times 60\% \times 60\% = 21.6\%$
    - Now, if the yield of step 2 were changed to 90%, our system will look like the following:

Step 1	60%
Step 2	**90%**
Step 3	60%

    - Now, the overall yield will be: $60\% \times \mathbf{90\%} \times 60\% = \mathbf{32.4\%}$

- The cost of the product should decrease as the yield increases. This is because much of the fixed costs (overhead, labor, maintenance) can now be spread over more product.
    - For example, if we have the following data for a batch:

Total COGS for downstream processes	$1000
Product achieved	50 *grams*

    - From this data, we see that the COGS associated with the downstream purification is: $1000/50g=$20 per gram of product.
    - Now, if the yield is increased from 21.6% to 32.4%, we get the following data:

Total COGS for downstream processes	$1000
Additional COGS from increased raw material required	$100
Product achieved	$50\ grams \times \frac{32.4\%}{21.6\%} = 75\ grams$

    - From this data, we see that the COGS associated with the downstream purification is: $1100/75g=$14.67 per gram of product, a decrease of 26.7%.

4.2.1.2 Resin utilization and cost

Chromatography resins lose their ability to bind proteins after they have been used and washed multiple times. After a column of resin is used for a separation process, it must be cleaned, equilibrated, and prepared for the next round. This process of binding, eluting, cleaning, and equilibrating has a "wear and tear" effect on the resin beads. The longevity of the resin depends on many factors:

- The type of resin
- The type of buffers used for eluting, cleaning, equilibrating
- Other conditions, such as salt concentrations and pH

For this reason, the lifetime of the resin needs to be determined for the specific circumstances of each process. This is determined empirically, and usually described in terms of cycle life. So, a cycle life of 100 means that the resin can be used for 100 cycles or runs before it

should be replaced. To determine the resin cost for each cycle, the following calculation is performed:

Resin cost	$1000/L
Resin cycle life	100
Resin volume for this process	100L

- To calculate the resin cost/cycle: $\frac{\$1000}{L} \times 100L\ resin \times \frac{resin}{100\ cycles} = \frac{\$1000}{cycle}$

This is an important cost to consider, as resins can be quite expensive, especially those containing Protein A.

4.2.1.3 Buffer consumption

In addition to expensive resins, a significant number of buffers are utilized during a purification process. They are used in the following ways:

- To transport the protein of interest
- To elute the protein off of the resin
- To transport other reactants/catalysts
- To wash and equilibrate the resins

The actual volume of buffer required for this step is often determined by the volume of the column. Typically, buffer requirements are often described as number of columns of solution required for each step. For example, if a column volume is 100L, and there are 5x column volumes of buffer A required for a certain step, then the total volume required is 500L. These numbers can become quite large, and if the buffer is expensive, the costs can be significant.

4.2.2 Current batch chromatography model

For the current batch process, I will use the following data (fictitious):

Upstream fermentation batch volume	10,000L
Titer	2mg/L
Product/batch	20g/batch

I will model the process such that there are three chromatography columns, one enzymatic reaction, and two filtration steps. The following diagram (**Figure 12**, fictitious) illustrates the flow of the protein product.

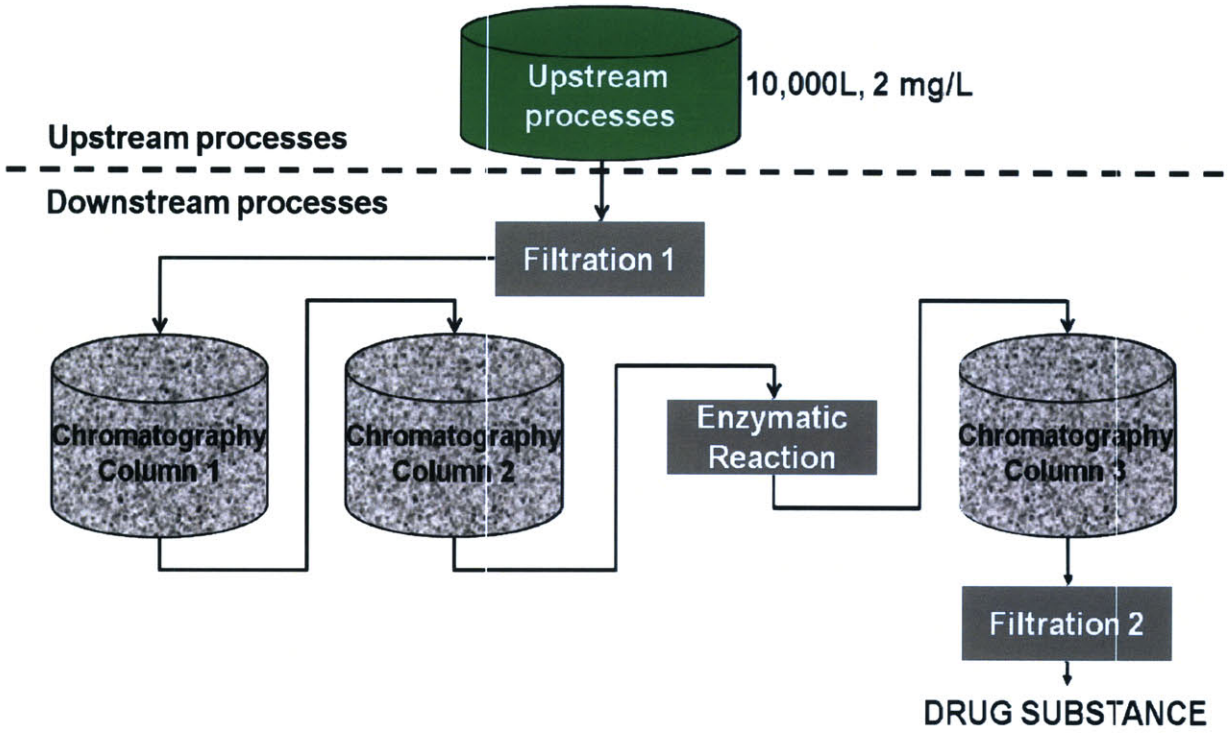

Figure 12. Biologic X batch process model

The following data (fictitious) characterize the downstream processes – both product yields and costs.

	Filter 1	**Chrom. 1**	**Chrom. 2**	**Enz. Rxn.**	**Chrom. 3**	**Filter 2**
Yield	95%	90%	90%	90%	70%	90%
Binding capacity of resin		20g/L	20g/L		10g/L	
Cost of Resin/L		$1000	$1000		$1000	
Resin cycle life		100	100		100	
Cost of filter (one time use)	$10,000					$10,000
Cost of buffer or reagent per cycle		$100	$100	$500	$100	

Using this data, we can model our process to determine the overall yield and cost per batch (see **Figure 13**). I use the following calculations:

- For the filters:
  - Input = output from previous step
  - Output = input*yield
  - Cost = cost of filter
- For the chromatography steps:
  - Input = output from previous step
  - Output = input*yield
  - Cost = resin cost (per cycle) + buffer cost
    - $resin\ cost = \frac{input\ (\frac{g}{batch})}{binding\ capacity\ (\frac{g}{L})} \times cost\ of\ resin\ (\frac{\$}{L}) \times \frac{1}{cycle\ life}$
    - $buffer\ cost =$

      $cost\ of\ buffer\ as\ listed\ \left(\frac{\$}{L}\right) \times volume\ of\ buffer\ per\ cycle\ (L)$
- For the enzymatic reaction:
  - Input = output from previous step
  - Output = input*yield
  - Cost = cost of buffer/reagent as listed above
- For the overall reaction:
  - $Overall\ yield = \prod individual\ yields$
  - Total product = input*overall yield
  - Total cost (downstream purification)/batch = $\sum individual\ costs = \$52{,}401$

