

**COST MODELING FOR
MONOCLONAL ANTIBODY MANUFACTURING**

by

Christina M. Simpson

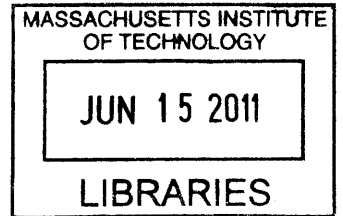
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Submitted to the MIT Sloan School of Management and the Department of Mechanical Engineering
in Partial Fulfillment of the Requirements for the Degrees of

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AND
Master of Science in Mechanical Engineering**

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ABSTRACT

The Novartis BioPharmOps division is responsible for manufacturing large molecule products, including monoclonal antibodies, for late stage clinical trials and commercial sales. The BioPharmOps site in Huningue, France is expanding their product line but is also trying to reduce costs; cost pressures are increasing as biotech products become a larger part of Novartis' pipeline.

The site uses a standard cost method to calculate their product costs. However, when using standard costs it can be time-consuming to extrapolate and predict costs when inputs and assumptions (such as product mix or process parameters) are changed. This project describes development of a model that allows the factory to quickly and easily simulate new product mixes and process flows. This model provides the site with a different view of their costs that will help them understand their cost drivers more completely and thereby help enable strategic decision-making at the site.

A model of this type can be used to provide unexpected insights but the data in it are not meant to stand alone. By using results from a cost model like this along with operational metrics like throughput time or changeover time, a site should be able to quickly predict the cost impact of process changes or changes in the production plan.

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1. Introduction

1.1 Problem Statement

Since Novartis A.G. was founded in 1996 with the merger of Ciba-Geigy and Sandoz, it has grown to be one of the largest pharmaceutical companies in the world. It employs over 100,000 people and has a well-developed product pipeline spread across pharmaceuticals, vaccines, and generic drugs. Over the past few years, the development of biologic products has grown in importance to the company. The biologics group appears well positioned for the future as well, with a pipeline that comprises about 25% of Novartis' new development. (Novartis AG)

As growth in biologics continues, the division faces new challenges. One area that will be of particular importance in the future is costs; what strategies can be pursued to continue to bring costs down? As belts keep tightening within the pharmaceutical industry, this focus on costs is likely to continue growing.

The focus on costs will extend throughout the product development lifecycle, and one important area within this is the manufacturing process. Companies would love to reduce manufacturing costs and receive higher margins. However, before any cost reduction can occur, it is necessary to understand which factors drive costs in the first place. Like most established companies, Novartis has a robust cost system in place that is used to value any biotech products already being produced. The system is used throughout the company and uses a common method for accounting, "standard costing," to track each division's finances and to report external results. This system, while sufficient for its intended purposes, was not designed to answer every potential question the division might have about its costs. Therefore, it can be time-consuming when it is used to predict costs for the future or to do sensitivity analysis of different scenarios.

The biotech manufacturing sites would like to address some of these challenges and find a solution that makes it easier for them to take action on their financial results. In particular, Novartis would like a different way of looking at their costs internally that will enable faster and easier analysis of different scenarios impacting costs (such as changes to the process or product mix) and will make cost data more intuitive to understand.

1.2 Hypothesis

As described above, a company's financial results can be difficult to understand and accounting methods like standard costing add a layer of complexity that is often not understood much outside of the finance department. The goal of this thesis is to show another way of looking at costs that will address some of these difficulties.

The thesis describes the development and use of a cost model that provides Novartis with a new view of their biotech production costs. This cost model uses the same financial data sources as the current system but aggregates and presents the data in a different way. Using these data, the model quickly and easily predicts the impact that process changes and new products have on the relevant outputs. For example, the model makes it clearer which costs are fixed and which are variable, thereby allowing users to focus on the costs that they can influence. It also shows users breakdown of each cost component so they can test changes in different variables to see their impact, which provides insight into the importance of each input parameter. This approach makes it easier to understand the interactions between different cost drivers than was previously possible. It also makes it easier to connect financial results with operational metrics that are tracked on the factory floor, which allows management to make educated and proactive decisions.

1.3 Results

Before the model was used, it was verified with several sets of historical results. This verification was completed for material costs, non-material costs, and allocation parameters. Through this process, it was shown that the model does give the same results as pre-existing (albeit more complicated) cost models at the site. Information about the verification process was provided so future users of the model will be able to find the data sources should they wish to verify their data as well.

The goal of this project was to show how a model of this type could be beneficial. Therefore, the next step was to provide examples of analyses that the model can complete. Several different scenarios were investigated. The model was first used to understand the breakdown of overall product costs. These results showed that fixed costs are a high proportion of overall costs, and within the variable costs the resins and filters are most significant. The next analysis showed how including a cost for idle time in overall product costs can produce misleading results. Finally, several analyses were done to show tradeoffs in various process parameters. For example, a scenario was tested where both the titer and fermentation time increased. The higher fermentation time will hurt costs, but this analysis showed that, in this case, the improved titer would have a larger impact and costs would still go down as titer goes up.

In another example, adding another product to the factory actually causes only a small increase in overall costs.

Through these results, it was shown that the model can be useful for a variety of cost predictions and scenario analyses and should be used for more of these in the future.

1.4 Thesis Goals and Organization

The intention of this thesis is to illustrate the background and development of the cost model and also to explain situations where the model can be used. It focuses on several areas:

- Explain several ways cost data are used by companies today
- Illustrate some challenges associated with this cost data and some potential areas for improvement
- Describe the cost model as one possible way to address these challenges
- Provide sample results and benefits

By explaining the cost model in the broader context, instead of focusing immediately on just one factory, it is possible to see how these concepts could apply to other companies and other industries outside of pharmaceutical.

The thesis is organized into sections that broadly relate to these overall goals.

Chapter 1, the **Introduction**, describes the problem statement as well as the motivation behind the development of this cost model. It also provides an overview of the project results.

Chapter 2 starts looking at the **Business Context** that surrounds the project. It outlines the pharmaceutical industry and emphasizes several of the features that make the industry unique. The organization and structure of Novartis are explained, as is the biotech production process.

In **Chapter 3**, the discussion of the project context is continued; however, this chapter focuses on the **Cost Modeling Context** instead of on the industry and company features. It explains the background for cost accounting methods used in various industries. From there, it explains several challenges with these methods and some solutions that have been used for cost analyses at other pharmaceutical companies.

The model development is introduced in **Chapter 4**, the **Method** section. This section describes the assumptions and criteria used to develop the model. For example, it illustrates several features that were integral to making the model successful. It also explains the selection process used to choose the model software.

Chapter 5 gets into the details of **Model Development**. It steps through the model layout and explains the input and output parameters. It also explains what drove the selection of each of these parameters.

The **Research Analysis** is conducted in **Chapter 6**. This chapter first shows how the model was tested and verified. From there, it shares several case studies that provide some sample results.

Finally, **Chapter 7** is a **Conclusion** that ties together the preceding chapters and explains how this research could be applicable to other areas and industries.

2 Business Context

This chapter sets the context for the cost modeling project. It first provides an introduction to the pharmaceutical industry. Several factors set this industry apart and impact the model development, such as very long product development timelines, extensive regulations, and a high level of uncertainty. The chapter then introduces Novartis as a company and explains where in the company the cost model fits in. Finally, it describes the production process used at Novartis for the biologic products it develops.

2.1 Industry Background

2.1.1 Industry Overview

The pharmaceutical industry started expanding late in the 19th century (Casper) and since then has grown into an established industry with revenues well over \$700 billion annually. (Zarur and Fleming) Pharmaceuticals come in many different varieties but products are commonly distinguished by specifying whether the drug is on-patent or off-patent and whether the drug is a small or large molecule.

While a product is on-patent, the company holding the patent is allowed to prevent anyone else from selling it. This allows the patent-holder to protect the value of the drug and to recover the investment made to develop it. Once a product goes off-patent, it is known as a “generic” drug. Other companies are now allowed to enter the market so competition increases and margins reduce dramatically. This thesis focuses on products that are still on-patent, although the methodology developed here could apply to both.

The other distinction, between small and large molecule drugs, does not describe the stage of development; instead, it describes the type of product. Many common medicines like Paracetamol (a pain killer) and Tetracycline (an antibiotic) are small molecules. These products are usually smaller than 100 atoms and are created using a process of chemical synthesis. Large molecule products (also referred to as biologics), which have only been developed since the 1970's, rely on biological growth instead of chemical synthesis. Factories for these products grow a group of genetically modified cells and then use those cells as miniature factories to produce the product in question. These products are typically much more complex than small molecules - some of them have over 25,000 atoms - but biologics often have enough similarities to one another that several products can be produced using a common platform. (Genentech, Inc.) Monoclonal antibodies (or mAb's) are a common example of a development platform. By changing aspects of these antibodies they can treat many different diseases. Therefore, since most

mAb's are produced in a similar way, they can often utilize the same facilities and factories for producing many products. This sharing greatly reduces risk, time for technical development, and capital investment.

One key feature of the industry is the combination of extremely long and costly product development cycles with very high risks. A typical product takes 10-15 years and \$800M – \$1B to develop from an early stage idea to a product that is ready for sale (see Figure 1).

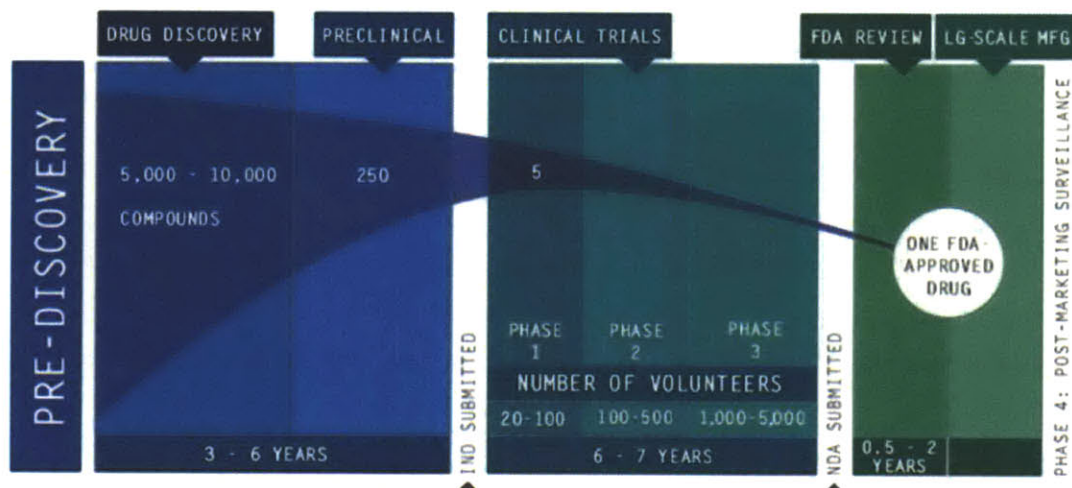


Figure 1: Pharmaceutical Product Development Cycle (innovation.org)

Adding to the uncertainty, very few products actually make it through the entire development cycle because testing often shows that they were not as effective or safe as they should be. For example, for a typical large molecule product, fewer than 15% of the products entering Phase I clinical trials will end up being approved by the FDA (Suresh and Basu, Improving Pharmaceutical Product Development and Manufacturing: Impact on Cost of Drug Development and Cost of Goods Sold of Pharmaceuticals). In order to undertake research of this scale, a company has to be prepared to shoulder high risk for a prolonged time period.

2.1.2 Industry Regulation

Another feature that distinguishes pharmaceutical companies from many others is the strict regulatory environment in which they operate. The drugs they produce can be life-saving to patients that take them, but they can also be life-threatening if side effects are not understood or if anything goes wrong during the manufacturing process. Because of these risks, various regulatory agencies audit and monitor both the

initial qualification and the ongoing manufacturing of all products. While this helps ensure that our medicines are safe, it also means that it can be difficult and time-consuming to make process improvements in a factory once a product is approved. These restrictions have contributed to the reluctance of companies to wholeheartedly pursue any cost improvement programs. (Suresh and Basu, Improving Pharmaceutical Product Development and Manufacturing: Impact on Cost of Drug Development and Cost of Goods Sold of Pharmaceuticals)

2.1.3 Industry Cost Structure

In part because of the high risks and large investment costs, the pharmaceutical industry has a different cost structure from many others. For example, the ratio of cost of goods sold (COGS) to sales in the automotive industry is typically well above 70% (YCharts). In contrast, many pharmaceutical companies will only spend 27% of their revenues on COGS, and the ratio for biotech companies is closer to 15% (Basu, Joglekar and Rai).

Understanding this structure helps explain why manufacturing cost reduction has not historically been one of the primary goals in the pharmaceutical industry. Since production costs were relatively low, it was more cost-effective and impactful to spend resources elsewhere. Companies would invest extensively in new research programs but there was less incentive to adopt manufacturing improvements like lean or Six Sigma. However, several changes in the industry are causing this cost climate to change. First, many key drugs are going off-patent over the next few years. For example, products generating over \$142 billion in sales will go off patent by 2016 (Zacks Equity Research). These losses mean that many companies will have fewer products to rely on for a steady revenue stream. In addition, with skyrocketing US healthcare costs and an increased focus on healthcare reform, the pharmaceutical industry is under unprecedented pressure to reduce prices. Due to these changes and others, many companies in the industry are starting to search for cost savings wherever possible. Since manufacturing is an area that has not been a focus in the past, it has the potential for high savings now. Therefore, the next few years will probably see many more cost-reduction programs being implemented across the industry.

2.2 Company Background

2.2.1 Company Overview

With nearly 120,000 employees and 2010 revenues of \$50.6 billion, Novartis is one of the largest pharmaceutical companies in the world. (Novartis AG) Historically, the company's focus was on small molecule products but the past few years have seen growing investment in large molecule products as well; biologics, including several monoclonal antibodies, now comprise 25% of Novartis' pipeline. (Novartis AG)

The company is divided into four divisions: Pharmaceuticals, Vaccines and Diagnostics, Sandoz, and Consumer Health. While each division is connected at a high level, they still operate very independently. Even within the same division there can be substantial separation between different groups. This project focused on work with the Pharmaceuticals division (aka "Pharma"). This is the area that does all development and manufacturing for prescription drugs (both small and large molecules) that are still patent protected. The project could also be relevant for Sandoz, the division that manufactures generics, since their methods for calculating costs and some of their production methods are similar to the methods used in Novartis Pharma.