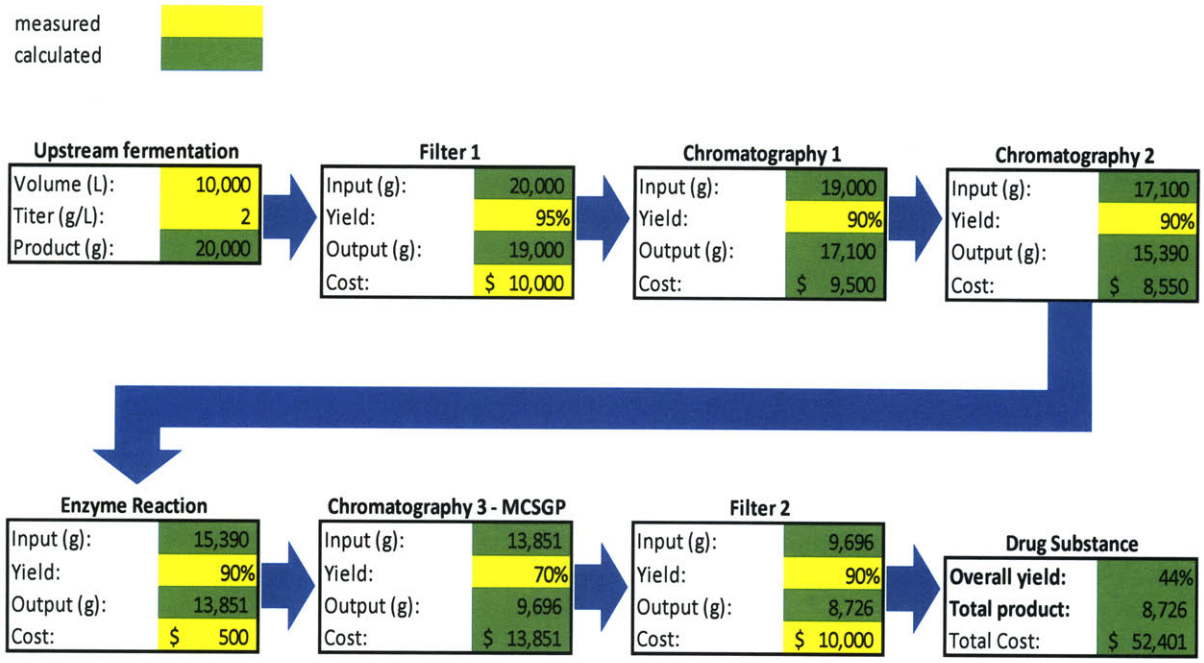

Figure 13. Yields and costs for the downstream processes of Biologic X

These costs reflect the variable costs associated with a batch. In addition, fixed costs must be spread over the many batches that are made over a certain time period. This includes overhead, maintenance, and labor. In the case of Biologic X, we have this data (fictitious).

Fixed cost per year	$10,000,000
Number of batches per year	40
Fixed cost/batch	$250,000/batch

So, when the variable costs are added to the fixed costs, the total cost of downstream purification for one batch is: $250,000+$52,401 = $302,401. This translates into a cost of $302,401/8,726g = ***$34.65/gram of drug substance***.

4.3 Model with MCSGP system included

4.3.1 Assumptions

In this hypothetical model, we will assume that we will replace the lowest yield chromatography step with the MCSGP process. This is because we want to generate the most savings as possible, and this is only possible when the initial yield is low. For example, with the

current batch process in the third chromatography step we can realize the following yield increase with MCSGP:

Loss of product with current batch process	30%
Factor decrease in loss of product from the literature	1.75x-3.5x[30]
Factor decrease used in this thesis (conservative estimate)	1.75x
New loss of product with MCSGP process	30%/1.75 = 17.14%
New effective yield with MCSGP	100% - 17.14% = 82.86%

When determining the factor decrease in lost product with the MCSGP process, I used the lower end of the range I obtained from the literature and the company. Thus, by dividing the lost product by 1.75, I was conservatively estimating the decrease in lost product with this new process. Specific numbers for Biologic X are not available, and there are no good mathematical models that can predict this result. The only way to determine the true effective yield increase is to perform an experiment with Biologic X and the specific resin to be used. Now, the overall yield for the process is increased (see **Figure 14**).

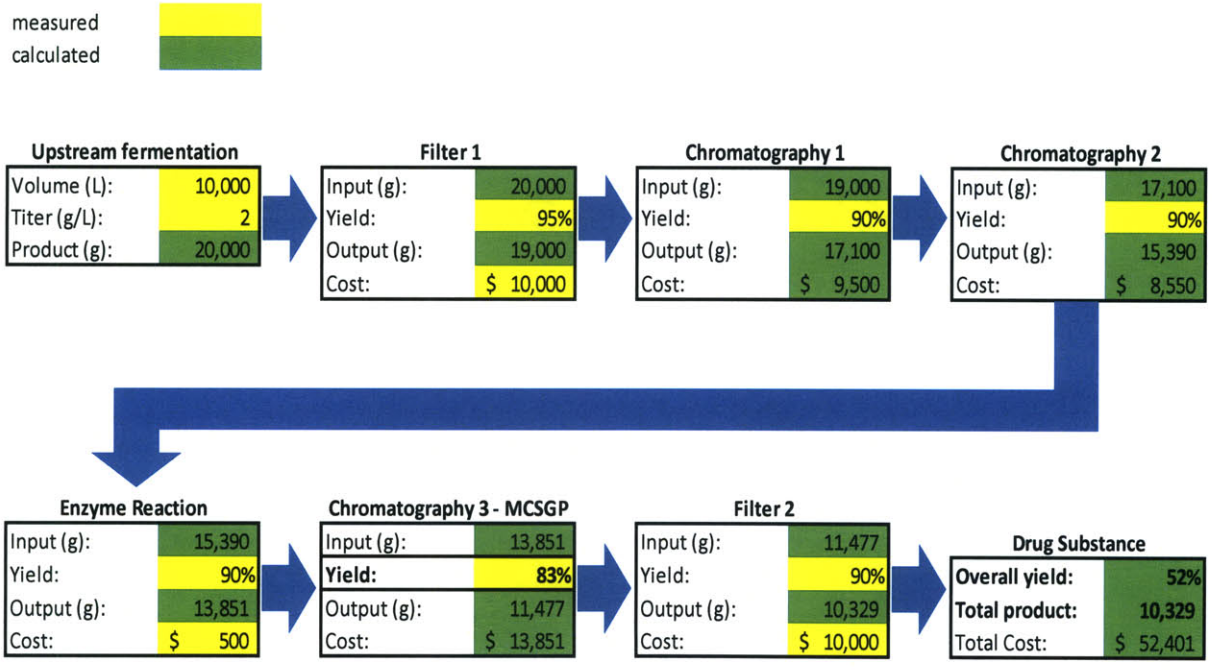

Figure 14. Yields and costs for the downstream processes of Biologic X with MCSGP

In addition, with MCSGP there are potential decreases in buffer utilization. For part one of this thesis, I will ignore this savings, as it turns out to be insignificant compared to the cost savings generated from the increased yield.

4.3.2 Results

Now, we can calculate the new cost per gram of drug substance. The variable costs have stayed the same, as have the fixed costs (we assume the process takes the same amount of time and utilizes the same amount of overhead). Also, because the only step after the third chromatography step is a filter step, there are no increased raw materials utilized during this purification stage. However, if the first chromatography step were replaced by an MCSGP, the increased yield would cause an increase in inputs into the subsequent steps, forcing them to utilize more raw materials (resin, buffers). This will be shown in the second part of the thesis. So, the cost per batch remains $302,401, with an output of 10,329 grams of product. Thus, the cost is $302,401/10,329g = ***$29.28/gram of drug substance. This results in a ($34.65-$29.28)/$34.65 = 15.5% decrease in COGS for the drug substance.***

Note that this number can be significantly larger with the following conditions:

- If the yield for the step was initially lower (for example, if the initial yield was 40%, the increased effective yield would be 66%, an increase of 26% vs. 13% used in this example)
- If the fixed costs represented a larger portion of the total costs
- If we included the decreased buffer requirements

In fact, with Biologic X, we were able to predict a significantly higher cost savings when we modeled one of its chromatography steps with the MCSGP technology (the lowest yield step).

4.4 Financial Analysis

With the data obtained from the previous section, namely the change in the COGS of the drug substance, we can determine the change of the estimated NPV of the projected sales of Biologic X. Initially, I created a forecast model, which included my own estimates of penetration and market size. However, it turned out that Sandoz had a much more sophisticated model that included sales in various indications, as well as different dosage forms. Within this

model, there was an input for the cost of the drug substance, which then directly affected the NPV estimate. I decided to use this model instead of the one I developed because it was more accurate, and it included much more information than what I was privy to. I used the data I obtained from the models described previously to obtain the potential savings from using the MCSGP technology:

- $eNPV_{batch} =$
  $expected\ NPV\ with\ Sandoz\ forecast\ model\ with\ cost\ of\ drug\ substance_{batch}$
- $eNPV_{MCSGP} =$
  $expected\ NPV\ with\ Sandoz\ forecast\ model\ with\ cost\ of\ drug\ substance_{MCSGP}$
- $potential\ savings = eNPV_{MCSGP} - eNPV_{batch}$

With the result obtained from the data from Sandoz, I was able to show a significant amount of savings with the MCSGP. However, I had to determine whether the benefit of developing this technology would outweigh the developmental risks and costs associated with novel technology (it is still in lab scale only). At this point, the next step would be to do a small experiment with Biologic X to determine if predicted yield increases can be realized. This will give Sandoz the additional knowledge required to decide whether or not to proceed with this technology. The experiment is expected to cost around $100K-$150K, but will add a lot of information about this particular system. The question I needed to address was whether it is worth doing this experiment, given all the uncertainties. To do this, I utilized a decision tree analysis, where I used the following inputs:

- The estimated "effective yield" increase (this is actually a factor by which the lost product is decreased by – see section **4.3.1, Assumptions**)
- The NPV of developing a commercially scaled MCSGP process
- The % probability that the MCSGP works
- The sensitivity (ability to detect a positive result) of an initial experiment
- The specificity (ability to know if the MCSGP does not work) of an initial experiment

The calculations for this decision tree are as follows (see **Figure 15** for diagram), using the following hypothetical data:

Estimated effective yield increase	1.75 (as per before)
NPV of development of MCSGP process	-$5,000,000 (an investment)
NPV of Biologic X with all batch processes (baseline)	$80,000,000
NPV of Biologic X with MCSGP process at third chromatographic step	$100,000,000
% probability that MCSGP works with Biologic X	30%
Sensitivity of experiment	60%
Specificity of experiment	80%

Initially, the decision is made whether to perform the experiment:

a. If Sandoz performs the experiment, there is a 30% chance that the MCSGP works and a 70% chance it does not work.
    i. If it does work, there is a 60% chance that this experiment will show this convincingly (that is, the experiment will show a significant yield increase) – this translates into an overall probability of 30%*60% = 18%.
        1. The payoff in this scenario is the NPV with the MCSGP ($100,000,000) plus the NPV of the investment (-$5,000,000) = $95,000,000.
    ii. If it does work, there is a 40% chance that the experiment will fail to show this – this translates into a 30%*40% = 12% probability.
        1. The payoff in this scenario is just the baseline NPV of $80,000,000, as the company does not invest in developing the MCSGP technology further.
    iii. If it does not work, there is a 100%-80% = 20% of a false positive – that the experiment will detect a significant improvement, when in fact future scale-up of the equipment will not provide the same result; this translates into an overall probability of 70%*20% = 14%.
        1. The payoff in this scenario is the baseline NPV of $80,000,000 (as the MCSGP process in this case does not provide significant benefits) minus the developmental cost of -$5,000,000 (because in this situation, Sandoz develops the MCSGP thinking that it would be very helpful) for a total of $75,000,000.

iv. If it does not work, there is a 70%*80% = 56% chance of the experiment confirming this result.

1. The payoff in this scenario is just the baseline of $80,000,000, as Sandoz does not invest in this technology.

b. If Sandoz does not perform the experiment, the NPV is the baseline, as shown in the above table.

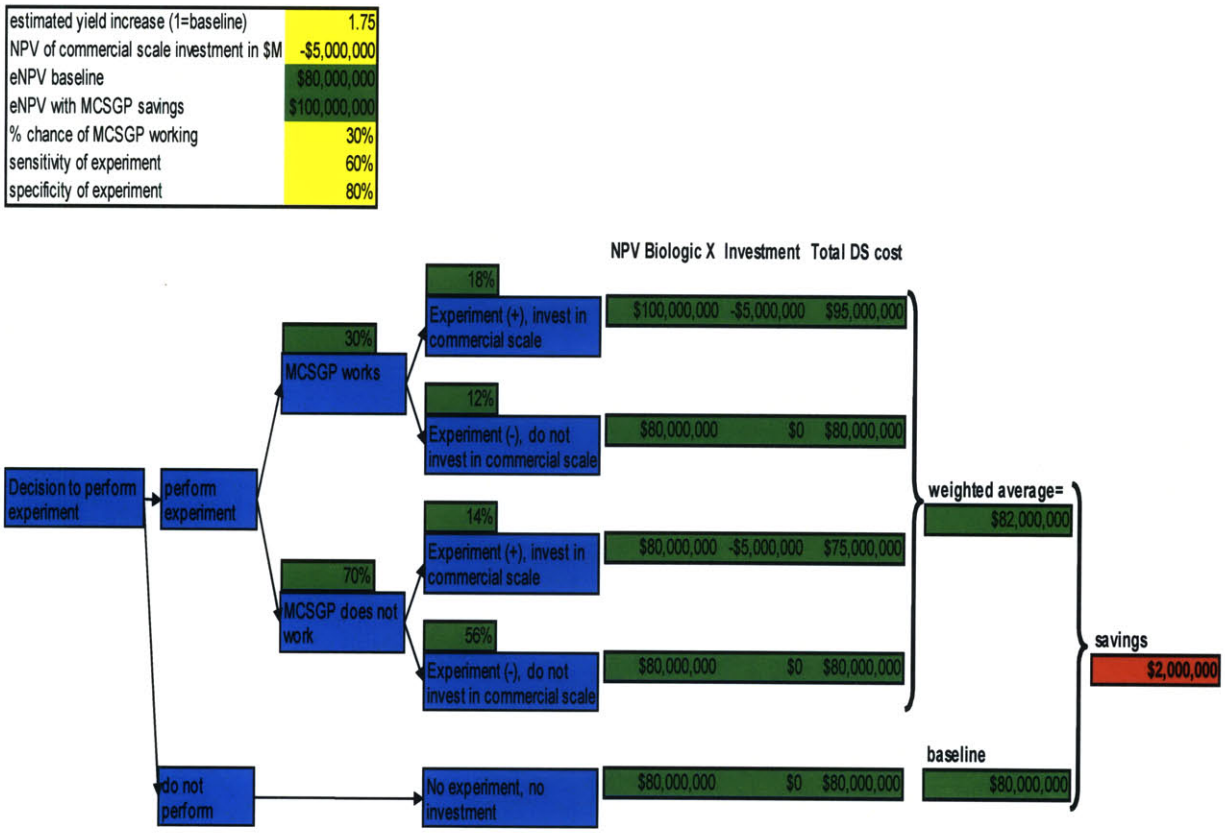

Figure 15. Weighted average of different payoffs with Biologic X

We see that with these hypothetical numbers the NPV of the potential savings is greater than the cost of the initial investment on the experiment, which would warrant an investment in this technology. This is indeed what happened when I used the data from Biologic X – this showed a positive NPV, and so the company has decided to move forward and perform future experiments.

4.5 Monte Carlo Simulations

The discussion from the previous section focused on a single set of assumptions. However, Sandoz must consider alternative situations, which may be better or worse than the baseline conservative estimates that I made. What if the "effective yield" increase was only 1.5x, or 3x? What if there is actually a 50% chance that the MCSGP works? By changing these factors, our results can change dramatically. To study this phenomenon, I performed some Monte Carlo analyses with the following scenarios:

	Worst case	Base case	Best case
Yield increase – eNPV of Biologic X	1.2x(minimal), which translates into eNPV of $85,000,000	1.75x(baseline), which translates into eNPV of $100,000,000	3x(max), which translates into eNPV of $150,000,000
NPV of commercial scale investment, standard deviation = $1,000,000		-$5,000,000	
% chance of MCSGP working, standard deviation = 10%		30%	
Sensitivity of experiment, standard deviation = 10%		60%	
Specificity of experiment, standard deviation = 10%		80%	

More specifically, I used Excel plug-in Crystal Ball to perform the simulations. I used a triangular distribution for the eNPV of Biologic X, and normal distributions for the other parameters (see above chart for exact numbers). These are all fabricated numbers, and one must carefully determine the limits to these parameters, as well as the likely distributions. The simulation yielded the following frequency chart (see **Figure 16**) after 5,000 runs:

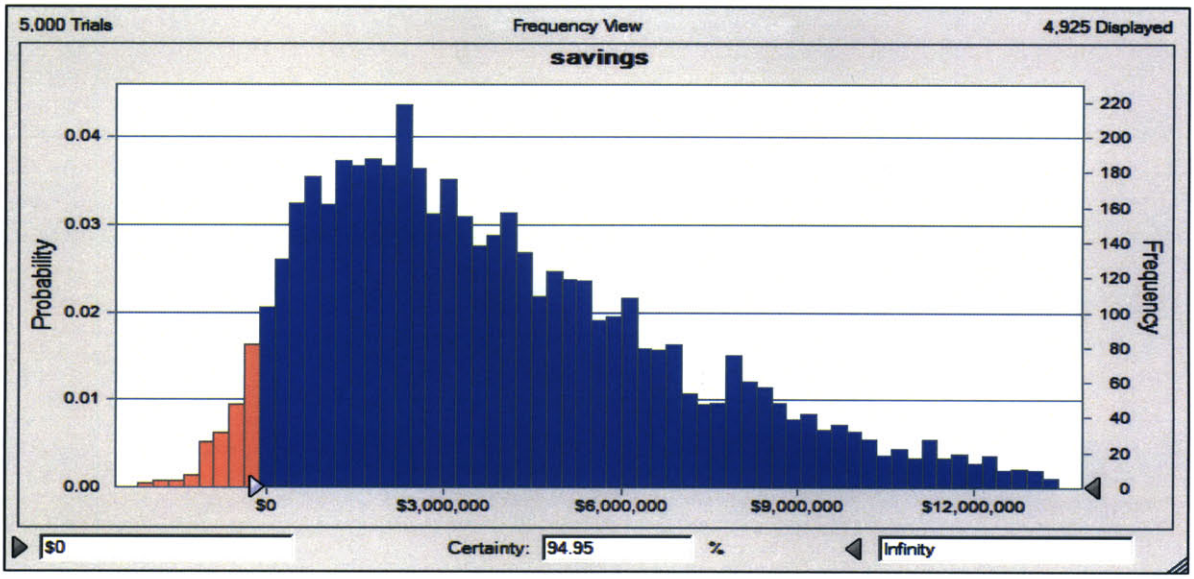

Figure 16. Monte Carlo simulation

The summary statistics are shown in **Figure 17**. They show that at the base case, as we expected, the savings from this technology is $2,000,000. This result justifies an initial investment into this technology, which will be significantly less than these forecasted savings. In addition, there is only a 5.05% chance of a negative NPV, clearly indicating there is much more upside with this technology.