2.2.2 Organizational Analysis

Research conducted at the MIT Sloan School of Management led to the development of a method for assessing organizational dynamics within a company. (Carroll) This assessment provides insights into company standards and behaviors using three different views, or "lenses": the **strategic, political, and cultural lens**. These insights can help in understanding the real-world issues that plague implementation of many projects. Looking at them here sheds light onto the way decisions are made within Novartis and also reveals (and helps avoid) potential challenges for project implementation.

The strategic view refers to the structure of the company and the way it is organized. For example, as stated above, Novartis is divided into four divisions. Each division is then broken down further into a number of different groups. For a simplified layout diagram of the Pharmaceutical division, see Figure 2.

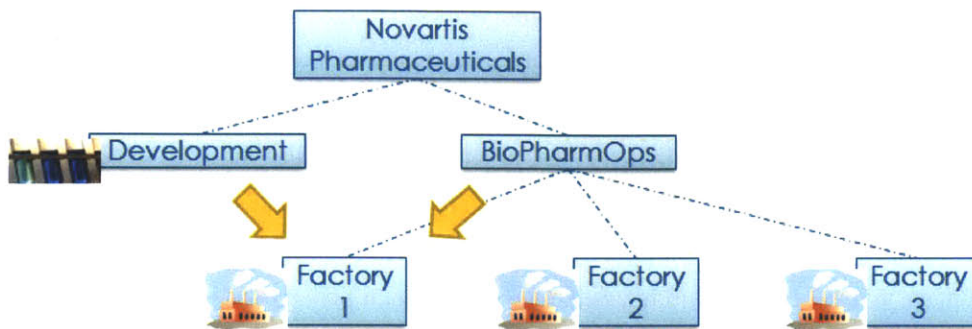


Figure 2: Simplified Structure of Novartis Pharma

The BioPharmOps group shown in this diagram is responsible for process development and manufacturing for all patented biologic products. The diagram shows how BioPharmOps is distinct from the Development organization. BioPharmOps owns all of the factories and manufacturing whereas Development discovers and develops the new products. Nonetheless, the groups still depend heavily on one another. For example, both Development and BioPharmOps need to use capacity in the BioPharmOps factories; BioPharmOps uses capacity to manufacture commercial products and Development needs a way to produce drugs for clinical trials. Since BioPharmOps owns the factories, Development relies on them to produce this clinical trial material. At the same time, Manufacturing relies on Development to come up with formulations for all new products.

This structure means that the two groups have to work closely together to manage capacity - and share the costs - for each factory. Since each group has a different set of incentives and motivations it can be challenging to determine who should pay for each aspect of production. The key takeaway for this project is that any model that is developed, in order to be useful, needs to consider the incentives and needs from both sides.

The cultural lens refers to the customs and standards for behavior within a company. People are accustomed to talking about the culture of a country, or cultural differences from one country to another, but each company (or even division) has a culture of its own as well. Cues for cultural aspects of an organization can be found anywhere. For example, signs posted on the wall, employees' working hours, or the arrangement of the desks all provide insight into the culture of a group. For example, Novartis BioPharmOps tends to be a fairly open and un-hierarchical group; it is easy to approach people and ask for help or to ask questions. This is apparent from peoples' verbal response when you ask to set up a

meeting but can also be inferred from the arrangement of the desks; six or more desks are clustered together in each office, which encourages a collaborative work environment. Another insight into the culture's division is found in the languages spoken at the site. Novartis is a Swiss company (located in the German-speaking area of Switzerland), but the company's official language is English. In Novartis' French biotech factory, the majority of employees are either bi or tri-lingual. Nonetheless, the language heard most commonly, and the one used in most wall decorations and site emails, is French. In this case, learning the local language is one way to become more integrated into the organization. These observations suggest that the division will be open to new ideas but it may be easier to implement change if it is done by working very closely with local employees.

The final organizational view, using the political lens, focuses on decision-makers and the control of information in an organization. As in any large company, decisions and information at Novartis are spread throughout the organization. Of particular relevance to this thesis is financial data. Novartis is understandably protective of its financial information. Not only is this data important for overall financial results but it can also be easily misrepresented; if someone looks at financial results but does not understand the assumptions behind them, it is easy to draw inaccurate conclusions. Because of these concerns, any project working with financial data must be carefully managed. These considerations suggested that the model should be developed in a modular way so it can be shared across the company without revealing confidential information.

2.3 Biotech Production Process

As described earlier, the production process for small and large molecule products is very different. Small molecule products depend on chemical synthesis whereas biologic products rely on cell growth. Despite the complexity of these biologics, the manufacturing process for different products is often surprisingly similar. For example, monoclonal antibodies share almost all basic steps from product to product. The function of each antibody may be very different but the fundamental structure is similar enough that many manufacturing steps and pieces of equipment can be shared.

There are two main stages in this antibody production process. The first stage is **Cell Culture**, which is where cells are grown and the antibody is produced. After this stage is completed, the product goes through the **Purification** steps where the product is cleaned and filtered. Most products follow similar sub-steps within each of these broad categories as well, so a company is able to develop each process much more quickly and can often use a factory for several different products.

This cost model was developed to model an mAb factory that could produce multiple mAb's during a given year. While the steps for each product are often the same, different process parameters (such as the material selection or cycle time) impact the product output. The following section describes details of the production process as well as some parameters that are important to the process reliability, efficiency, and cost.

2.3.1 Cell Culture

The cells used during production are essentially miniature factories for the mAb product. To begin production, the company creates a “master cell bank”, or a group of cells that have been encoded with instructions for producing the antibody. During cell culture, the product proceeds through a series of steps where cells are grown and then antibody is produced. (Abu-Absi, Yang and Thompson) There are two common types of cell culture production, called fed-batch and perfusion; this model is designed for a fed-batch process.

Inoculation: Cells from the master cell bank have been replicated and are now used to start production of each new batch.

Cell Culture: After the batch is begun, the cells are given food so they can grow and multiply. More food is added regularly and cells are transferred into larger vials and tanks as they grow. Once the final tank is reached, the cells stop dividing and produce the mAb. At the end of the cell culture process, factory workers measure the concentration of product in the tank, commonly referred to as the titer. This is a key parameter since it largely defines how much product will be obtained from each batch.

Harvest: The drug substance is removed from the final tank and sent through a centrifuge. During this step, the product (the antibody) is saved and the larger pieces (cells, DNA, and other remnants) are discarded.

2.3.2 Purification

The final drug substance must not contain any impurities. The goal of the purification steps is to isolate the antibody and remove all unwanted materials. (Kelley, Blank and Lee, Downstream Processing of Monoclonal Antibodies: Current Practices and Future Opportunities)

Clarification: The solution is filtered for the first time. Many filters used during purification steps are expensive and comprise a significant part of the production cost.

Protein A Chromatography: The solution is run past a special material called a resin. The product attaches to the resin and is saved while much of the debris, not captured by the resin, is discarded. Each batch of Protein A resin can be used for multiple batches of product before being discarded but it is still one of the most expensive materials used during production.

Chromatography 2: A purification step with a new resin removes additional impurities.

Chromatography 3: A third chromatography step removes even more impurities. The resins for Chromatography 2 and 3 are still expensive but they are far less significant than the Protein A resin.

Ultrafiltration / Diafiltration: The substance is filtered one final time and the product concentration and composition are adjusted. Filters used during this step can also be costly.

Final fill: The solution is frozen so it can be put into vials or syringes at a later time.

2.3.3 Batch Production

Although the production process is similar from product to product, it is challenging to run different products in a factory at the same time. Therefore, products are run in campaigns, where several batches of the same product are run in sequence before switching to the next product. When one campaign is coming to an end the factory completes a changeover and initiates production for the next product.

The raw materials and consumables described above, such as food for the cells or filters for purification, are a substantial component of the production costs. However, a large part of the cost comes from overhead expenses for the many non-material costs. For example, the factory equipment is expensive and needs to be paid for, as do direct labor and support personnel working at the site. These factors are investigated in later sections and will be considered alongside material costs in the cost model.

3 Cost Modeling Context

Reporting a product's cost seems like it should be straightforward; calculate what was spent for all individual cost components (such as raw materials, consumables, depreciation, and labor), add them up, and you should know how much your product costs. Unfortunately, implementation is much more complex than the theory and tracking and allocating the extensive data required for this process is a formidable task. By reviewing some literature relevant to this topic and by examining practices in use at companies today, this chapter describes a method commonly used for cost accounting today as well as the history that led to the this method's implementation. Looking at the questions these studies are designed to answer helps explain what data companies use to make decisions. From there, the chapter explains what some of the gaps are: what information do companies want from their cost data that they cannot currently acquire without an extensive and in depth study? These gaps are usually not due to a misunderstanding or misuse of a company's financial data. Instead, they often arise because we try to use the system for something it was not intended to do. The final step is to explain how the cost model can help bridge the gap between the data that are currently available and the questions that companies would like to answer.

3.1 Current Cost Accounting Method

Like many companies, Novartis uses a method called "Standard Costing" to evaluate and report their costs. There is substantial literature related to the development and use of this method. Essentially, the theory behind standard costing is that a manufacturing company establishes a standard – or expectation – at the beginning of the year for the amount they plan to spend. Using a "standard cost" and a "standard quantity", they then predict what they expect to spend for the year. These standards are related to the expected inputs they will use during production. (Baggaley and Maskell)

One important aspect of standard costing is related to allocations. Some components of cost are easy to attribute to a specific product. For example, money paid for the reagents used to make a batch of product should clearly be a part of the product's cost. However, many costs are harder to determine. For example, in a factory that produces 10 different products, which product should bear the cost for the factory manager? Standard costing allocates these indirect costs to different products using different allocation keys. Ideally these keys are based on the actual amount of time that the manager spends on each product but it is hard to get the allocations to be completely accurate.

During the year, as product is produced, the site “absorbs” costs. The goal at the end of the year is to have absorbed 100% of the costs. However, a company never ends up producing or spending exactly what they expected. Instead, they have “variances” from expectations. These variances take many forms (such as an “efficiency variance” or a “price variance”), but they all reflect the idea that actual spending was different from expected. If variances are high, companies often spend a significant amount of time and focus tracking down the potential root cause. (Crosson)

3.2 Current Pharmaceutical Cost Studies

Standard costing is a system that was developed for use by the finance group to calculate product costs for external reporting. However, employees outside of the finance group make many cost-based decisions that rely on financial data as well. In many cases in the literature, the required data were not readily available and a new model or analysis was completed in order to aid with these decisions. In particular, there are three areas addressed in the literature that are of particular relevance. First, there are many studies into the impact that specific process parameters have on results such as run rate, COGS, or capacity utilization. Second, there are several studies that look at the future of capacity utilization in biotech and discuss its importance for costs; these studies emphasize the importance of looking at overall results and of relating financial performance to operational metrics. Finally, there is research into the software tool that is most useful to address these questions. This chapter reviews each area and refers to some representative papers that describe them.

Impact of Process Parameters on Costs

Various studies try to predict the impact that changes to a specific parameter will have on a factory’s overall results. For example, an article by Suzanne Farid evaluates many parameters impacting downstream costs. For example, she examines how titer, downstream yield, and batch success rate could drive costs. (Farid) Another article discusses how optimization depends on both yield and run rate. (Han, Nelson and Tsai) Articles like these try to break down the impact of different cost drivers so employees can understand which factors to influence.

Relating Financial and Operational Metrics

When management looks at the cost of a product, they tend to look at the overall product cost, including any overhead that is allocated to that product. However, that view can be misleading. When a new batch

is run, the actual additional cost to a factory tends to be much lower than the overall product cost would imply. This problem leads into the theme of the next group of articles: the importance of seeing the overall picture instead of focusing in on just one cost. For example, the article mentioned above by Han, Nelson, and Tsai talks about the tradeoff between higher material costs and higher overall costs. It emphasizes that sometimes a higher material cost will lead to better overall results. “Trends in Capacity Utilization” reflects the difficulty of looking at only financial results because often the risk of running out of capacity is a much higher concern. This perspective highlights the point that financial and operational results should be viewed together. (Langer) In “Improving Pharmaceutical Product Development and Manufacturing,” the authors discuss how up front investments in process development can lead to manufacturing savings down the road. (Suresh and Basu, Improving Pharmaceutical Product Development and Manufacturing: Impact on Cost of Drug Development and Cost of Goods Sold of Pharmaceuticals)

Software Selection

Finally, several articles discuss the development and selection of a software package. For example, one study evaluates the two most common biologic process simulation programs, Aspen Batch Plus and SuperPro, in eight performance categories. (Shanklin, Roper and Yegneswaran) Another paper analyzes the choice of production method using a “decision support tool.” (Lim, Washbrook and Titchener-Hooker) A final study uses Excel and a process modeling software tool to analyze downstream operations to predict whether new operations will have to be developed to meet capacity requirements. (Kelley, Very Large Scale Monoclonal Antibody Purification: The Case for Conventional Unit Operations) These studies all show the tradeoffs between using different analytical tools.

3.3 Gap between Available and Required Cost Information

The companies who completed the research described in the previous section may not have stated it explicitly but they implicitly recognized the challenge addressed by this cost model: there is a dichotomy between data calculated for financial reports and their operational metrics. Although they each approach it from a different direction, each article reflects the need for additional modeling and testing that can be used to make informed decisions.

There is nothing inherently wrong with standard costing. It compiles data in a way that is useful and relevant for certain types of manufacturing. However, in many environments it will provide contradictory incentives. In these cases, standard costing causes several problems.

This section outlines the history of some cost accounting systems and then uses scenarios and examples to describe some of the relevant challenges.

3.3.1 Cost Accounting System Origins

Cost accounting systems as they are known today developed in the early 1900's and were used to value the worth of a company. At the time, this was a simple process. Most companies made just one product and that product would only contain a few components. Since then, part complexity has grown by several orders of magnitude and the valuation process has evolved along with it. Financial systems today are governed by an extensive set of rules to ensure that all public companies report their results accurately and fairly. There are a variety of methods that companies can use to value their inventory and assign costs to each product. However, whether a company uses activity-based costing, standard costing, or something else, the end goals are the same: to know where money is being spent and how much money is being earned. (Huntzinger)

These systems were originally created to report companies' results externally, but since products were so simple this same data could easily be used for internal management to make decisions as well. However, as product complexity increased, this became increasingly difficult. To explain some of these difficulties, we look at several simple case studies.

3.3.2 Challenges with Cost Accounting Methods

These hypothetical examples may sound familiar to many employees since they arise in companies and industries around the world. These concepts provide the foundation for the creation of the cost model.

Scenario 1: A manager in a factory generally has good performance but continually has high variances and cannot figure out how to reduce them.