Statistic	Forecast values
Trials	$5,000
Base Case	$2,000,000
Mean	$4,068,289
Median	$3,323,699
Standard Deviation	$3,337,116
Variance	$11,136,344,681,960
Skewness	1.13
Kurtosis	4.82
Coeff. of Variability	0.8203
Minimum	($2,172,897)
Maximum	$29,267,649
Mean Std. Error	$47,194

Figure 17. Summary statistics for simulation

Finally, the simulation shows that the savings derived from this technology is most sensitive to the yield increases provided by the MCSGP process (**Figure 18**). This makes sense, as I have shown how much yield increase can affect the potential savings.

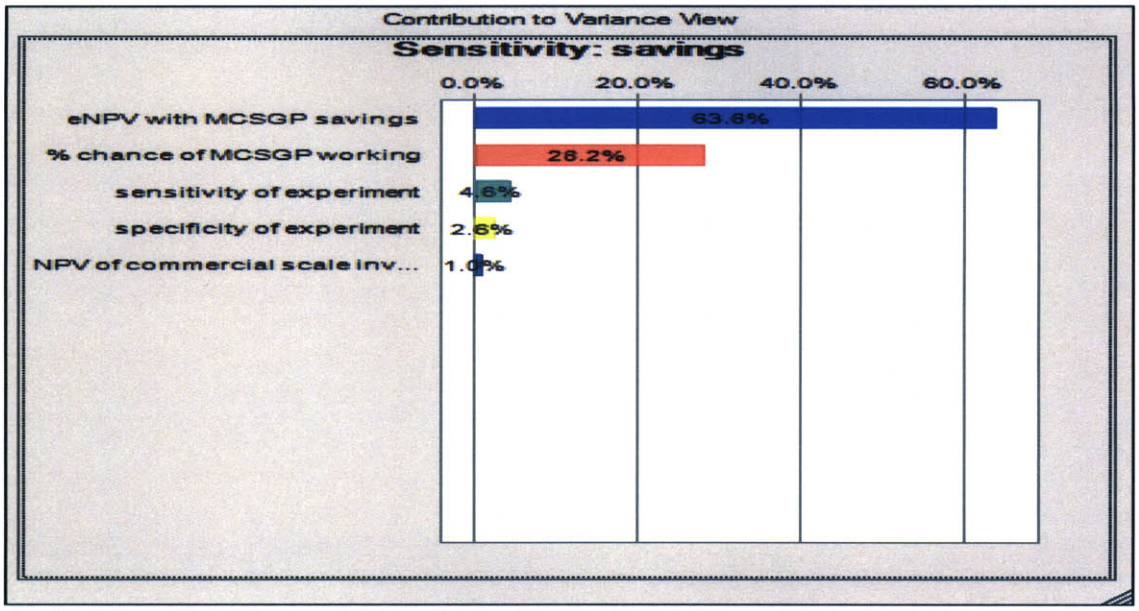

Figure 18. Sensitivity analysis

There are other factors that need to be considered with this project. There are regulatory hurdles and costs associated with implementing this system, which I have not included. There is the added benefit of potentially using the know-how obtained during this project for other biologics in development. In fact, currently, there are processes which have low-yield chromatography steps that could potentially benefit greatly from the MCSGP technology. Thus, there are many other pros and cons that need to be factored in; however, my initial assessment shows that it is financially advisable to take the next step forward – a laboratory-scale experiment with Biologic X.

CHAPTER 5
PROCESS DATA AND MODEL FOR BIOLOGIC Y

5 Process Data and Model for Biologic Y

5.1 Sources of data

I was able to supplement my literature review with a tour of this facility, as well as in-depth discussions with the scientists and engineers involved in this effort. The data that I obtained in this part of the project were very similar to that from the first part:

- Yield of each step
- Time spent in each step
- Cost of raw materials
- Cost of overhead for running the line that will produce Biologic Y

I was able to obtain the engineering and scientific data from Dr. Martin Ludwicek, Dr. Norbert Palma, and Dr. Bernhard Widner, and financial information from Dr. Valentin Resinger, Dr. Johannes Reiter, and Martina Messner.

5.2 Model of current batch chromatography processes

5.2.1 Assumptions

Similar to the first part of this project, after I collected the data, I determined which were the most accurate and representative campaigns (with the help of my supervisor and Martin Ludwicek), and then averaged the data from those runs. This gave me the following data that would be used in my model:

- Volume and yield of product in upstream process
- Yield at each downstream process step
- Overall yield of downstream processes

Thus, for the model that I submitted to the company, I assumed that the average of the last several campaigns could accurately predict the product yields in future runs. However, as

more data is collected, and the runs become more efficient, the company must update the model. The purification process for Biologic Y is more complicated than that of Biologic X.

5.2.1.1 Yield data

The yield data is treated in a manner similar to the first part of this project (see **Section 4.2.1.1** for more details).

5.2.1.2 Resin utilization and cost

My treatment of resin costs are similar to that from the previous chapter (see **4.2.1.2**). In addition, as I will be using the BioSC process in the model, my resin utilization in these instances will change. I was able to obtain data from the company (Novasep) regarding the increased resin utilization they were able to achieve with similar biologics – this ranged from 85% to 140%. For my calculations, I used a conservative estimate of 75%. Thus, if as in the previous section, the first chromatography step had a resin utilization of 20 g/L, the predicted utilization with the BioSC process would be:

- $new\ resin\ utilization = batch\ resin\ utilization * 1.75(factor\ increase)$
- $new\ resin\ utilization = \frac{20g}{L} * 1.75 = \frac{35g}{L}$

5.2.1.3 Buffer consumption

The treatment of buffer consumption in this section is very similar to that in the previous section, except now I will incorporate the potential savings associated with decreased buffer consumption. This is because several chromatography columns will have high initial yields, so applying the MCSGP process will not impart the significant cost savings associated with yield increases that were observed with Biologic X. As such, the savings from decreased buffer consumption will become more significant.

With both the MCSGP[31] and BioSC[32] processes, buffer consumptions can be decreased significantly (as discussed with company representatives). For my calculations with these two technologies, I used a conservative estimate of 40% as the decrease in buffer requirements. So, for the first chromatography step, if 3L of buffer A is typically required for the batch process, then we would expect the following:

- $New\ buffer\ requirement = old\ buffer\ requirement * (1 - factor\ decrease)$
- $New\ buffer\ requirement = 3L * (1 - 40\%) = 1.8L$

5.2.2 Current batch chromatography model

For the current batch process, I will use the same upstream data as the previous model:

Upstream fermentation batch volume	10,000L
Titer	2mg/L
Product/batch	20g/batch

I will model the process such that there are three chromatography columns, and one enzymatic reaction. I will not include the lyophilization step, which will be discussed later. The following diagram (**Figure 19**, fictitious) illustrates the flow of the protein product.

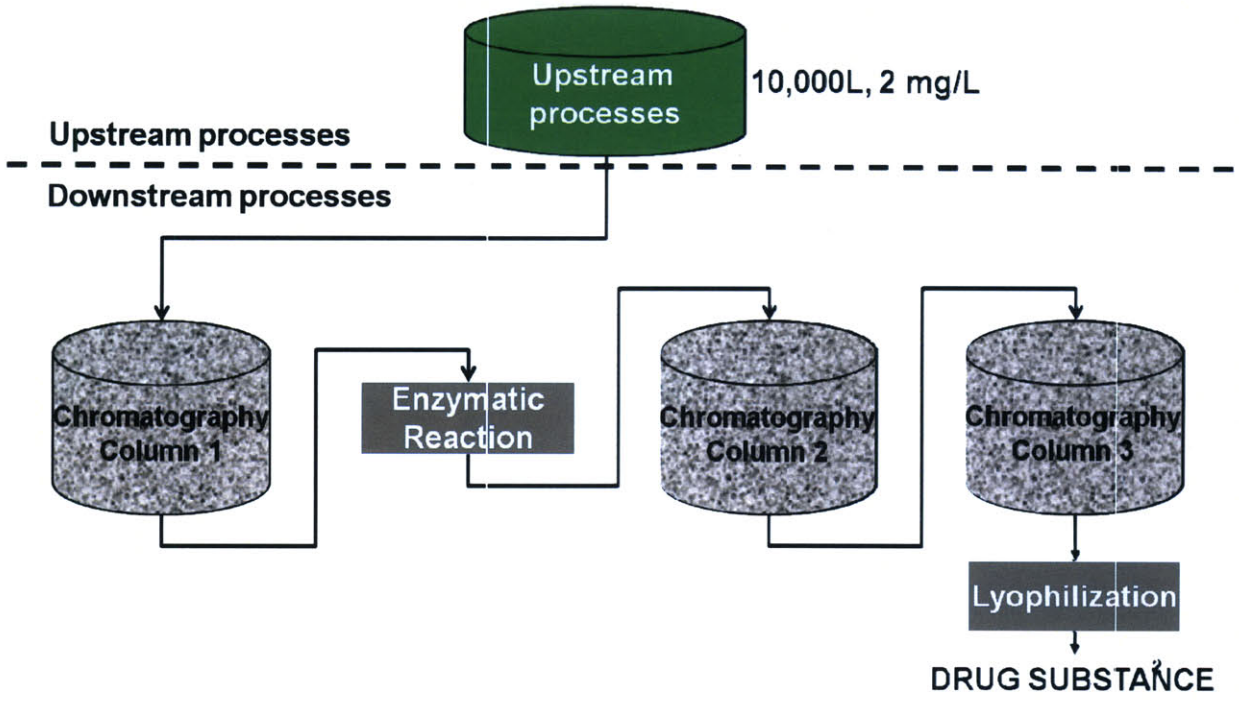

Figure 19. Biologic Y process model

The following data (fictitious) characterize the downstream processes – both product yields and costs. To make matters simple, I will assume that each chromatography step requires only one buffer (though in reality, they require many for the different steps – cleaning, pre-equilibrating, equilibrating). In addition, I assumed that for the enzymatic reaction, the buffer

and reagent required are dependent on the amount of protein product from the previous step (grams output from chromatography step 1).

	Chrom. 1	Enz. Rxn.	Chrom. 2	Chrom. 3
Yield	90%	95%	50%	90%
Binding capacity of resin	10g/L		20g/L	20g/L
Cost of resin/L	$5,000		$1,000	$1,000
Resin cycle life	100		100	100
Buffer + reagent required for enzymatic reaction (L/gram of protein product)		0.05		
Cost of buffer + reagent required for enzymatic reaction ($/L)		$2/L		
Buffer volume for chromatography step (in column volumes)	10x		5x	5x
Buffer cost/L	$5/L		$1/L	$1/L

In addition to the calculations made in the previous chapter, I determined the following values (see **Figure 20** for flow sheet):

- Column volume – this will be important to determine the amount of buffer required for this step: $column\ volume = \frac{input\ into\ chromatography\ column\ (g)}{binding\ capacity\ of\ resin\ (\frac{g}{L})}$
- Buffer required for chromatography step: $buffer\ volume = column\ volume(L) * buffer\ volume\ per\ column$
- Buffer/reagent volume needed for the enzymatic reaction – depends on the input from the previous step: $buffer + reagent\ volume = output\ from\ previous\ step\ (g) * volume\ required\ per\ gram\ protein\ (\frac{L}{g})$
- Buffer costs: $costs = buffer\ vol.required(L) \times buffer\ cost(\frac{\$}{L})$

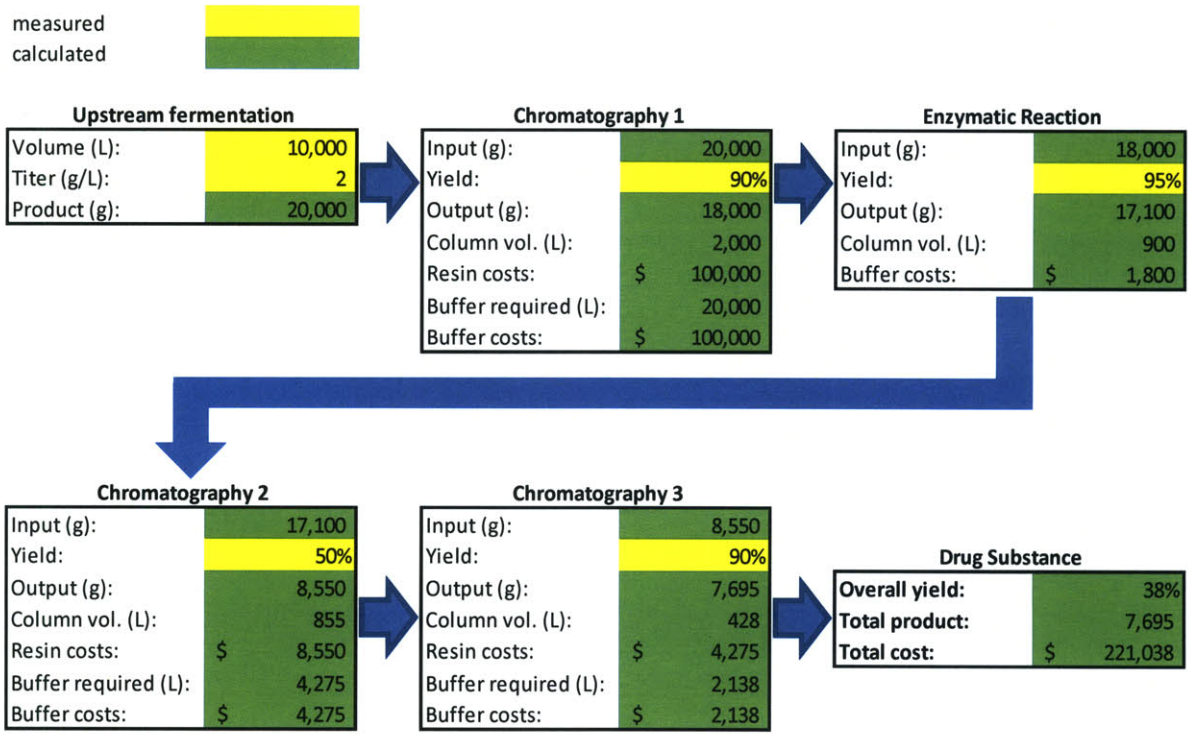

Figure 20. Yields and costs for the downstream processes of Biologic Y

We see that the total cost per batch is $221,038, to which I will now add the fixed costs (I will use the same fictitious data as I did with Biologic X).

Fixed cost per year	$10,000,000
Number of batches per year	40
Fixed cost/batch	$250,000/batch

So, when we add the variable costs with the fixed costs, we determine that the total costs of downstream purification for one batch is: $250,000+$221,038 = $471,038. This translates into a cost of $471,038/7,695g = ***$61.21/gram of drug substance***.

5.3 Continuous Model

For the second part of my internship, I modeled the purification process of Biologic Y as continuous. To do this, I did the following (see **Figure 21**):

- For each of the chromatography steps, there are three potential options: the traditional batch process, the MCSGP process, and the BioSC process. The implications of each one will be discussed in the following subsections.
- For the enzymatic reaction, I did not assume any savings from potential decreased time, space, or labor requirements. This is because the key parameters still need to be determined. For example, with specific enzymatic reactions, it is unclear whether using a tubular reactor will decrease the time requirements. Similarly, it is unclear whether the tubing will be more expensive, or require less space. It will, however, allow for continuous processing, so it is important to consider. The only influence on the costs of this step will be the amount of output from the previous step, as it will change the amount of buffer/reactant required.

In the following subsections, I will break down the cost changes as I implement different technologies into the model.