Root Cause 1: The manager may be performing well but there is a good chance that he finds the financial results difficult to comprehend and hard to take action on. The variance terms in the financial report do not make sense to him since they are not connected to the operational metrics

he manages. In addition, he does not even have control over about 60% of the budget items in his department; these items were allocated to him from a different group. He would prefer to spend time improving items he already understands and knows how to fix.

Scenario 2: A factory has met all customer demand for the year but they are told by upper management to produce extra batches in December so they can absorb their remaining overhead costs and meet their annual financial targets.

Root Cause 2: The customer demand (and therefore the amount of absorbed costs) may have changed, but the factory’s cost targets and variance calculations have not. By producing more, factories are able to absorb more of their costs and reduce their variances, but they also have to produce unneeded materials and carry extra inventory.

Scenario 3: A division chooses to outsource a product even though internal capacity is available and variable costs are low.

Root Cause 3: The table below (Table 1) shows one way this could happen. Both the internal and external groups would have expenses of \$1,000 if they received the contract. They charge \$6,000 and \$5,500 respectively since these are their “total costs” for producing. If internal capacity is available then the best decision for the company would be to produce internally. However, that decision is obscured by the cost calculation because the company is only looking at their product cost calculation instead of their overall value stream cost.

Table 1 : Production Cost Options

Option	Produce internally	Outsource
Variable Cost	\$1,000	\$1,000
Fixed Cost	\$5,000	\$4,500
Total Cost to Division	\$6,000	\$5,500
Total Cost to Company	\$1,000	\$5,500

Scenario 4: A manufacturing site would like to lower new product costs by changing some process parameters but cannot figure out how to explain to the development organization that the investment in process improvements is worthwhile.

Root Cause 4: Financial results can be confusing for someone to understand without the right background knowledge. In addition, the financial system is designed to be reactive rather than proactive. Most financial accounting systems are designed explicitly to report results, which

means by definition that the results have already happened. Management would like a tool that can predict financial performance if certain process or product parameters change, a goal which was never expected when the system was designed.

In all of these cases, the players involved (both in manufacturing and in finance) are trying to make the correct decisions for the business but there is a conflict between the decisions they would like to make and the indicators available to inform those decisions.

Keep in mind that companies are not automatically making poor decisions just because the financial systems are not designed to report data in a certain way. There are many reasons that financial analysis is done the way that it is that are not discussed at length in this thesis; this data is essential for many aspects of financial control and reporting. In addition, it is still possible to avoid many of the conflicts described above, even without an entirely new cost system. Employees in finance are often aware of these conflicts and can take steps to reconcile and reduce some of the differences between groups. Nonetheless, these issues still arise frequently and it is important to watch out for them. In addition, by analyzing and compiling the financial data in a different way it is possible to address these struggles more directly and to make it easier to get the right measurements when they are needed.

3.4 Bridging the Gap with the Overall Cost Model

As described above, there are several specific challenges that arise from using the same financial method for both external and internal financial results. In particular, several issues stand out:

Results that are hard to understand and take action on: Standard costing calculations lead to variances which can be hard for managers to relate directly to their business and results. Budgets also include many costs over which managers have no control.

Conflicting metrics: Financial data reveals only part of the picture. If the finances are not reviewed alongside the operational metrics such as capacity utilization and product demand, then each set of metrics will pull managers in different directions.

Focus on product-specific instead of overall costs: A factory that focuses on each product in isolation runs the risk of optimizing one at the expense of the others. Managers should look at the impact on their overall costs when they are considering any changes.

Metrics that are reactive instead of proactive: It should be possible to easily analyze several different scenarios in a factory and get a prediction for their impact on costs.

These challenges are especially daunting in the pharmaceutical industry where the cost of manufacturing is a low percentage of overall costs and regulatory hurdles are extremely high. However, manufacturing is an area with much potential for improvement and is a powerful lever that companies can pull to increase profitability. Therefore, especially in a time of increased focus on cost reductions and efficiency, these hurdles can be overcome.

This thesis presents one tool to address some of these concerns. It focuses on providing a different view of costs that makes cost analysis easy and predictive. A customized cost model will allow the site to intuitively understand their costs and where they come from, and also to predict the potential cost impact of process and product changes. By understanding their finances and knowing how to take action on them, managers will be able to make more educated and holistic decisions.

4 Method

Now that the context and drivers for the cost model are understood, it is time to discuss the implementation. As previously described, the goal of this model is to provide an easier and more intuitive way to understand costs that helps predict the cost impact of product and process changes. However, there will be many users whose interests and goals span a wide range of topics. Creating a model that can address such a variety of users' needs requires a balance of many components. This chapter describes several critical design features that were considered during model development, including selection of a software package, and reviews the main assumptions that impacted the model.

4.1 Model Considerations and Goals

Financial results depend on decisions made at all levels of a factory and stakeholders use this financial data for a multitude of purposes. For example, a financial planner at headquarters might analyze how much it would cost to produce a few more batches next year; a capacity analyst calculates the return on investment for choosing to produce in one factory versus another; a tool operator does not even realize that the extra piece of tubing he uses for every batch is costing the company thousands of dollars per year. Each employee makes decisions that influence the final cost of the product that is produced and being able to understand the impact of those decisions can help employees work more effectively.

On the other hand, financial data are incredibly complex. A factory may track their work by dividing into dozens of cost centers, each of which includes hundreds or thousands of lines of expenses. Behind each expense is a person or team who is responsible to choose how and when to spend that money.

Forecasting budgets, calculating variations from the plan, and keeping groups on track are not easy tasks.

How does this impact the cost model? The financial data are often managed and kept within the financial groups due to some of the challenges and complexity described above. However, one goal of this model is to make these data accessible and understandable to a broader community. Therefore, somehow the complex financial data have to be presented in a way that the financial planner, the capacity analyst, and the tool operator can all understand and relate to their jobs – and it has to do this without requiring much setup and without distorting data.

A few guidelines were established to keep the model focused and to ensure that these requirements would be met. These were drawn directly from the hypothesis explained in chapter 1: the model must be quick and easy to set up, it must provide intuition about the various cost drivers, and it must help connect

financial and operational metrics. The following paragraphs summarize these considerations. Later, when the model is described in more detail, we discuss how these requirements were met.

4.1.1 Easy to Use

A model that confuses its users will not end up being used or, even worse, is likely to be interpreted incorrectly. A central principle for this model is its ease of use.

In practical terms, that translates into several criteria. For example, calculations in the model should flow logically from one place to the next. In other words, it should be clear where the user is supposed to input data and where they look to find the outputs. This reduces the time that users have to spend looking for input parameters and, since many input parameters are grouped together, it reduces the risk that a parameter will be missed.

It also means that different users should be able to see clearly which inputs they are responsible for. The finance group understands the budget data very well but they are not expected to be experts on the process flow information. The process development group has an opposite view; they understand process parameters such as product concentration, filtering speed, and material selection but they are less involved with fine details of the budget. The groups have to work together to supply the model inputs but they should only be held responsible for their area of expertise. This separation of knowledge led to development of the model in two separate cost models that tie into one another: the “Process Flow Cost Model” and the “Overall Cost Model.” This design makes it clearer which users should set up which part of the model and reduces confusion as users learn the model for the first time.

4.1.2 Provides Intuitive Results

After all inputs are entered, users want to use the model to draw conclusions. Like the inputs, these results should be easy to understand.

When standard costing is used, COGS is reported as a base number with variances added to it. These variances could include a purchase price variance, a labor variance, a materials usage variance, and more. On the other hand, when standard costing is not used, COGS can be reported directly as a sum of the individual components. Although in theory the variances help focus on specific changes from a company’s plan, in practice the root cause of a variance is often extremely difficult to track down. (BMA Inc.)

The results in this model are reported in a different way that avoids the use of variance. The meaning of the results is the same as that obtained using standard costing but this method of reporting makes it easier to relate to operational metrics on the factory floor. Therefore, this model uses simple metrics like “material costs” and “labor costs” that are more easily adopted as a common vocabulary and can facilitate communication between groups.

Again, we should emphasize that neither set of results is incorrect; they are just used for different purposes. In this case, the second set is more applicable for the goals of this model.

Another way to make costs intuitive is through their presentation. The model should not have a lag time for calculations, so all calculations are done automatically whenever the user updates any parameters. Next, the most relevant results are presented graphically; these graphs also update automatically whenever anything changes. Finally, several input options allow the user to compare several scenarios at the same time. This allows them to do side-by-side cost comparisons extremely easily.

4.1.3 Connects Finance and Operations with the Right Data

It is good to have easy-to-understand inputs and results but without the right data these features are meaningless. This is perhaps the hardest feature to get right. Again, how do you get the financial planner, the capacity analyst, and the tool operator all aligned, and how do you give them all the same incentives so poor decisions are not made? This section explains how the “right data” was chosen to include in the cost model.

Fixed versus Variable Costs

When calculating costs for a manufactured product, it is clear that these costs include materials and consumables. For example, biologic product costs should include the cost of food for the cells and the cost of filters used up for a given batch. These are variable costs and the expense to the factory increases in direct proportion to the number of batches. In general, some element of fixed costs is also assigned to a given product’s cost. For example, if a product runs in the factory for two weeks, then two weeks’ worth of equipment depreciation is assigned to the product. When new batches are added, the overall cost to the factory changes by the amount of the variable cost multiplied by the number of batches.

At Novartis and at many other companies, the division between fixed and variable costs is not as clear as it might sound. For example, producing a batch might be very energy intensive but you also need to

provide electricity to the factory even if it is shut down. In that case, how much of the utilities cost is actually variable and how much is fixed? A similar question applies to direct labor. As the number of batches increases, are additional personnel hired or does the scope of work for the current personnel simply increase? The diagram below represents the process of examining costs at the Novartis factory, some of which were assumed to be fixed, and breaking them into smaller pieces to pull out elements that were actually variable.



Figure 3 : Determining Variable Costs (VCs)

One other consideration is the timeframe being examined. Some costs might be fixed in the short term, such as the salary for the site manager at a plant. However, long term it is possible to close the factory down, in which case the factory’s fixed costs would reduce to zero.

Since the goal of this cost model is to help managers understand their costs and have more control, it is important to hone in on variable costs so managers can understand conceptually which products are really incurring higher costs. Therefore, this model provides several different views of output, one of which explicitly lists all costs that are variable. The Assumptions section later in this chapter will explain how the variable costs were selected for this model.

Cost of Idle Capacity

The capacity utilization at a factory will change from year to year and sometimes even from month to month. In some types of cost reporting, costs for any idle capacity are included in the product cost. This means that factory overhead costs are distributed across the products being run. Supposed that three batches are run in the factory but the plant’s capacity is four. In this case, capacity utilization is 75% and the factory could add one more batch without incurring any additional fixed overhead costs. The figure and table below illustrates this example.



Figure 4 : Different Allocations of Idle Capacity

Table 2 : Impact of Idle Capacity on Costs (plant capacity = 4 batches/yr)

# batches	3 Idle Allocated	3 Idle Separate	4 No Idle
Overall factory overhead	\$1,000	\$1,000	\$1,000
Overhead per batch	\$333	\$250	\$250
Variable cost per batch	\$500	\$500	\$500
Total variable cost	\$1,500	\$1,500	\$2,000
Product cost	\$833	\$750	\$750
Value stream cost	\$2,500	\$2,500	\$3,000

In this example, one result stands out: when idle time is allocated across the products, it looks like the product gets cheaper when capacity utilization goes up. However, the actual work and expenditure per product has not changed. This discrepancy can lead to situations where managers believe their product costs have changed when in reality it is only the plant utilization that is different.

For this model, we decided to report the idle costs separately so that managers could understand the actual incremental cost for a product. If they determine to allocate those costs later on then they can do so as a quick secondary calculation.

Value Stream Costs versus Product Costs

The method of allocating idle time described above is not strictly incorrect. Running a batch really does require the use of the factory’s equipment, and if those three batches were not being run then the entire factory would not be needed. In that case, closing the factory would save a large amount of money. However, this view can be misleading. The table above (Table 2) also includes a line called “value

stream cost,” which refers to the overall cost of running a product. Looking at a product’s value stream instead of batch by batch costs encourages a high-level view and allows managers to see the interaction between different cost drivers. Several of the articles reviewed in chapter 3 focused on this challenge. As they discussed, it is important to see how various drivers, such as run rate and yield, interact with the costs. This method of looking at overall costs instead of product-specific costs can be very effective but is still not widely adopted; product costs are used too extensively for things like transfer pricing and cost per unit calculations. Nonetheless, having both views available requires only a few additional calculations once the data are available and can reveal interesting insights. Therefore, this model reports both product by product costs as well as overall costs.¹ By including both views of data, users can decide which one will be most relevant and can hopefully avoid some misguided decisions. In the example where the manager decided to outsource his product even though internal costs would have been lower, a view like this could have helped him make the most appropriate decision.

4.2 Assumptions

Cost calculations are complex because they are influenced by many factors. To make a cost model feasible, these calculations have to be simplified. Simplifying the model and focusing on the most important elements helps in two ways. First, it allows the model to be easier to use; by choosing the correct assumptions, this ease of use can be accomplished without sacrificing too much model precision. Simplification also ensures that model users can understand where results come from and which factors influence them.

Many assumptions were used in the model to achieve these goals. This section describes the most relevant assumptions that were made.

Allocation of Fixed Costs (Overhead)

Many costs in the factory are not related directly to a specific batch or product. Instead, these costs are related to general overhead that is needed to run the factory. The high cost of overhead is especially

¹ The overall costs reported in this model are not strictly the same as value stream costs. A true value stream will include all aspects of product creation, spanning all the way from raw material acquisition to customer receipt of the product. The overall costs described here only include factory costs and, most notably, do not include any revenues from product sales. Nonetheless, this approximation will still give insights as a starting point for analysis; this can be extended as the results prove useful.

apparent in the pharmaceutical industry where there are extensive regulatory requirements that a company needs to satisfy. For example, support groups (such as HR and Finance), some research labs, costs for the cafeteria, and salaries for site management are generally unrelated to specific products that are run. To come up with overall product costs, companies typically use an allocation key to assign a percentage of overhead costs to each product. They then add this amount to their variable costs to get a total product cost. (See Figure 5 for a visualization of the product cost components.)