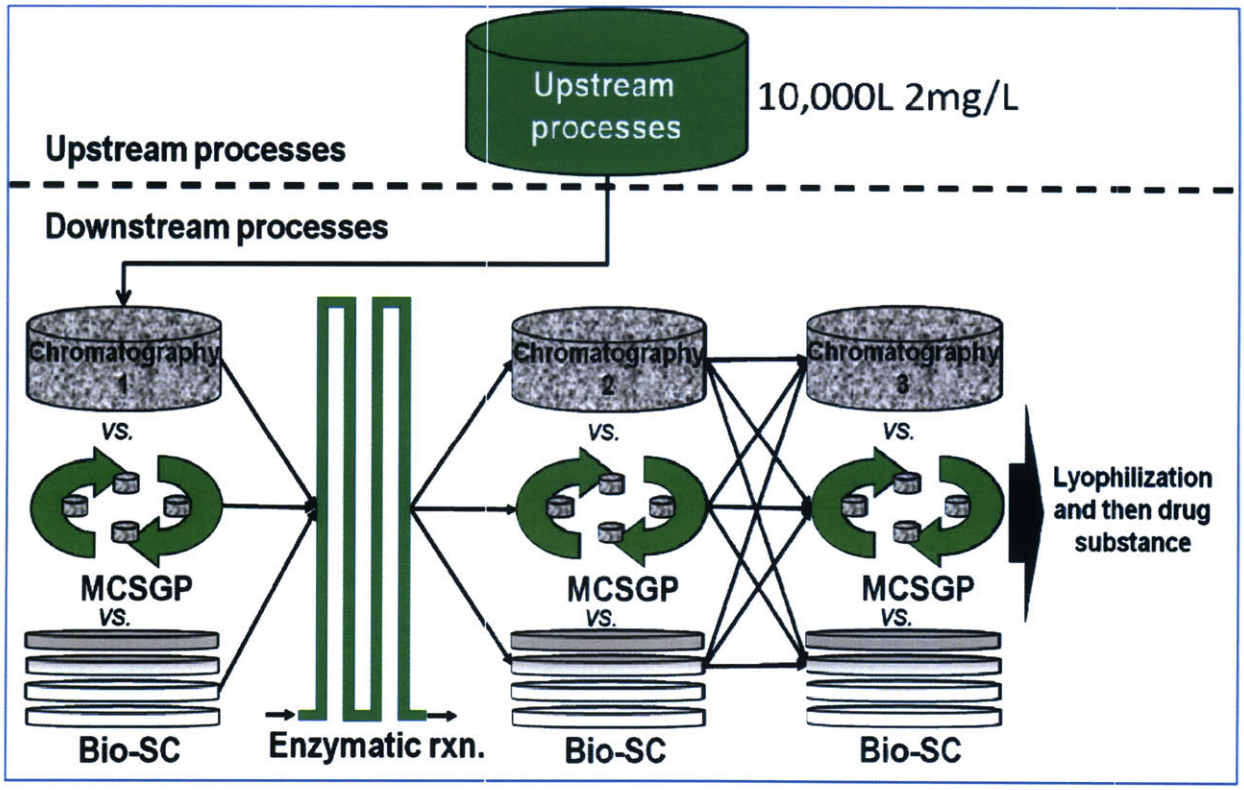

Figure 21. Biologic Y continuous process model

5.3.1 Resin and Buffer Costs

To illustrate the potential savings with resin costs, I will use the first chromatography step as an example. However, this should be applied to all of the steps.

- If the chromatography step is in batch mode, the following values apply (**Figure 22,** taken from **Figure 20**):

Chromatography 1

Mode:	Batch
Input (g):	20,000
Yield:	90%
Output (g):	18,000
Column vol. (L):	2,000
Resin costs:	$ 100,000
Buffer required (L):	20,000
Buffer costs:	$ 100,000

Figure 22. Chromatography step 1 if batch

- If we change the mode to MCSGP, then we need to account for other factors, such as increased yield and buffer costs:
    - For resin, we assume that the amount of lost product goes down by a factor of 1.75, increasing the "effective yield" – see section 4.3.1 for the necessary calculations. We add another cell in the model to account for this increase in yield, which then causes the actual yield and output to increase (**Figure 23**).

Chromatography 1

Mode:	Batch
Input (g):	20,000
Yield:	90%
Increase in yield:	**1.75**
Final yield:	**94%**
Output (g):	**18,857**
Column vol. (L):	2,000
Resin costs:	$ 100,000
Buffer required (L):	20,000
Buffer costs:	$ 100,000

Figure 23. MCSGP model with increased yield

- However, we also have to consider the decrease in buffer requirements, and their subsequent cost savings (as per above, decreases by 40%). As the buffer requirements assumed in this model are the same for the MCSGP and BioSC process, these changes are applied when either of these models is chosen. The following figure shows the first chromatography step as completely modeled to reflect the potential financial impact of the MCSGP process – the yield increase and the decrease in buffer costs.

Chromatography 1

Mode:	**MCSGP**
Input (g):	20,000
Yield (if batch):	90%
Increase in yield if MCSGP:	1.75
Final yield:	94%
Output (g):	18,857
Resin utiliz. if batch (g/L):	10
Increased utiliz. if BioSC:	1.75
Actual resin utiliz. (g/L):	10.0
Column vol. (L):	2,000
Resin costs:	$ 100,000
Buffer required if batch (L):	20,000
Decreased buffer requirement if MCSGP or BioSC:	40%
Actual buffer required (L):	12,000
Buffer costs:	$ 60,000

Figure 24. Chromatography step 1 completely modeled as MCSGP

- If we change the mode to BioSC, then we need to consider an additional factor – the increased resin utilization:
  - For resin, we assume that the resin utilization increases by a factor 1.75 (as above). This needs to be added to our model. This decreases the size of the

column, effectively decreasing the amount of resin required from 2,000L to 1,143L:

$$column\ volume = \frac{input\ of\ product\ (g)}{binding\ capacity\ \left(\frac{g}{L}\right) * factor\ increase\ for\ BioSC} = \frac{20{,}000g}{10\frac{g}{L} * 1.75}$$

$$= 1{,}143L$$

- In addition, the BioSC has the added benefit of decreased buffer requirements, as described in the MCSGP section. The chromatography column, when modeled as a BioSC process has the following attributes (see **Figure 25**). Note that the yield remains the same as when it is a batch reactor.

Chromatography 1

Mode:	BioSC
Input (g):	20,000
Yield (if batch):	90%
Increase in yield if MCSGP:	1.75
Final yield:	90%
Output (g):	18,000
Resin utiliz. if batch (g/L):	10
Increased utiliz. if BioSC:	1.75
Actual resin utiliz. (g/L):	17.5
Column vol. (L):	1,143
Resin costs:	$ 57,143
Buffer required if batch (L):	20,000
Decreased buffer requirement if MCSGP or BioSC:	40%
Actual buffer required (L):	12,000
Buffer costs:	$ 60,000

Figure 25. Chromatography step 1 modeled as BioSC process

- Comparing the three different options, with all of the new features included in the model, we see the benefits of both the MCSGP and the BioSC (see **Figure 26**). However, there are some benefits that have not yet been considered:
  - Decreased space requirements associated with the decreased buffer requirements
  - Implications of the increased yield associated with the MCSGP.

Chromatography 1

Mode:	Batch
Input (g):	20,000
Yield (if batch):	90%
Increase in yield if MCSGP:	1.75
Final yield:	90%
Output (g):	18,000
Resin utiliz. if batch (g/L):	10
Increased utiliz. if BioSC:	1.75
Actual resin utiliz. (g/L):	10.0
Column vol. (L):	2,000
Resin costs:	$ 100,000
Buffer required if batch (L):	20,000
Decreased buffer requirement if MCSGP or BioSC:	40%
Actual buffer required (L):	20,000
Buffer costs:	$ 100,000

VS.

Chromatography 1

Mode:	MCSGP
Input (g):	20,000
Yield (if batch):	90%
Increase in yield if MCSGP:	1.75
Final yield:	94%
Output (g):	18,857
Resin utiliz. if batch (g/L):	10
Increased utiliz. if BioSC:	1.75
Actual resin utiliz. (g/L):	10.0
Column vol. (L):	2,000
Resin costs:	$ 100,000
Buffer required if batch (L):	20,000
Decreased buffer requirement if MCSGP or BioSC:	40%
Actual buffer required (L):	12,000
Buffer costs:	$ 60,000

VS.

Chromatography 1

Mode:	BioSC
Input (g):	20,000
Yield (if batch):	90%
Increase in yield if MCSGP:	1.75
Final yield:	90%
Output (g):	18,000
Resin utiliz. if batch (g/L):	10
Increased utiliz. if BioSC:	1.75
Actual resin utiliz. (g/L):	17.5
Column vol. (L):	1,143
Resin costs:	$ 57,143
Buffer required if batch (L):	20,000
Decreased buffer requirement if MCSGP or BioSC:	40%
Actual buffer required (L):	12,000
Buffer costs:	$ 60,000

Figure 26. Comparison of the three potential models

- When we apply this model to all of the three chromatography steps, we get the following combined model (**Figure 27**):