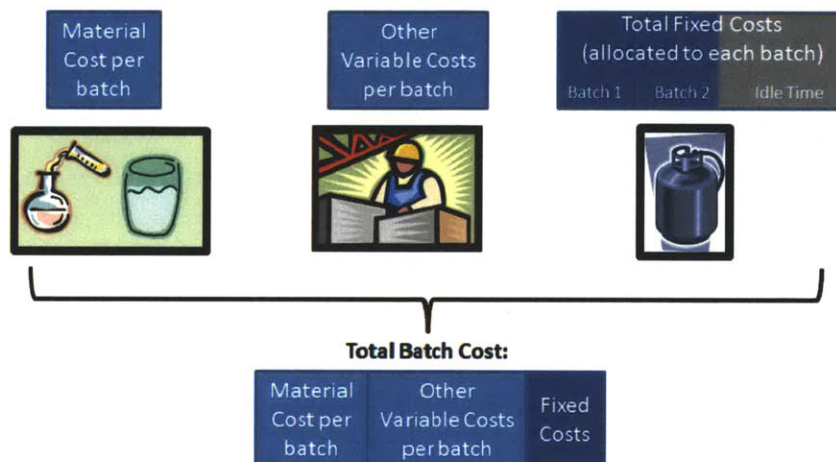


Figure 5: Representation of Product Cost Components.

The total cost is calculated by adding the cost for materials (e.g. buffers and food for the cell), other variable costs (e.g. direct labor), and the allocated fixed costs (e.g. a percentage of equipment depreciation).

The “Model Considerations” section above reviewed several ways that allocations can be misleading. However, since cost allocations are still used at Novartis for product cost calculations, a method was needed to allocate costs in this model.

The goal for a cost allocation is that it be as accurate as possible while not requiring much additional time for data collection. In this model, a simple assumption was used: the amount of overhead allocated to a given product was directly proportional to the percentage of the year that this product used the factory. Allocating it this way is a simple yet understandable method to approximate where overhead costs come from.

The model does not just look at the way costs vary from product to product. It also reviews the way costs are distributed across different process steps within a batch. Therefore, costs had to be allocated within

batches as well. This allocation was done with slightly more granularity. The Novartis factory has already compiled data on the average number of labor hours and equipment hours that are required for each process step. Using these data, it was possible to allocate those particular overhead expenses (for direct labor and equipment depreciation) to each process step based on the number of hours it takes to run. This method is not perfect – the data for the labor and equipment hours has some variability in it, and there are many other factors that influence how costly a process step might be - but it is a good balance of simplicity and accuracy.

Because no allocation method can be completely accurate, these allocated overhead costs were reported separately in the model results from the variable costs. This allows model users to look at the data that they find most relevant.

Variable Costs

Variable costs were calculated based on the number of batches run. Since these could be calculated more directly, they did not have to be allocated to a given campaign. Understanding which costs are fixed and which are variable (that is, which ones will increase or decrease in relation to production volumes) is a critical distinction to understand.

The cost timeframe is also relevant. In some cases, costs may be fixed in the short term but variable in the long term. For example, a factory that is open this year will have a utilities charge whether it is producing medicines or not. However, in several years that factory could be shut down and would no longer have any charges associated with it. For this model, we assume that a cost is fixed if it will not be changed during the next year.

For this model, two categories of expenses were determined to be purely variable: raw materials and consumables. The consumables were broken down further into resins (an especially expensive consumable used during production) and non-resin consumables. These variable costs scale in direct proportion to the number of batches that are run.²

² The resin cost is actually not completely proportional. Each resin can be used for multiple batches. When many batches of a product are run, the resin will be used up completely and it is accurate to assume an average cost for the resin per batch. When only a few batches are run (for example, when a product is part of a clinical trial), the resin may have extra capacity left when the product is completed and the resin is discarded, which then increases the apparent price per batch. To account for these changes, one of the input parameters is related to the number of batches that will be run with each resin.

Many other expenses, such as depreciation for the factory building, are clearly fixed in the timeframe used for this model. However, for some costs, like direct labor, it is harder to understand how much of the expense is fixed and how much is variable. A more detailed description of costs for direct labor, utilities, and quality follows below.

Variable Cost: Direct Labor

Calculating the number of people needed to run a campaign requires an extensive amount of detail. For example, to calculate it exactly, you could count the exact number of hours that each person spends on each product and then assign wages for those hours to that product cost. Any hours that were used for general tasks could be split evenly across the different products. However, what would you do with hours where the employees did not have much work to do? Can you hire or fire employees? And how do you collect all of these data reliably? This process of assigning personnel costs is a challenging task and, in the end, may not be accurate enough to really be worthwhile. For example, if one product requires fewer personnel hours than another, it does not mean that the factory will lay off workers for just the few months while this product is being produced; they still have to pay the workers who are doing less work. On the other hand, the factory may decide to hire a few temporary workers if one product is significantly more time-consuming than another.

Understanding the complete impact the number of batches and product selection have on the personnel costs could be the subject of future research. For this model, a simplified model was used that will at least give management an idea of the personnel costs. If these costs are determined to be important, it is possible to adjust the assumptions in the future.

The model assumes that at a certain “Standard” number of batches every year, the user knows the percentage of the labor force that is variable. For example, the graph below represents a scenario where running 40 batches in a year means that 10% of direct labor will be variable (Figure 6). When there are zero batches run in a year, it is assumed that all remaining employees are required and are unrelated to production volumes. Therefore, at zero batches per year, 0% of the labor force is variable. By using these assumptions, the direct labor costs for different product levels can quickly be calculated. The input table on the left is included in the cost model to allow users to change those assumptions.

Input Table: Personnel Details	
Standard # batches	40
% of labor budget that is variable at the standard # batches per year	
Direct labor	10%

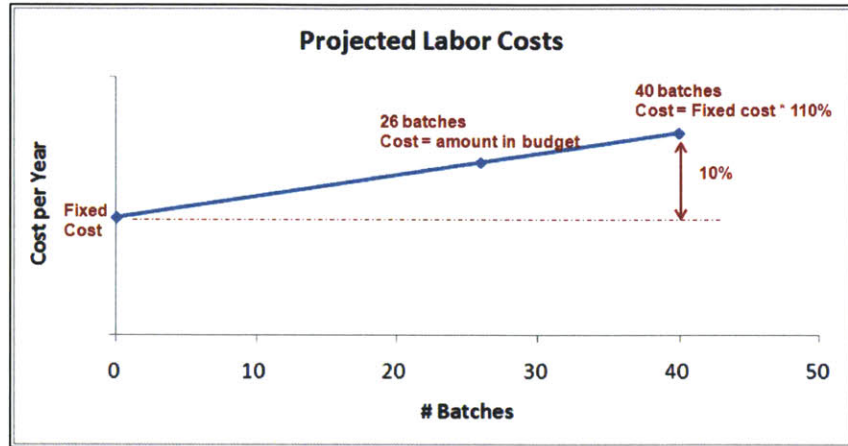


Figure 6: Projected Direct Labor Costs

Variable Cost: Quality Control and Quality Assurance

Quality costs in the pharmaceutical industry are high due to the importance of making sure the product is safe and the extensive regulations to ensure compliance that go along with that. This model assumes that the amount of money and time spent for quality checks on each product is proportional to the amount of time the product takes to run in the factory. This assumption is a large simplification. Some products clearly consume more resources in the quality department than others. For example, every time there is a deviation (or unexpected event) the quality group has to investigate it. Deviations are raised for nearly every small change and usually they do not have any impact on the product quality. However, to be sure, the quality group has to investigate them. Some products have just a few simple deviations every week whereas others have over a dozen more complicated deviations. Those more complicated products consume significantly more time and money in lab tests and equipment. However, focusing in and understanding exactly which product consumed how much money was not the focus of this thesis. Quality costs are under 10% of overall costs and, while this is certainly significant, it could take hours of manual data collection to understand exactly how much of this budget was used for each product. For this version of the cost model, that investment was determined not to be worthwhile. In the future, this could be an area for further investigation and an added level of detail.

Variable Cost: Utilities

There are four main utilities used in the Novartis biologics factory each month: water, wastewater, steam, and electricity. For each of these, the engineering group has data on monthly expenses for the past

several years. By comparing these historical data to historical production levels, it was possible to link utilities costs to the production level. There is some variation from this average, but the historical level gives a point to start from and the model is set to follow the historical trend exactly.

Batch Consistency

It would be interesting to see how much is really spent on each batch and to see how expenditures change from batch to batch. However, this cost model is focused on average and expected costs. Therefore, in this case, the model assumes that each batch is consistent and costs are the same from one batch to another. Some operational metrics already collected in the factory can be used more precisely for this type of batch-to-batch tracking.

4.3 Model Software Selection

Several options exist for cost modeling software, some of which were introduced earlier in Chapter 3. This section focuses on the details of four software packages: SuperPro, Aspen Batch Process Developer, BioSolve, and Microsoft Excel. It explains how their capabilities differ and then explains why Microsoft Excel was chosen for this project.

4.3.1 SuperPro

Along with Aspen Batch Process Developer, SuperPro is the most functional of the software packages. It is a customizable biotech process flow software that allows the user to input details about each step in the process. It gives the user a multitude of options and has been tested extensively on a variety of products, in particular monoclonal antibodies. For example, it has models for over 140 unit operations, material and energy balances, and equipment sizing modules, built directly into the software. Since it is more customized, it does have a longer learning curve and is more complex than some of the other options. (Intelligen, Inc.) This software was used once in the Novartis factory several years ago but the intern who used it is no longer at the company; it has not been used since then and his project was not continued.

4.3.2 Aspen Batch Process Developer

Aspen Batch is similar to SuperPro in that it is customized biotech software. (Aspen Technology, Inc.) For a detailed comparison of these two programs, see the article titled “Selection of Bioprocess Simulation Software for Industrial Applications” (Shanklin, Roper and Yegneswaran). As seen in this

article, Aspen Batch has several differences from SuperPro but “economic analysis is a strength of both software packages;” it would probably be possible to use them both to acquire the desired cost model information. The Novartis site has not used this software before but they do have plans to implement a new process flow model using it in the near future.

4.3.3 BioSolve

BioSolve is an Excel-based program that models the cost of monoclonal antibody processes. Since it is Excel-based, this software would have fewer capabilities than most other options but it would also be easier to use. It was not able to analyze multiple different products run in a factory at a time; each product analysis would have to be conducted separately. One additional benefit is that it includes databases with common data sets that you can compare to, so when a site does not have the data they could use the commonly accepted value. The learning curve would be lower than Aspen Batch or SuperPro, as would the cost.

4.3.4 Microsoft Excel

The final option was to design the software from scratch in Microsoft Excel. This would not have as many options built in but it would be easiest to use and would be customized exactly for the Novartis process and setup. Although the learning curve is low, there is also a high risk that users would use the model without fully understanding the assumptions that go into it. To mitigate this risk, the use of the model would have to be restricted to a few trained users and good documentation would be essential.

4.3.5 Software Selection

The following table (Table 3) is a summary of the analysis from above.

Table 3: Simulation Software Analysis

	Capabilities	Ease of Use	Cost	Acceptance at Novartis	
Importance	Low	High	Medium	High	
Software Package	SuperPro	★★★	★	★★★	★
	AspenTech	★★★	★	★★★	★
	BioSolve	★★	★★	★★	★★
	Excel	★	★★★	★	★★★

Based on this analysis, we decided to design and build a customized model in Excel. Based on discussions with future users at Novartis, their main criterion was ease of use; they were concerned that using one of the pre-designed software packages would require too much of a learning curve and they would never allocate enough resources to get someone trained to use it effectively. Although another model platform would have enabled more detailed analysis, this version of the model is more likely to be used and will therefore be more effective in the long run.

5 Model Development

In the previous chapter, the model goals were finalized, assumptions were articulated, and the software package was selected. Using that foundation, it is time to get into the details of model development. This chapter first describes the overall layout of the model. From there, it describes the detailed setup of the two main cost model sections. It explains the different types of analysis that can be completed, such as an in-depth process analysis or a high-level product comparison. It also explains the meaning of the key inputs that are sent to the model and the calculations and significance of the end results.

5.1 Model Layout

A diagram of the overall model follows below (Figure 7). As the diagram shows, there are two main parts to the model: the *Process Flow Cost Model* and the *Overall Cost Model*.

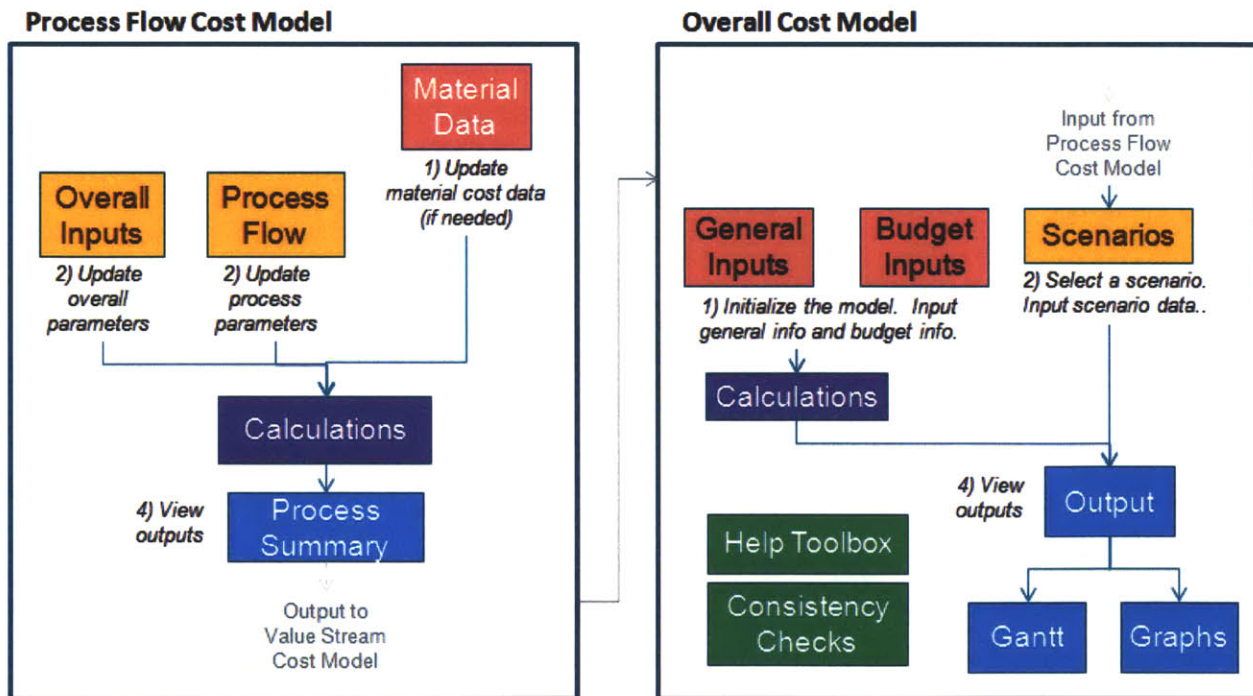




Figure 7: Cost Model Layout

Note: each box in the layout diagram represents a worksheet within the Excel file

The model is separated in this way because there are two different levels of detail in the data and stakeholders will be interested in different sets of information. For example, the *Process Flow Cost Model* does just what its name suggests: it analyzes the process flow for a particular product. This section is designed to get into the details of the manufacturing process. Specific parameters such as descriptions of the raw materials consumed, the product concentration, and the step yields are all incorporated here. The main outputs are the overall costs for materials used in one batch. The model also calculates the amount of time each batch could (theoretically) take to process, although the actual processing time usually ends up being longer due to other parameters such as resources and supply of cleaning materials. This type of information is useful for employees in product development or perhaps for process engineers working in the factory.