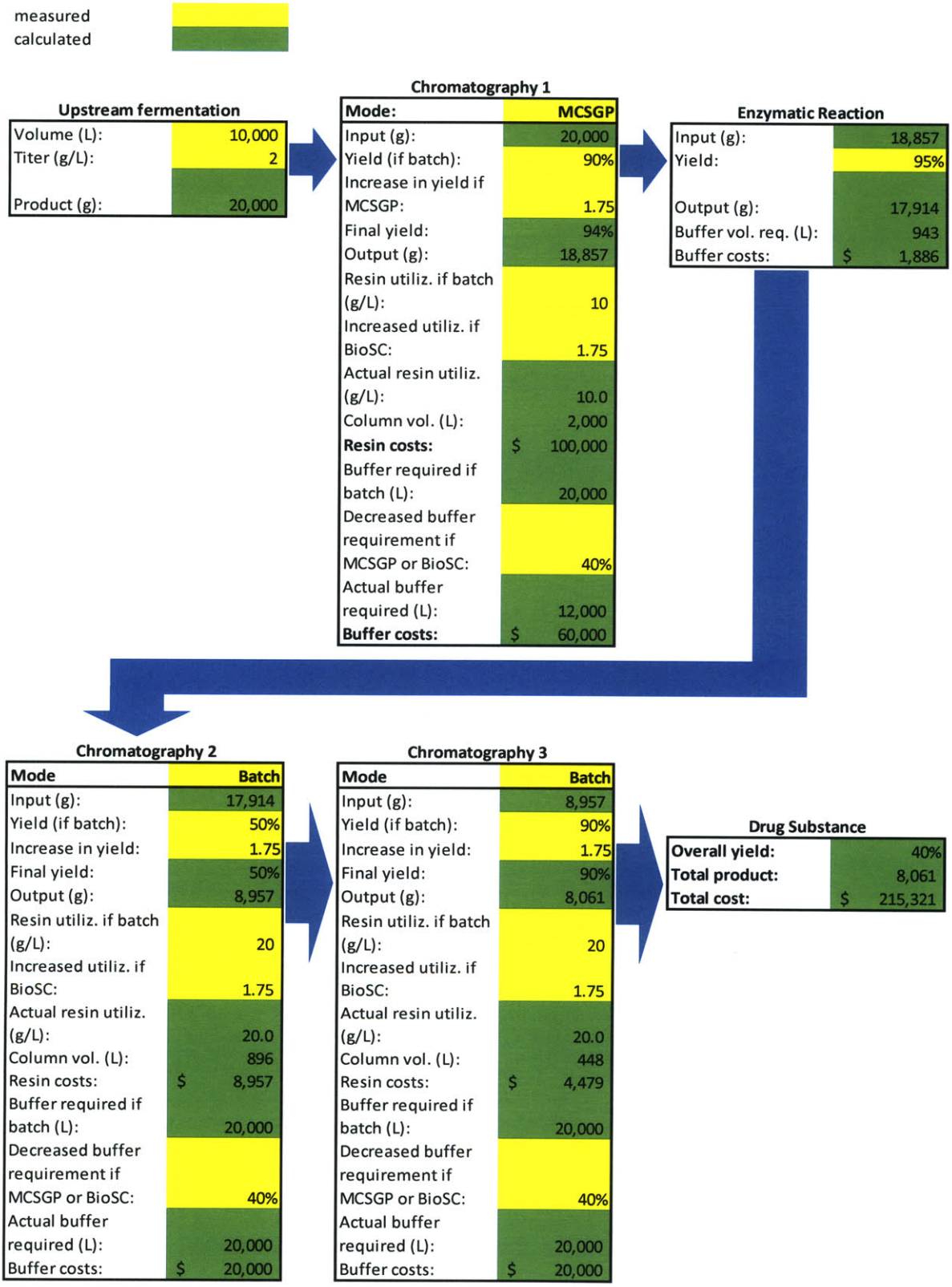

Figure 27. Downstream purification process for Biologic Y

5.3.2 Inventory Holding Costs

With the proposed continuous technologies, we expect decreased resin and buffer requirements. For the former, the increased yield offered by the MCSGP process, and the increased resin utilization offered by the BioSC process could significantly decrease the amount of resin the company needs to hold during the year. Similarly, for the latter, the MCSGP and BioSC processes will also use less buffer. Unfortunately, when I discussed the issue of inventory holding costs with the finance department, this was not a metric they considered in their calculations. However, given the decreased holding requirements associated with this technology, I will include this calculation, as it should be considered. I conservatively used an inventory holding cost of 20%, even though most industries use higher numbers such as 25%.[33]

Regarding resin, after talking with the engineers in the plant, I made the assumption that the company will always have a volume of resin in inventory in the case that the currently used resin is damaged and needs to be replaced quickly. For example, in the case above, 2000L of resin is required for the first chromatography step, so there will be 2000L of that same resin in inventory. Because the resin costs \$5000/L, the annual inventory holding cost will be: $inventory\ holding\ cost = \$5{,}000\ per\ L * 2000L * 20\% = \$2{,}000{,}000.$

Regarding the buffer, I assumed after talking with the engineers that the plant would hold 4x the amount of buffer required for one batch – this number is likely higher. In this case, then, the inventory holding for the buffer used in the first chromatography step is: $inventory\ holding\ cost =$

$column\ volume * buffer\ volume\ required * buffer\ cost\ per\ L * inventory\ holding = 2000L * 10x * \$5\ per\ L * 20\% = \$8{,}000\ per\ year.$

5.3.3 Space Costs

To determine the costs associated with the decreased buffer requirements if one or more of the chromatography steps are modeled as continuous, we must first determine how much buffer storage space costs. To do this, I obtained the reinvestment cost of the plant in Kundl that was producing Biologic Y – \$50M (fictitious). I was then able to find the total surface area of the plant, and the surface area dedicated to reactors: 6,000 m^2 and 4,000 m^2, respectively. I then assumed that the cost per square meter of buffer storage tanks was somewhere between the per

area cost of reactor space and the whole space (which includes walkways and other less productive areas). I then used the surface area ($500m^2$) dedicated to buffer storage tank to determine the total cost of space dedicated to buffer tanks:

Reinvestment cost of Biologic Y plant	$50,000,000
Surface area, total and just for reactors	6,000 m^2 and 4,000 m^2
Cost per m^2, total and reactor	\$8,333/m^2, and \$12,500/m^2
Average cost per m^2 for buffer storage area	\$10,417/m^2
Space dedicated to buffer storage	$500m^2$
Cost of buffer storage space	$500m^2$*\$10,417/m^2=\$5,208,333

Now, to determine the cost savings associated with the different continuous technologies, I took a baseline calculation of the total buffer required (from all steps) when all of the chromatography steps are set in the batch mode. This is the situation where the cost of the buffer space is $5,208,333. Then, when specific steps are switched to continuous, the amount of total buffer required is then decreased. I took the ratio of this new buffer requirement to the baseline, and then multiplied by the baseline cost. This is a rough estimate of the amount of capital that could potentially be saved if those specific steps are continuous.

Total buffer required (baseline)	60,900 L
Total buffer required when all steps are MCSGP	36,943 L
Expected cost of buffer storage space with greenfield plant	(36,943 L/60,900 L) * \$5,208,333 = \$3,159,453
Potential Savings	\$5,208,333-\$3,159,453 = **\$2,048,880**

Note that this savings is realized once, during the investment in a greenfield plant.

5.3.4 Financial Analysis

For the financial analysis, I had to make several assumptions, as there are many moving parts in my model. For example, with the MCSGP the output increases, while with the BioSC savings are realized through different means. I decided to use the cost of the downstream purification per gram of drug substance as my financial metric. My assumptions are:

1. The amount of time to process one batch of upstream product is the same. That is, even if the process is completely continuous, we would expect the fixed costs to be the same as if they were all batch processes. In other industries, continuous technologies have been

associated with decreased labor and overhead costs, but in this model, I will assume they will stay the same.

2. There is enough demand so that any increase in yield delivered by MCSGP processes can be sold.
3. The inventory holding savings are realized on an annual basis.
4. The space savings are only realized once, and only if there is a greenfield plant being built.
5. There are 40 batches to be made over the year.

Using these assumptions, and then calculating the potential savings for the many different scenarios, I was able to determine the potential savings. Because the MCSGP process causes increases in yields, I calculated an annual production cost (includes variable and fixed costs) per gram, assuming 40 batches per year. I then multiplied that number by the baseline output (when all the processes are in batch) to get a "normalized" production cost so we can compare production costs with similar outputs. This is reasonable, as one can imagine for a certain desired output, with the MCSGP process and its associated higher yield, the plant does not have to be run for as many batches during the year, lowering the fixed costs appropriately. The scenarios I have displayed are the baseline (all batch), when only one of the chromatography steps is either MCSGP or BioSC, when all are MCSGP, and when all are BioSC. Picking these scenarios allows for the evaluation that follows. Here are the assumptions:

- I used a tubular reactor in all scenarios.
- The scenario shows the sequence of steps, so B-T-B-B means the first chromatography step is batch, the enzymatic reaction is set as a tubular reactor, the second chromatography step is batch, and the third chromatography step is batch.
- $production\ cost\ per\ gram = [(raw\ material\ cost\ per\ batch\ (from\ model)) * 40\ batches\ per\ year + fixed\ costs(\$10{,}000{,}000)] \div (output\ grams\ per\ product\ per\ batch * 40\ batches\ per\ year)$
- $total\ annual\ costs = normalized\ production\ cost\ per\ year + inventory\ holding\ costs$
- $normalized\ production\ cost = production\ cost\ per\ gram\ of\ product * product\ output\ with\ baseline\ scenario\ (all\ batch\ processes)$