The second section, the *Overall Cost Model* also does what its name suggests: it pulls together all elements of cost to provide an overall picture of the Novartis factory costs. This section takes some inputs directly from the *Process Flow Cost Model*. The user adds additional inputs related to the production plan and budget and then the model calculates the overall product cost. In this case, outputs are not focused on a detailed analysis of the process flow. Instead, this model encourages users to compare costs between products. It also helps users understand how process inputs impact overall (and not just material) costs. Results from this model are summarized in a worksheet outlining each element of costs as well as a Gantt chart that shows the approximate production schedule. Since it is higher-level, this information would probably be more useful to a factory manager or a capacity planner.

Although these models are in two separate Excel files, they were designed to be used together. Separating them into two excel files simply makes them less unwieldy to use; because different users are responsible for providing different sets of inputs, separating the data into two areas allows users to focus

in their area of expertise. The diagram in chapter 4 (Figure 5) also shows how these costs can be separated.

5.2 Process Flow Cost Model

This part of the cost model describes details of the production process. It allows users to input key process parameters, which it then uses to calculate the processing time and material cost for the step. For example, for the Protein A Chromatography step, the user inputs parameters such as resin capacity, resin lifetime, and the diameter of the chromatography column. The model uses that information to calculate the amount of resin needed for each batch.

5.2.1 Inputs

Users input this process information in the main “Process Flow” worksheet. Figure 8 below shows the worksheet layout. This is a simplified view but each process step and several key process parameters are listed. All calculations are done directly in this worksheet so they are simpler for users to follow. Since the model is designed for a fed-batch monoclonal antibody (mAb) process, and this process is very similar for most mAb’s, the model can be modified relatively easily for new products by changing a step from “Active” to “Inactive”.

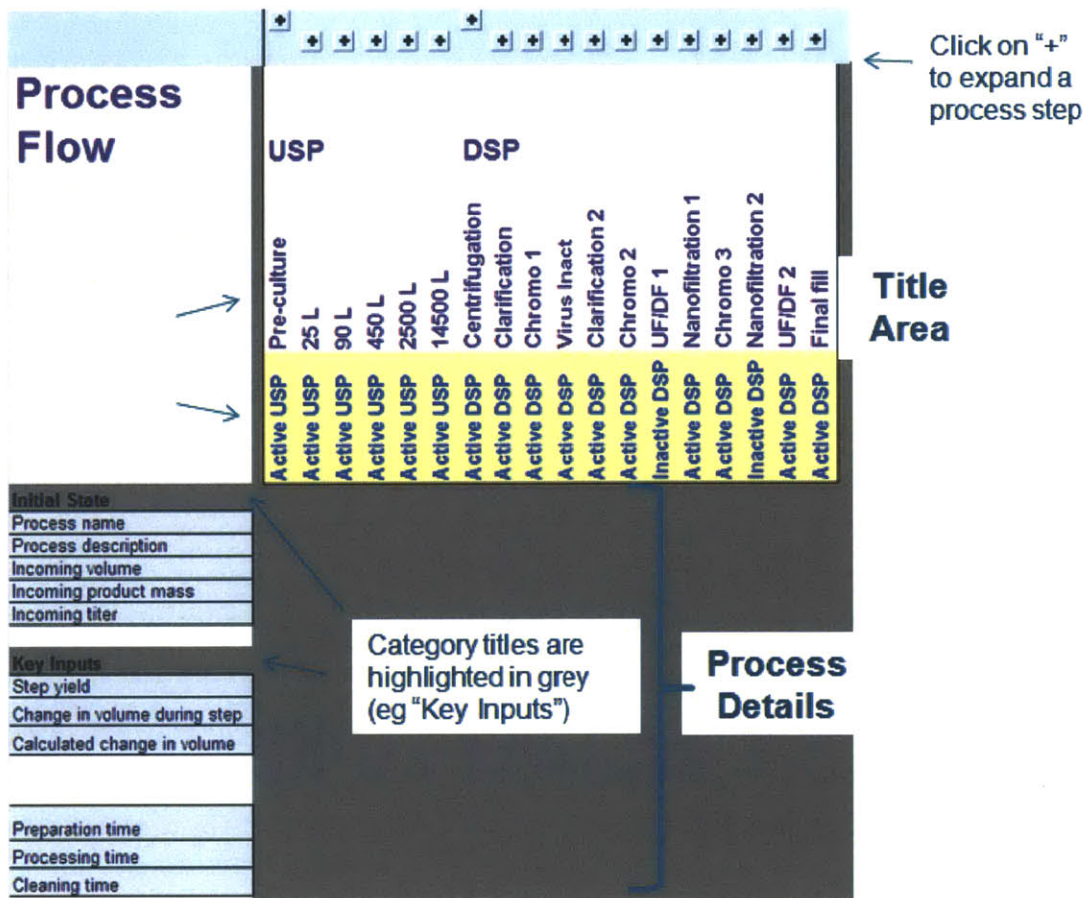


Figure 8: Process Flow Layout

From these user inputs, the model summarizes how much of each material is used at each step.

It also needs to know how much each material costs per unit so it can calculate a total cost; the “Material Input” worksheet is used for that. In this sheet, all materials are listed along with a unit price.³ By organizing the model in this way, the Material Input sheet only needs to be updated if a new material is added or if a material price changes.

³ In the context of this model, “materials” include three things: raw materials, resins, and (non-resin) consumables.

5.2.2 Outputs

Once all inputs are provided, the model calculates and summarizes the final product mass as well as the cost for materials used at each step. It then summarizes this information in a table (Figure 9) that will be fed into the *Overall Cost Model*.

Information by Process Step (per batch)

Step information			Step information				Step-specific costs		
Step Number	Col Number	# Columns Between Steps	Step	Step Characterization	Active/Inactive	USP/DSP	Assigned raw material costs	Assigned resin costs	Assigned non-resin consumable costs
1	3	4	Pre-culture	Active USP	Active	USP	13 €	- €	- €
2	7	4	25 L	Active USP	Active	USP	39 €	- €	- €
3	11	4	90 L	Active USP	Active	USP	145 €	- €	252 €
4	15	4	450 L	Active USP	Active	USP	885 €	- €	252 €

Figure 9: Process Flow Summary Table

Material costs and processing times are the only parameters that are significantly affected by the process flow. Therefore, once this output table is compiled, the *Overall Cost Model* can be effectively separated from the process details. That way, if people with different interests are using the model, the process expert can update this part of the model and the other user (such as an upper level manager or a finance employee) can update the other part.

5.3 Overall Cost Model

As the previous section explained, the *Process Flow Cost Model* analyzes the process flow for a given product. Once the user inputs the key process parameters, the model calculates how much will be spent on the various material types. This information is useful to verify how much the factory is spending on materials right now, but its use is not constrained to the current state. By inputting hypothetical sets of process parameters, the model can be used to support recommendations to the factory on future parameter selection.

The *Overall Cost Model* takes the materials data and expands on it. The main output from this model is a summary of overall costs. In particular, an employee can use this model to analyze scenarios and get a prediction of what each one will cost. For example, what if the number of batches run per week changes from one to two? Or what if a change to the process allows throughput time to decrease by three days? The model allows employees to explore different options without any risk.

5.3.1 Inputs

Several sets of inputs are necessary for this model to work: material costs (which are all variable), non-material costs (including both fixed and variable), and details about the scenario to be run. The input method for each of those is explained here.

Inputting Material Costs

The first information required is the materials costs that were already calculated using the *Process Flow Cost Model*. A user can either type these in or can link directly to the *Process Flow Cost Model*. Also, depending on user preferences, material costs can be entered per process step or as an overall figure. Either method is fine; the choice will just slightly impact which results can be calculated.

Inputting Non-Material Costs

The next required set of inputs is information about all other costs in the factory: how much is spent in a baseline year? The cost predictions in the model are extrapolated from this baseline information. This financial information (referred to as Period Cost Expenses, or PCE at Novartis) could be entered in many different formats. For this model, cost data are entered in a grid (see Figure 10) that divides costs by different criteria. The column labels, or “cost categories”, are classifications for the type of expense in question, and the row labels, or “cost types”, refer to the group within Novartis that incurred the expense. This division is a method of analysis that Novartis Finance already uses so it is an easy input method for them to employ.

Costs in Budget (both Fixed & Variable)	Personnel	Personnel - 3rd Party	Eqpt. Depreciation	Building Depreciation	Infrastructure (utilities & ecology)	Materials	Other
Direct Labor	2,357	357	0	0	0	0	360
Equipment Costs	0	0	1,662	401	491	1,430	1,010
Production Area Overhead	1,357	303	550	260	652	1,571	812
Quality	1,657	482	421	248	0	0	383
Material Handling	1,177	339	467	330	574	472	782
Utilities	0	0	582	803	1,172	257	885
Ecology	0	0	387	286	586	266	429
General Factory Overhead	2,296	281	1,206	1,199	1,494	298	1,313
	8,844	1,761	5,275	3,526	4,969	4,295	5,975
	Total in Budget:						34,644

Figure 10: Novartis Budget Information⁴

The exact layout of these inputs is relatively unimportant as long as it is clear which costs are variable and which are fixed. In this particular layout, the variable costs are isolated in just eight of the squares, which are highlighted for emphasis. They can be summarized as follows.

Summary of Variable Costs	
Direct Labor	<i>Partially variable</i>
3rd Party Direct Labor	<i>Partially variable</i>
Quality Labor	<i>Partially variable</i>
3rd Party Quality Labor	<i>Partially variable</i>
Utilities	<i>Partially variable</i>
Materials	<i>100% variable</i>

Figure 11: Variable Costs

When costs for a scenario are calculated, these variable costs are the only ones that are revised. These costs are modified and predictions for the scenario cost are calculated using the assumptions described in the previous chapter. The remaining PCEs are all fixed. This means that they are not expected to change, regardless of the scenario, so their values are taken directly from this table. There are many more fixed costs than variable costs but variable costs are still large enough to have a significant impact on the results.

Inputting Scenario Information

The information entered so far has been focused on cost data that are required before analysis can begin. The final information required from the user is specifications for the actual analysis to be run. This

⁴ All tables and figures have been modified to protect the confidentiality of Novartis data. Numbers shown in these figures are meant to explain the concept but they are not representative of actual results.

information centers on the type of products and the duration of campaigns that the factory will be running. After all of this information is gathered, the model is able to analyze the production process given all of the process parameters and predict the actual production costs. As discussed several times, the main goal of this model is to predict the cost in a hypothetical future scenario. And, as discussed, the main items that go into this overall product cost are any materials consumed, any variable personnel or utilities, and any overhead (that is, fixed costs) allocated to the product. Most of those data have already been compiled; the previous steps reviewed methods for inputting the cost per batch and the overhead costs. The final step is to input any parameters that will impact the total variable costs or the allocation of overhead to the different steps.

Since the total variable costs depend on the number of batches, that will be a key parameter. The user inputs the number of batches per campaign along with the other scenario information. The overhead depends on the amount of time a product is using the factory. Since each campaign overlaps slightly the time dedicated to a campaign is defined as the time from the end of the previous campaign to the end of the current campaign. The following figure shows the inputs and several built-in calculations that are necessary to complete this calculation:

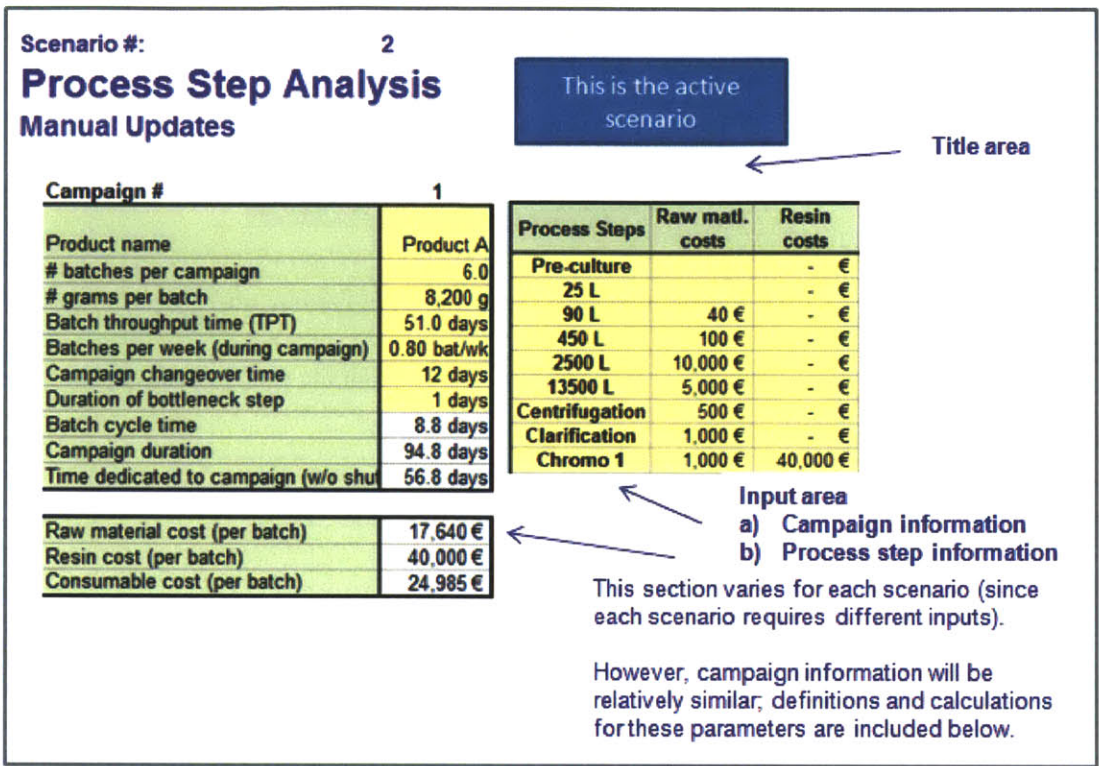


Figure 12: Sample Scenario Input Area

More descriptive definitions of all of these parameters are included in Appendix 1, but the figures below define them graphically.

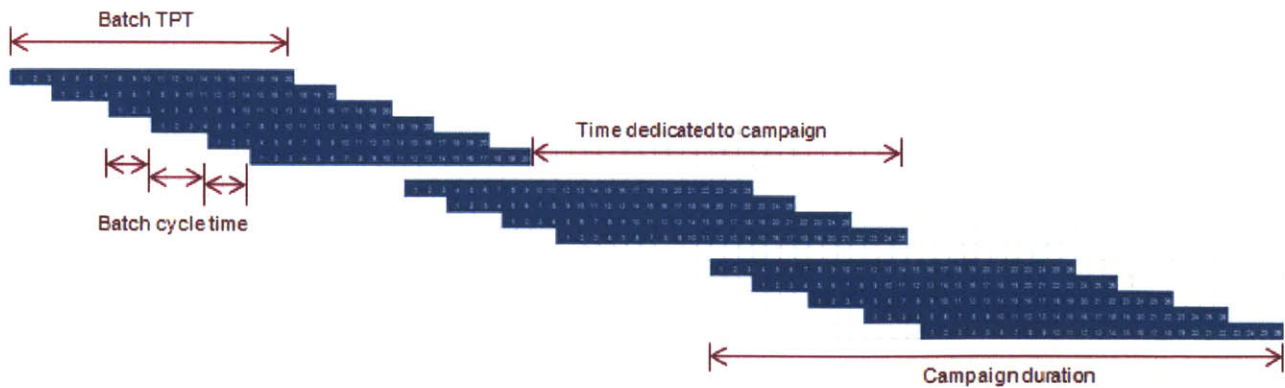




Figure 13 : Visual Representation of Scenario Input Parameters

The calculations that are built into the model all depend on the inputs from the user. These are the calculations used to calculate those parameters:

Equation 1: Batch Cycle Time

$$\text{Batch Cycle Time} = \frac{7 \text{ days/week}}{\# \text{ Batches/week}}$$

Equation 2: Campaign Duration

$$\text{Campaign Duration} = (\# \text{ batches per campaign} - 1) * \text{Batch cycle time} + \text{Batch TPT}$$

Equation 3: Time Dedicated to Campaign

$$\text{Time Dedicated to Campaign} = \text{Campaign duration} + (\text{Changeover time} + \text{duration of bottleneck step} - \text{batch TPT})$$

The time dedicated to the campaign is the key used to allocate overhead costs to different products; overhead is allocated to a product proportionally to the percentage of the year that the factory is dedicated to running that product.

The user can enter data for up to 10 campaigns and can analyze a wide range of options with each scenario. For example, the data could be used to analyze the exact production plan for the coming year. It could also be used to test a small change to the plan, to look at just one product, or to compare 10 campaigns with different parameters on each one and to do a sensitivity analysis. More information about the output data is included in the next section.

5.3.2 Outputs

The three areas described above (material costs, PCEs, and analysis details) are the only places where inputs are required. Once these inputs are complete, the output is automatically calculated. It can be found in the “Output” and “Gantt Chart” worksheets.

Gantt Chart

The Gantt Chart worksheet is mostly used as a double check to ensure that all parameters were entered correctly. Based on the inputs that were entered, this worksheet produces an approximate production plan. If a campaign is much shorter than expected or the batches are running too quickly, then the user knows to go back and check the inputs. The diagram below is representative of what the Gantt chart looks like for a sample production plan, where each cell represents one day.

Campaign #	1	2	3
Product name	A	B	C
# batches per campaign	3.0	3.0	3.0
# grams produced	5,000 g	5,000 g	5,000 g
Batch throughput time	18.0 days	15.0 days	16.0 days
# batches/wk	2.0 bat/wk	3.0 bat/wk	2.0 bat/wk
Campaign changeover time	4.0 days	4.0 days	4.0 days
Duration of bottleneck step	2.0 days	2.0 days	2.0 days
Batch cycle time	3.5 days	2.3 days	3.5 days
Campaign duration	25.0 days	19.7 days	23.0 days
(without shutdown)	13.0 days	10.7 days	13.0 days

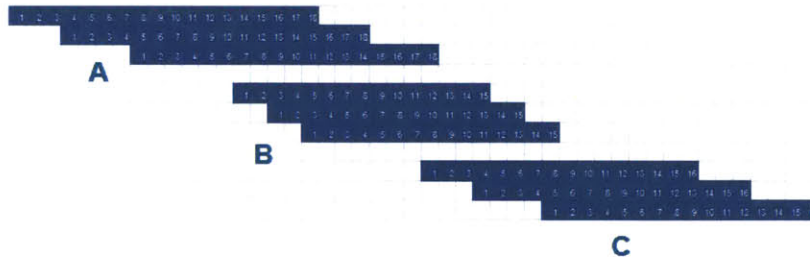


Figure 14: Sample Gantt Chart

Summary of Costs

The output table can easily be modified depending on the specific results the user is looking for, but the current table includes a wide variety of parameters that should apply to most situations.

In Figure 15, you can see an example of some key output information with three different views of the same costs. Depending on the information that is required, a different view may be more relevant. For example, the first table breaks costs into fixed and variable components, whereas the second table breaks them down by cost type and category.

Summary of expenses for entire year (without raw materials)

View 1 of Costs: Fixed and Variable	Fixed Part	Variable Part	
Direct Labor	2,198	147	
3rd Party Direct Labor		329	
Quality Labor	1,594	58	
3rd Party Quality Labor		445	
Utilities	1,500	400	
Materials		1,500	
All other	25,031		
Total	30,323	2,879	33,202

View 2 of Costs: by cost center and cost type	Personnel	Personnel - 3rd Party	Eqpt. Depreciation	Building Depreciation	Infrastructure (utilities & ecology)	Materials	Other
	FR7010	FR7020	FR7040	FR7041	FR7050	FR7090	Other
Direct Labor	2,344	329					360
Equipment Costs			1,662	401	491	1,500	1,010
Production Area Overhead	1,357	303	550	260	652		812
Quality	1,652	445	421	248			383
Material Handling	1,177	339	467	330	574	472	782
Utilities			582	803			885
Ecology			387	286	1,900		429
General Factory Overhead	2,296	281	1,206	1,199	1,494	298	1,313
Other							
	8,827	1,696	5,275	3,526	5,110	2,793	5,975
					Total:		33,202

View 3 of Costs: fixed and variable by							
Fixed Costs	8,622	1,367	5,275	3,526	4,710	1,293	5,975
Variable Costs	205	329			400	1,500	
	8,827	1,696	5,275	3,526	5,110	2,793	5,975
					Total:		33,202

Figure 15: Cost Summary Data

Campaign Summary

The following figure shows the calculation of costs per campaign for several different campaigns. In this example, each campaign has a different cycle time. Fixed costs are allocated to campaigns based on the percentage of the year that they occupy the factory and variable costs all depend on the number of batches that are run.

Campaign Summary

Campaign Information	1	2	3
Product name	A	B	C
# batches per campaign	3.0	3.0	3.0
# grams per batch (output)	5,000 g	5,000 g	5,000 g
Batch TPT (input)	25.0 days	25.0 days	25.0 days
Batches per week (during campaign)	1.0 bat/wk	1.5 bat/wk	2.0 bat/wk
Campaign changeover time	8.0 days	8.0 days	8.0 days
Duration of bottleneck step	2.0 days	2.0 days	2.0 days
Batch cycle time	7.0 days	4.7 days	3.5 days
Campaign duration	39.0 days	34.3 days	32.0 days
Time dedicated to campaign (without shutdown)	24.0 days	19.3 days	17.0 days
Time dedicated to campaign (with shutdown)	24.9 days	20.1 days	17.7 days

Total Costs per campaign	1	2	3
Direct labor (fixed) (per campaign)	150 €	121 €	106 €
Personnel in quality (fixed) (per campaign)	109 €	88 €	77 €
Other Personnel (fixed) (per campaign)	393 €	316 €	278 €
Eqpt. Depreciation (assigned to eqpt.) (per campaign)	113 €	91 €	80 €
Eqpt. Depreciation (unassigned) (per campaign)	247 €	199 €	175 €
Other OH (per campaign)	1,059 €	853 €	750 €
Subtotal: fixed OH per campaign	2,070 €	1,668 €	1,466 €
Direct labor (variable) (per campaign)	59 €	67 €	67 €
Personnel in quality (variable) (per campaign)	63 €	63 €	63 €
Other Personnel (variable) (per campaign)	- €	- €	- €
Utilities (variable) (per campaign)	133 €	133 €	133 €
Subtotal: variable OH per campaign	256 €	263 €	263 €
Resin cost (per campaign)	240 €	240 €	240 €
Consumable cost (per campaign) (not resins)	200 €	200 €	200 €
Subtotal: Consumables per campaign	440 €	440 €	440 €
Total PCE per campaign	2,766 €	2,371 €	2,170 €
Raw material cost (per campaign)	60 €	60 €	60 €
Additional Transfer Costs (per campaign)	- €	- €	- €
Total Cost per campaign	2,826 €	2,431 €	2,230 €

Figure 16: Campaign Cost Information

6 Research Analysis

The previous sections explained the context for the model and the steps leading to its development. This chapter starts by reviewing the accuracy and precision of the model; how exact are the results expected to be? The rest of the chapter looks at several case studies to showcase certain conclusions the model helps make clear.

6.1 Model Verification and Data Sources

Before getting into the verification of the model, it is important to remember what the standard is. The goal of the cost model is to be **at least as accurate** as the standard cost models that are in use today, while also being easier and more intuitive to use. This means that the gold standard for verifying this model's accuracy will be the standard financial models in use today. Therefore, when a cost is calculated "exactly", then it is equal to the standard financial model to which it is being compared. Comparisons for some cost components are straightforward since the new model uses some data directly from the finance group. However, other cost components will have some level of inaccuracy in them, and still others will require more verification at Novartis before the model can be used extensively. This section explains the data sources for the model, the expected accuracy of the results, and areas where there is room for improvement.

In the *Method* chapter, Figure 5 summarized the steps required to calculate the overall product costs: (1) calculate material cost components; (2) calculate other variable cost components; (3) calculated fixed overhead cost components; (4) determine how to allocate the fixed costs across products; and (5) add each component together to compute the overall cost. The accuracy of the model depends on both the accuracy of the data inputs (items 1 through 3) and the calculations built into the model (items 4 and 5). The following sections describe the process for model verification in each of these categories.

6.1.1 Data Inputs: Material Cost Components

Results for each section are calculated differently since inputs come for a variety of data sources. These sources include locations such as the SAP Materials Requirements Planning system, the factory's budget, tracking spreadsheets from factory planners, standard operating procedures, and more. In the first area of costs, material costs, the data sources are especially varied.

The materials consumed during production include Raw Materials, Resins, and Consumables. These are all variable costs and change directly with the number of batches. The user initializes the model by inputting the list of materials used for a product. The model then predicts the actual cost and quantity consumed for each material based on the process parameters the user has selected.

It is relatively simple to verify baseline results for raw materials and resins. The Novartis SAP system already calculates raw material costs for each batch that is run so model results are just compared to those pre-calculated numbers. It is also possible to calculate the resin cost exactly since there are only three resins used for each product and only a few parameters impact the resins' costs. When the model is used to predict process changes, raw material costs are a little harder to confirm. One of the model's main benefits is its ability to predict the cost impact of process changes, and the reason this is such a benefit is that no system is capable of doing this today. Luckily, in most cases only a few materials make up the large majority of the raw material cost, so the approximate accuracy of those numbers can be verified by focusing on those materials.

For consumables, there is no easy way to verify the results. Today, each group in the factory adds up the amount they expect to spend based on the amount they spent last year, adjusted to the best of their ability based on their knowledge of the process. In historical cost models, consumable costs are not impacted by changes to process parameters. The total consumable cost is prorated across all products based on the number of batches that are run. This new model adds in much more detail and allows the user to see how changes to the process will impact those consumable costs. This ability is extremely useful, but since it was not done before it is harder to verify. For now, consumable costs are verified individually based on a consumable-tracking spreadsheet developed by a Novartis employee. Like raw materials, there are only a few consumables that make up a large percentage of the costs so verification can focus on these items. Consumable-tracking is an area that Novartis plans to make more robust in the future but the current approximation in the model is a step in the right direction.

Table 4 : Verification of Material Costs

	Data Source for Cost Model	Baseline for Comparison	Approximate Comparison: baseline case	Impact of Process Flow Changes on Costs	Comments
Raw Materials	Raw materials included in Process Flow Model	SAP material cost calculation	Model includes 94% of raw materials	3 materials are 81% of costs; look at the impact of the process change on these materials	The model calculates costs for all materials listed by the user; any missing materials can be added.
Resins	Calculation built into Process Flow Model	Finance group calculation	100%	No impact; same calculation is used	
Consumables	Standard Operating Procedure	Consumable tracking sheet	100%	2 materials are 60% of costs; look at the impact of the process change on these materials	This is an area for future improvement

As shown in this section, some analysis can be fine-tuned in the future but there are still steps that can be taken to verify each datum that is entered.

6.1.2 Data Inputs: Non-Material Cost Components (both Variable and Fixed)

The previous section dealt only with materials that were actually used during production. This section deals with all non-material expenses at the site. These costs include items from labor to depreciation to utilities and more. While the material costs were entirely variable, these costs are not so straightforward. Some (like overhead and depreciation) are entirely fixed and independent of the number of batches, while others (like personnel and utilities) have both fixed and variable components. The following paragraphs provide verification for the non-material cost calculations.

Since many of these costs are fixed in the short term they can be grouped together; there are only a few costs that required additional analysis and verification. More details follow below in Table 5.

Table 5: Verification of Non-Material Costs

	Data Source for Cost Model	Baseline for Comparison	Approximate Comparison: baseline case	Impact of Process Flow Changes on Costs	Comments
Personnel	Budget is used as baseline; personnel is assumed to change as batches change	Budget	100% (budget is used as baseline)	Small; see comments	This is another area Novartis can research further in the future to understand better how personnel costs are impacted by process parameters.
Utilities	Historical utilities data	Budget		Minimal; ~10% of costs	A relationship was calculated between utilities and the number of batches; about 10% of utilities costs are impacted by production volume.
Equipment depreciation	Finance group	Budget	100% (budget is used as baseline)	None; fixed cost	This will change if new equipment is purchased but is fixed in the short term.
Other Overhead	Budget	Budget	100% (budget is used as baseline)	None; fixed cost	These costs are taken directly from the budget and are all fixed.