#	Scenario: B=batch C1=MCSGP C2=BioSC T=tubular reactor	Production costs per gram	"Normalized" production cost per year	Annual inventory holding costs	Total annual costs	Annual savings from baseline	Savings on greenfield plant
1	B-T-B-B	$2,623/gram	$20,185,000	$2,369,940	$22,554,940	-	-
2	C1-T-B-B	$2,309/gram	$17,766,818	$2,350,223	$20,117,041	$2,437,899	$680,516
3	C2-T-B-B	$2,192/gram	$16,870,714	$1,480,797	$18,351,511	$4,203,429	$680,182
4	B-T-C1-B	$1,814/gram	$13,956,800	$2,400,183	$16,356,983	$6,197,957	$680,182
5	B-T-C2-B	$2,562/gram	$19,718,429	$2,290,254	$22,008,683	$546,257	$680,182
6	B-T-B-C1	$2,464/gram	$18,962,045	$2,363,540	$21,325,585	$1,229,355	$680,182
7	B-T-B-C2	$2,572/gram	$19,791,714	$2,326,897	$22,118,611	$436,329	$680,182
8	C1-T-C1-C1	$1,496/gram	$11,512,235	$2,375,811	$13,888,045	$8,666,895	$2,048,880
9	C2-T-C2-C2	$2,081/gram	$16,010,857	$1,358,069	$17,368,926	$5,186,014	$2,052,545

From studying these data, we can come up with the following observations regarding the two different continuous chromatography technologies:

- When comparing scenario 2 to scenario 3, we see that the latter provides significantly greater savings. This is because of the following reasons:
    - This product already has a high yield of 90%, so increasing the "effective yield" by 1.75x does not increase the absolute value of the yield significantly.
    - The product uses very expensive resin, with an initially low utilization rate. This means that with the BioSC process, the benefits of the increased resin utilization are quite significant.
- Scenario 4 has a very significant savings benefit. This is due to the following:
    - The yield is very low at 50%. This means that an increase in "effective yield" by 1.75x would be very significant.
    - This is further downstream, so the protein product that an increase in yield saves is more "expensive" than upstream product. Basically, it is more expensive because it has been processed more.
- The savings associated with scenarios 5 and 7 are significantly lower than the other scenarios. This is due to the following:
    - The resins in these steps are not very expensive, and small quantities are consumed in each step.
- The savings associated with scenario 8 are greater than that of scenario 9. This is due to the following:

- The savings associated with the MCSGP process are generally greater than that with the BioSC process. This is because yield is very important with these expensive products. If we added the upstream production costs, this difference would be even more magnified.

These observations lead to the following conclusions:

1. The MCSGP technology is good for low yield steps where the input stream is very expensive.
2. The BioSC technology is good for processes in which expensive resin is used inefficiently (low resin utilization).
3. Both processes are good when large volumes of expensive buffer are used.
4. Savings on space can be significant, and should be calculated when a greenfield plant is being considered.

CHAPTER 6
CONCLUSION

6 Conclusion

From my work at Sandoz Biopharmaceuticals, I am convinced that continuous chromatography should be explored by innovator and generic companies that want to improve their current manufacturing methods of biologic molecules. There is clearly a lot of risk – both financial and regulatory – but the rewards outweigh them. Furthermore, with the increased cost pressures that are being applied to pharmaceuticals and biologics, it is imperative for companies to find ways to cut costs to preserve their profit margins. The MCSGP can offer significant savings, but the risks are significant. Companies must weigh the benefits and risks on a case by case basis to determine if it makes good business sense to pursue this technology. Conversely, the BioSC can also impart savings, and it has much less developmental and regulatory risk. It, too, must be analyzed on an individual basis to determine its applicability to specific products.

Tubular reactors should be used to help make downstream purification processes truly continuous. As they also confer other advantages, such as better control and potentially lower residence times, companies need to look at their systems on a case-by-case basis. A more thorough investigation of this technology would require a separate thesis.

Spray drying offers an alternative to the lyophilization/freeze drying technique that is currently used in many purification processes. There are some important issues that need to be determined – yield and product breakdown (proteins subject to intense heat break down in structure). Sandoz has had mixed results; however I would recommend furthering discussions with Professor Gerhard Winter at the Ludwig Maximilian University in Munich.

6.1 Biologic X Conclusions

From my work with Biologic X and the MCSGP technology, I was able to make some very critical observations that support its development. However, first, we must step back and acknowledge the following facts:

1. This technology is very novel – it is only in laboratory scale size now.

2. There are significant developmental risks associated with upsizing the technology.
3. There are regulatory risks and costs associated with using a new technology to mass-produce biologics that will be used in humans.

With these conditions, I will now recapitulate and analyze the results I obtained from my internship:

1. The MCSGP has a significant advantage over other continuous chromatography technologies because it allows for the increased yield of particular steps. This is especially beneficial for processes that have a low baseline yield, as modest increases in yield percent translate to significantly higher absolute yields.
2. As biologics are very expensive to produce (their raw materials, such as resins, can be costly), increasing yields is particularly attractive.

The results I obtained for Biologic X were very compelling. I was able to show a significant decrease in COGS of the drug substance, with an eNPV of savings that would justify the development of this technology, even given its risks. However, if one considers the many other products in development that could benefit greatly from this technology, the MCSGP becomes even more attractive. Once the company develops a commercially scaled MCSGP process for Biologic X (assuming the experiments show significant yield increases with this molecule), the costs of applying this technology to other products will be much less costly. The know-how acquired during this process could potentially be used to save much more with other products.

6.2 Biologic Y Conclusions

From my work with Biologic Y, I was able to study and compare the benefits of the MCSGP technology and BioSC technology. As the latter does not provide for an increase in product yield, the potential savings are usually less than that with MCSGP. However, if the initial yield is already high, the resin costs are high, and the resin utilization is low, then the BioSC process could impart more cost savings than the MCSGP. In addition, the BioSC process is much more advanced, and poses less developmental and regulatory risk. So, when the expensive Protein A resin is used in the purification of monoclonal antibodies, the BioSC process can be used to impart significant savings. A basic decision tree can be helpful to determine which technology is more appropriate (see **Figure 28**).

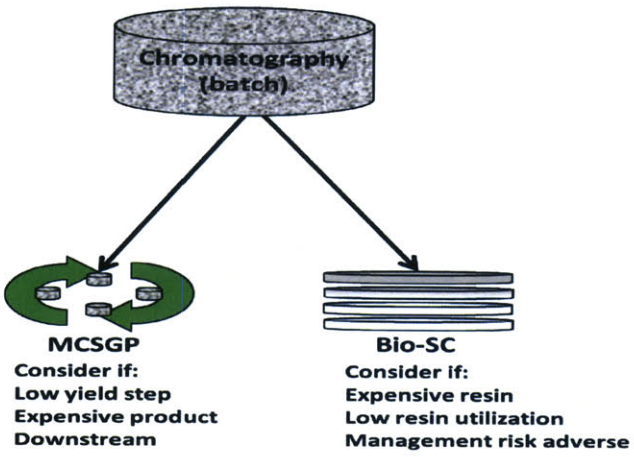

Figure 28. Decision tree for continuous chromatography

6.3 Management Aspects

Throughout this internship, I had the full support of Dr. Andreas Premstaller, who was instrumental in helping me get buy-in from the various stakeholders. During the process, I was able to interact with many different people from across the organization, many of whom were not aware of my project or familiar with the LGO program. There was initial skepticism from many parties, which required some careful maneuvering. During the process of talking with these different stakeholders, I was able to utilize the following techniques that allowed for the success of my internship.

6.3.1 Recognize the different stakeholders

In a large organization that is as complex as Sandoz and Novartis, it is important to identify the different stakeholders who would be involved in one's project. I was able to do this during the first month of my project, which turned out to be critical for the rest of the internship. I carefully mapped out my project, and then identified all whom could be potentially affected by my work. Once I met with all of the stakeholders, I started to build credibility.

6.3.2 Build credibility across the different stakeholders

It is important to have a good standing with all of the stakeholders, especially as an intern. I was able to achieve this by following certain guidelines:

- Be prepared for any meeting – this means doing all the background reading necessary to sound educated during the meeting. This also showed my stakeholders that I respected their time.
- When necessary, mention corroboration of important people within the organization. I did this when I encountered skepticism. Most of the time this technique helped me gain traction with the person I was meeting with.
- Bring the relevant data, as it is hard to argue with data.

6.3.3 Listen to the stakeholders and learn what metrics are important to them

This technique helped me learn more about my stakeholders, as well as the project. As many of them had a better working knowledge of the current processes than I had, listening to them was an educational process. Also, by finding out what metrics they used, I was able to learn what metrics were important. I then used the data to calculate those metrics to determine whether the project was worthwhile to them. This was an important step, as I wanted to make sure that my proposal would genuinely fit with their interests. Fortunately, my data supported the decision to invest further into the MCSGP technology. In addition, the process of listening attentively to stakeholders also has the effect of building credibility and a good working relationship.

CHAPTER 7

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