6.1.3 Cost Allocation Parameters

The previous sections discussed all costs related to a production campaign. This area addresses the calculations used to allocate costs to different products. Since the calculations used for this cost model are the same as those used in the finance group for previous models, the allocation parameters should be identical.

Table 6: Cost Allocation Parameters

	Data Source for Cost Model	Baseline for Comparison	Approximate Comparison: baseline case	Impact of Process Flow Changes on Costs	Comments
Campaign duration	Model Calculation	Predicted campaign duration	100% (if assumptions are the same)	Indirect; user will have to update it manually	The model uses the same calculations as the old model; if the assumptions are the same then the results will be equal.
Capacity Analysis	Model Calculation	Predicted capacity utilization	100% (if assumptions are the same)	Indirect	"

6.1.4 Overall Costs

Once the costs are calculated and allocated, the final step is to calculate overall results. If the individual cost components are verified, then the overall cost is just a matter of adding up each component. This was verified with several sample products and the models were shown to match. This confirms that the new cost model uses the same calculation method as the old version, so when the same assumptions are used they should provide the same results.

6.2 Research Analysis

The last section showed how the cost model can give results that are comparable to or more accurate than the current standards used for predicting costs. The real benefit from the model comes in the way it is used; this model should be easier to use, faster to setup, and more intuitive to understand than the current method. This section looks at some questions that commonly arise in the pharmaceutical industry and shows how the model helps answer them. It also shows how important it is to have a holistic view of costs and other metrics at a site. The analysis starts by examining some general results from the model calculations, and then several case studies are examined that show the sensitivity of costs to key input parameters.

6.2.1 Results

Once the model is initialized with input data for a particular product, a wide variety of results and metrics are immediately available. If any input parameters (such as the number of batches per week or the yield at a given process step) are changed, then the model results update automatically. It is important to remember that results are calculated for a specific product and are dependent on the assumptions and parameters that are used. The results provided in this section use data for a representative Novartis product to give examples of ways in which the model can be used.⁵ This section starts by looking at a breakdown of costs for a specific product. It continues with analysis of the overall product cost.

Cost Overview

One of the first questions managers are curious about is “where do we spend most of our money?” The following charts (Figure 17 and Figure 18) show how costs are broken down within a given product.

⁵ The scale in these results has been removed to protect confidentiality of Novartis data.

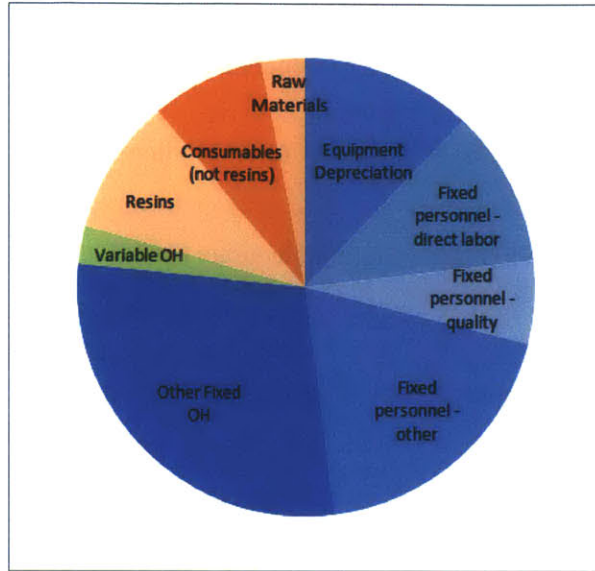


Figure 17: Overall Product Costs by Cost Type – View 1⁶

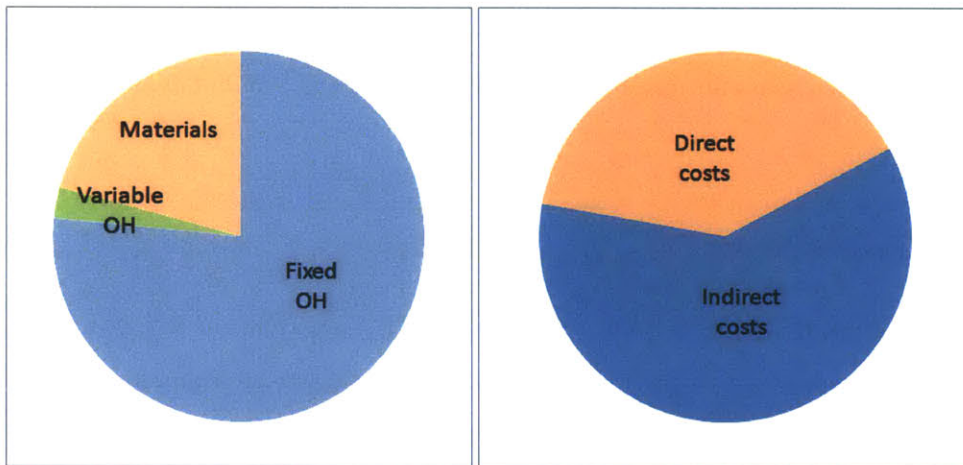


Figure 18: Overall Product Costs by Cost Type – View 2

(Materials vs. Overhead and Direct vs. Indirect)

As the charts show, variable costs - which include materials and variable overhead - are actually a small component of overall costs. Most of the factory budget is used for longer term expenses such as non-temporary personnel and depreciation. After a year or more some of these expenses could be reduced, and the cost structure might also change if production is moved to a new factory, but for now the fixed

⁶ This specific scenario assumes that four batches were run during a campaign.

costs cannot be changed. Likewise, direct costs – those costs that can be attributed directly to a process step without being allocated - are a smaller part of the budget than indirect costs.

These results suggest that factory employees should only be held responsible for a relatively small percentage of their budget since those are the only costs they can influence. Upper level management should work with the managers within the factory to initiate larger changes that can reduce fixed overhead in the longer term.

This also suggests that it is very important to design incentives and performance metrics that are tailored to the specific goals of each level of the organization. For example, while the factory manager can decide to hire more employees or to run more products, the shift supervisor is more focused on the amount of extra resin they decide to hold in stock before a given campaign. If the shift supervisor's performance metrics are largely tied to labor utilization rates, he may not work as efficiently as possible because this is not something he can control. By designing metrics that align with achievable targets, an organization can provide stronger incentives for groups to improve.

The next several paragraphs discuss the cost breakdown for the materials and for the direct costs in more detail.

Material Costs by Type and Process Step

When looking at process development, material costs are one of the areas that can be optimized and improved. In particular, there are a few key materials that end up costing a large amount of money for each batch. See Figure 19 to understand how the material costs are broken down throughout the process for this particular product.

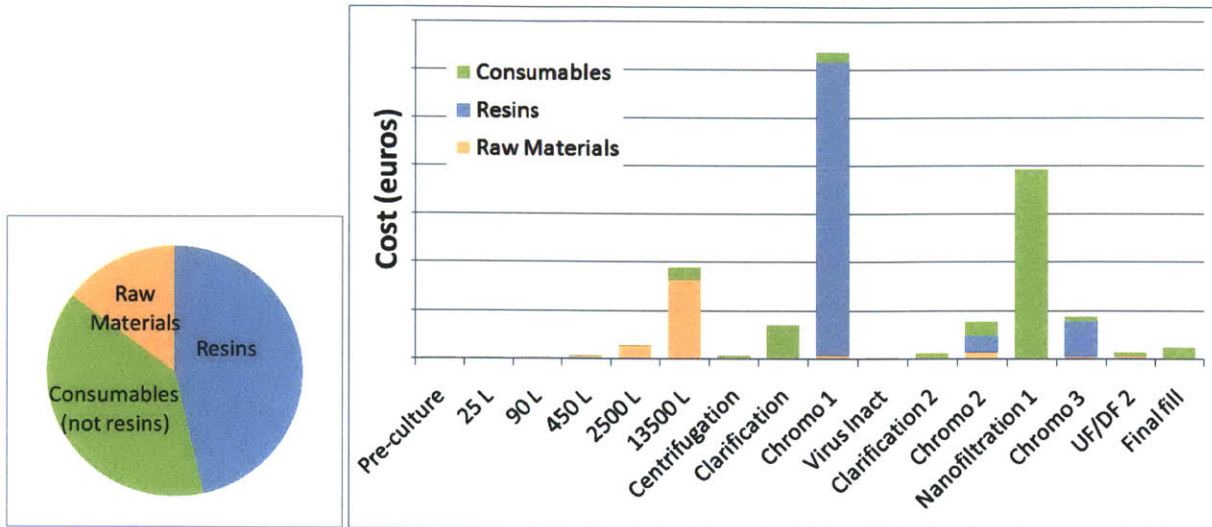


Figure 19: Material Costs by Process Step

The graphs show how material costs are focused in a few specific steps. In particular, the raw material for the largest bioreactor, the resin at the Protein A chromatography step, and the filter for the nanofiltration step all add significantly to the costs. If managers are trying to make reductions to their material costs, they probably should not focus too much on improvements during other steps; honing in on these three areas is likely to give them the highest potential return.

Direct Costs by Process Step

Only a few costs in a factory can be related directly to a specific process step. For example, it is clear where each material is used during the process flow but groups like quality control and finance support the entire factory. To charge a process step for wages of employees in the quality group, those wages would have to be allocated using an allocation key. These costs are called indirect costs since there is no direct link between them and the process. These graphs show which costs are direct and how those costs are broken down across process steps.

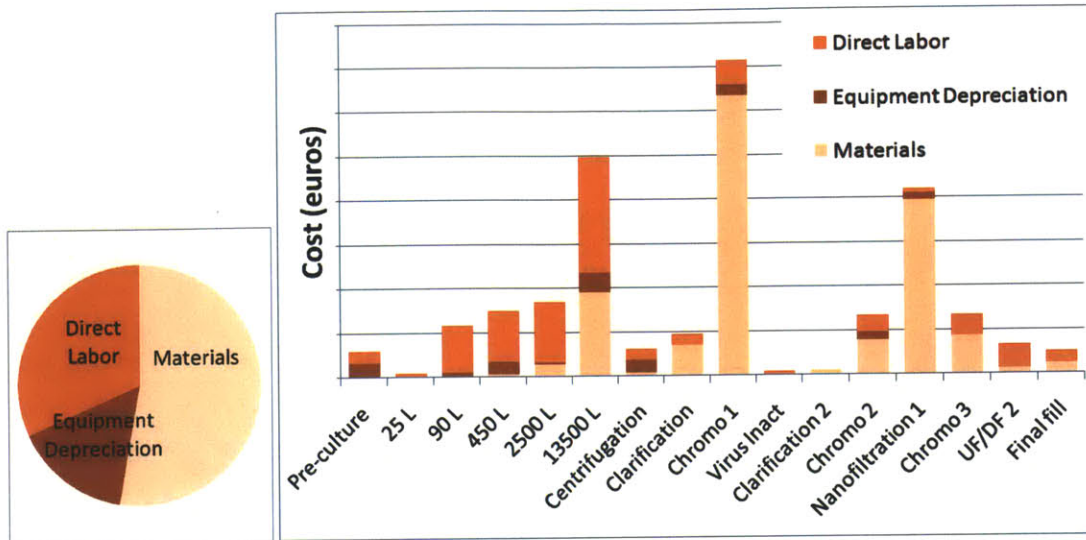


Figure 20: Direct Costs by Process Step

When a factory manager looks at costs for a specific step, the direct costs are the ones he is most likely to be able to control. Again, comparisons like this help employees focus on potential areas for improvement. For example, for this product it looks like direct labor is highest at the large bioreactor, whereas materials costs are high at many of the steps.

6.2.2 Case Studies

The results above help users understand what costs look like in a specific scenario. To get more complex insights, sensitivity analyses can be conducted to understand the impact of one parameter more completely. This section looks at several common parameters to shed light onto their behavior. It also showcases the type of studies the model can be used for.

The first two analyses are focused on changes to the process. The final two are focused on changes to the overall product parameters.

Increasing Titer with Fermentation Time

A common question within biotech production is the impact that a change to the titer would have on manufacturing costs. Knowing this answer could potentially have an enormous impact on production costs because the development organization could tailor the titer in a way that optimizes production.

Usually, changing the titer is possible through a tradeoff with fermentation time; for example, increasing the titer also requires higher fermentation times. The analysis in Figure 21 looks at several combinations of the two parameters.

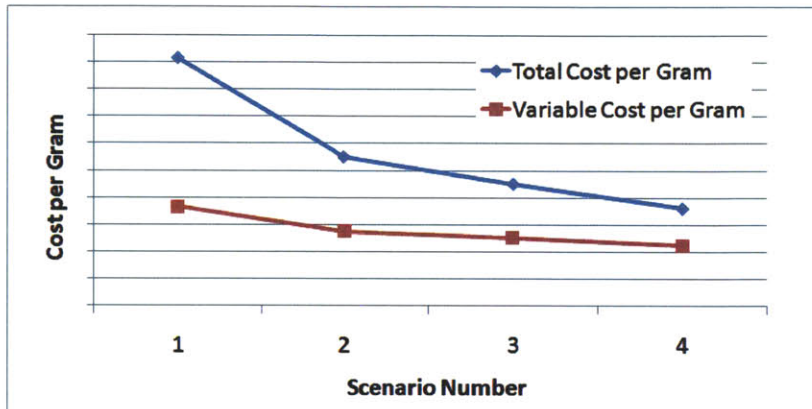


Figure 21: Impact of Titer on Cost per Gram

Scenario 1 has the lowest titer and fermentation time; #4 has the highest titer and fermentation time

This graph shows how increasing the titer for this product is probably a beneficial decision even if it means the fermentation time has to increase.

There are several items to note in this graph. First, there is the bend in the lines at scenario #2. This is the point where the bottleneck in the process changes from the upstream processing steps (for scenarios 1 and 2) to downstream (for the remaining scenarios). Second, the variable cost per gram does not actually improve very much. This is because the cost for materials (especially resins) increases significantly per batch as the titer increases, thus obscuring some of the gain achieved by improved yields.

Increasing Resin Cost with Binding Capacity

Suppose that a more expensive resin was found that could purify more grams of product per liter of resin. How much more efficient would the resin have to be in order to make the switch worthwhile? This scenario assumes that the resin cost will increase by 20%. It then looks for the percentage increase in binding capacity that would be required to justify this change.

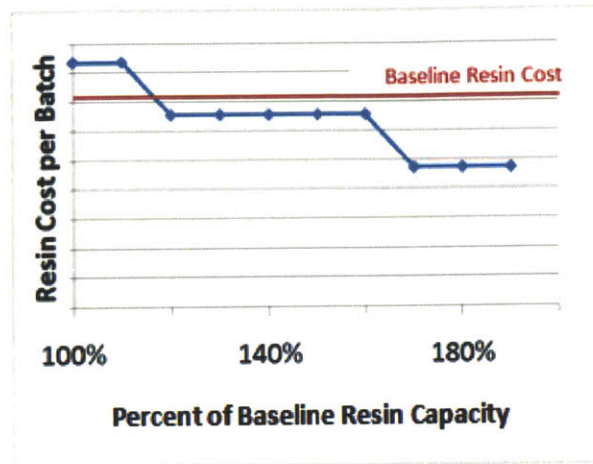


Figure 22: Impact of Resin Parameters on Costs

This graph shows that a more expensive resin would pay off once the binding capacity improved by at least 20%.

This graph has a step pattern which may not be immediately intuitive. This pattern is related to the way that resins are loaded into a container called a chromatography column. Before running a batch, a column is filled with resin. The product batch is split up and run through the column in cycles. The amount of product allowed per cycle is proportional to the binding capacity of the resin; after that binding capacity is reached the resin has to be cleaned before being used again. The amount of resin per column is fixed since the column has to be full whenever it is used. Therefore, the amount of resin needed per batch is determined by how many cycles are required. For example, if a product requires 200L of resin but the chromatography column is 150L, the product would still have to run through the two full cycles. In this analysis, the number of required cycles per batch reduces once the binding capacity hits 120% of its baseline and then again at 170%.

Variable Costs and Idle Capacity

Chapter 4 showed how allocating idle costs to the products that are run in a factory could distort the perceived costs. The following example shows two different ways of analyzing a decision. In this case, the factory is trying to understand how their costs will change if they run four products during the year instead of three. The first set of graphs compares the scenarios with idle time included; the second scenario reports idle time separately.

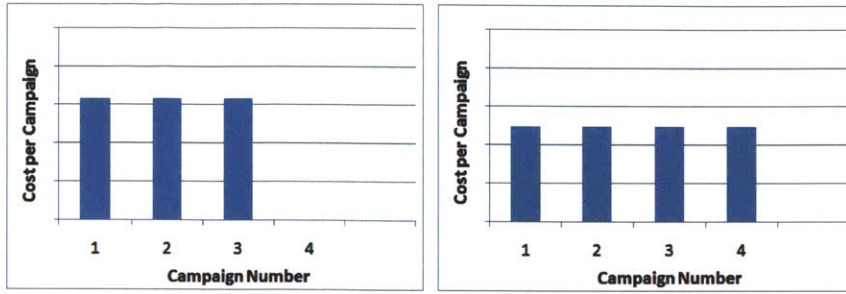


Figure 23: Cost Comparison: 3 vs. 4 batches, Idle Costs Included

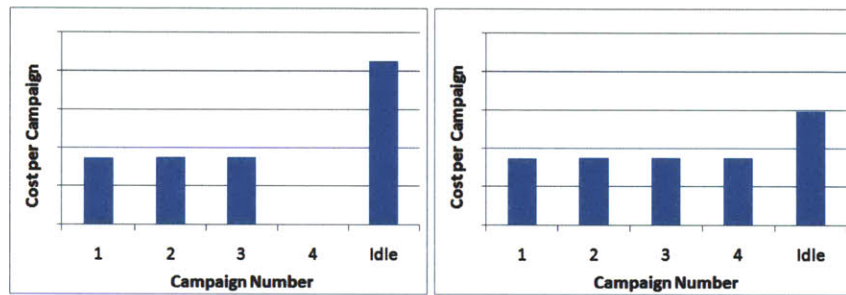


Figure 24: Cost Comparison: 3 vs. 4 batches, Idle Costs Separate

In the first analysis, where idle costs are included in the overall product cost result, increasing to four batches makes it look like the cost per batch has significantly decreased. In the second analysis, the costs are more accurately represented; the cost per batch has not changed substantially but the costs for idle time have gone down. These results may seem intuitive but the first analysis is frequently used because companies know that someone has to pay for the idle time. However, allocating idle time across the products initially obscures the true cost. Managers have to be careful to understand exactly where their results come from before making impactful decisions, and this cost model helps them do just that.

Capacity Utilization and Value Stream Analysis

Look again at the first graph in **Error! Reference source not found.** If you add another campaign that costs the same as the first ones, how much additional money is the factory actually going to spend? The most immediate answer is that the value of the campaign is equal to the size of that first blue bar. However, this answer is incorrect; that blue bar includes many fixed costs in addition to the variable costs. This challenge demonstrates why it can be useful to look at value stream instead of product-specific costs.

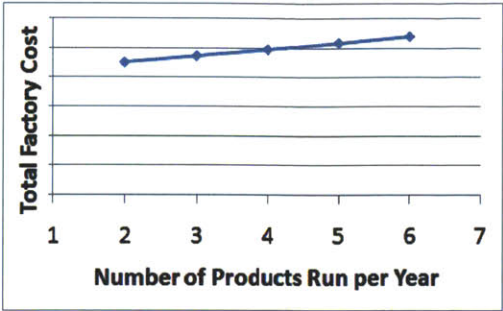


Figure 25: Change in Cost as Capacity Utilization Increases

This chart shows how little costs actually increase as additional campaigns are added. This chart does include one significant assumption: for the scenario simulated here, no additional capacity would be needed to manufacture the additional products added to the factory. If a new factory is needed, then new capital investment will have to be made, which does end up impacting costs. However, that cost would impact your value stream analysis as well, which would make your factory cost drastically increase at a certain production level. While capacity is standing idle, increasing utilization is usually fairly inexpensive. However, whether capacity is available or not, looking at the overall factory costs instead of focusing on the product details can be a useful tool.

7 Conclusion

This cost model helps make the Novartis financial results much easier for internal management to understand and take action on. For example, the graphs in chapter 6 make it clear that, for the product examined in this study, raw materials are a relatively unimportant part of costs. Or, from a broader view, fixed costs are a large percentage of costs overall so there should be efforts to reduce those in the long term; in the short term the most impactful materials to focus on are the first chromatography resin or the nanofilters.

The model can also help predict the cost impact of changes to the process flow or product mix. As shown here, adding more batches is not a large expense when a plant has extra capacity, but can be much more so as utilization goes up. The same was true for titers; in some situations, this is one of the most important parameters, but in others it was not at all.

However, the primary benefit of this model is not the specific results that were reported here. Each scenario that was analyzed has a common thread: straightforward questions were asked that led to clear answers. Managers should use this to increase their understanding of the process and to develop intuition about their financial results. For example, since the model connects financial costs to operational parameters (like the example that showed the impact of fermentation time and titer), factory managers can see how their decisions impact costs. By setting up the model with inputs from Finance, Process Development, and Manufacturing, each of these stakeholders can see how their areas interact and they can work more closely together. A model of this type will not have all the answers, but the results will be usable and actionable and employees will be able to connect the results directly to their own work.

7.1 Applicability to other Companies and Industries

The problems described here are applicable across industries. Each company and industry has a different cost structure; for example, some companies have a much higher percentage of variable costs with lower overhead, whereas others spend almost no money on materials. However, the idea of visualizing costs in an easy to use way is universal.

The most immediate connection is other factories within Novartis that produce biologics. For these sites, the model could be used with minimal modifications to model and predict factory costs. If this concept were to be extended and used in other industries, the model layout would have to be recreated since the

process flow would change. Nonetheless, the concepts and steps taken to create the model would be the same.

7.2 Potential Future Research

There are several areas mentioned in this thesis that would be worthwhile for further research. Several of them are described below.

Model Improvement

This model predicts results based on the assumptions it is given. As described earlier, some of the assumptions, such as the description of labor costs, are oversimplifications. To improve the accuracy and robustness of the model, additional analysis could be done on these assumptions to improve their level of detail.

Model Implementation

The model development is complete but it has yet to be fully implemented within the Novartis factory. In order to make this happen, additional verification of the model should be completed and shared with the various stakeholders to increase the level of confidence in the model results. Once that is complete, the model can start to be used alongside some of the currently utilized cost models. Over time, this new model can start replacing the other models and improving the level of analysis that can be done.

Connect to Lean Business Management Initiative

A different group at Novartis is already investigating many of the concerns raised in this thesis. For example, they are looking at ways to align key process indicators across different levels of the organization by creating linkages between the different goals. They also plan to encourage the use of combined financial and operational metrics to aid decision making. This project has a wide breadth and a several-year time horizon but the goals are very closely related to the goals described for this model. As the Lean Business Management group starts implementing pilot programs in several factories, they can look at ways to use the model's data to help with their goals.

7.3 Conclusions

The goals stated for this project were to create an easy to use method that would make cost results and cost drivers easier to understand. Several key conclusions can be drawn from this model's development and use:

- **A cost model can simplify financial analysis:** Managers have to keep track of a wide variety of information every day and they do not want to spend unnecessary time chasing down cost data. A cost model that simulates the production process can simplify results and make them more accessible to employees. A model like this is not restricted to use in just one area; it could also be used to simplify financial decisions in different divisions of the company.
- **Idle costs can be misleading:** These costs should be listed separately so employees can understand their true impact. When idle costs are wrapped up in the product cost, it is easy to assume that a product costs more than it really does. By separating them out, employees are able to understand the true expenses for a given product.
- **Costs are often dominated by several critical components:** When costs are broken down by type, there are actually only a few elements that comprise a very large percentage of overall costs. In addition, when employees focus on the costs they can control, these elements (such as resins and nanofilters) are even more significant. Employees can have an immediate impact on costs by focusing on reducing these elements.
- **Operational and financial metrics should be used together:** This thesis looked at several examples where either operational or financial metrics could be misleading when viewed on their own. For example, while fixed production costs do affect a product's cost, the overall financial impact that these fixed costs have varies depending on the factory's capacity utilization. By modeling costs and operations side by side, these conflicts can be understood and mismatched incentives can be avoided.

The results and analysis presented here provide insight into cost drivers for one particular product, but the findings are much more widely applicable. By using these recommendations as guidelines, Novartis can use this cost model to help reduce their costs and make more effective decisions.

Appendix 1 - Worksheet Layout: Details of a Process Step

Chromo 1
Active DSP

Title Area

Parameter Name	Inputs	Parameter Name	Details
Process name	Chromo 1		
Process description	Protein A chromatography		
Incoming volume		16 410 L	
Incoming product mass		13 458 g	
Incoming titer		82 g/L	
Step yield		93%	
Pool Batch (ending volume in CV)		2.5 CV	
<i>Note: in this case, final volume depends on pool batch</i>			
Input Times (compare to calculated times)			
Preparation time			
Processing time		12 hrs	
Cleaning time			
Outgoing volume		1 649 L	
Outgoing product mass		12 516 g	
Outgoing titer		7.6 g/L	

Process Details

Cells in yellow are inputs, blue are labels, and white are calculations.

Appendix 2 - Worksheet Definitions

Definitions of many of the model parameters are included here.

Key Process Flow Parameters

This first set of tables includes parameters used in the *Process Flow Cost Model*.

Initial State	Description
Process name	Title of the process step
Process description	Description of the process step (optional)
Incoming volume	In USP, this is a user input; it is not always necessary to put the entire volume from one bioreactor into the next one. In DSP, this is equal to the outgoing volume from the previous step.
Incoming product mass	In USP, this field is not needed until the final bioreactor (either 2500 L or 14500 L). In DSP, this is equal to the outgoing mass from the previous step.
Incoming titer	In USP, this field is not needed until the final bioreactor (either 2500 L or 14500 L). In DSP, this is equal to the outgoing titer from the previous step.

Key Inputs

Step yield	This is usually input by the user. However, in a few cases (eg centrifugation) the number of discharges will impact the yield so it is calculated within the model.
Change in volume during step	Calculated based on the volume of buffer and media added (or lost) during the step.
Preparation time	Amount of time used to prepare for a process step. This is currently a user input and is not used to calculate the batch throughput time.
Processing time	Amount of time needed to process a batch at one step. This is input for USP and calculated in DSP. (This field should be updated; the values in it are approximate for now)
Cleaning time	Amount of time used to clean up from a process step. This is currently a user input and is not used to calculate the batch throughput time.

Key Outputs

Outgoing volume	Calculated based on the incoming volume and the change in volume during the step.
Outgoing product mass	Calculated from the incoming mass and the step yield
Outgoing titer	Calculated from the outgoing volume and mass

Other Inputs

There are many possible "other inputs".
Some examples are: filter part number, chromatography column bed height, resin binding capacity, etc.
For details and definitions, see the SOP.

Processing Details

There are also many possible "processing details".
For details and definitions, see the SOP.

Extra Section (if needed)

This is used for any additional consumables or parameters that were not included elsewhere.

Material Summary

All of the results from above are summarized in this section.

When the "Calculations" sheet summarizes the materials that are used, it pulls the data from this "Material Summary" section

Key Overall Cost Parameters

This table includes a list of parameters from the *Overall Cost Model*.

Campaign#	Self-explanatory
Productname	Self-explanatory
# batches per campaign	Self-explanatory
# grams per batch	The final # grams per batch (after accounting for yield loss and batch success rate)
Batch TPT	Throughputtime; time from the beginning to end of one batch. See below.
Batches per week (during campaign)	# batches that can be started (and finished every week).
Campaign changeover time	# days from end of bottleneck step of last batch of a campaign to beginning of bottleneck step in first batch of next campaign. Equals the number of days between the beginning of the batches. See below.
Duration of bottleneck step	Self-explanatory
Batch cycle time	# days between batch starts. Equals 7 days / # batches per week. See below.
Campaign duration	# days a campaign actually runs (from beginning to end). See below.
Time dedicated to campaign (w/o shutdown)	# days allocated to a campaign; calculated from end of previous campaign to end of current campaign. Conceptually equal to the number of days that running one campaign prevents you from running another campaign in your factory. Used to determine how much overhead to allocate to each campaign. See below.
Raw material cost (per batch)	Can calculate using process flow sheet or can get from finance group.
Resin cost (per batch)	Can calculate using process flow sheet or by using "help toolbox" tab, or can get from finance group.
Consumable cost (per batch)	Can calculate using process flow sheet or can get an approximation from finance group.
Transfer costs (on top of base quality & MT costs)	Any additional campaign costs can be added here.

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