The Business Case for Continuous Manufacturing of Pharmaceuticals

By

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Bachelor of Science in Chemical Engineering, Rensselaer Polytechnic Institute, Troy, 2002

Submitted to the MIT Sloan School of Management and the Department of Chemical

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Master of Business Administration

AND

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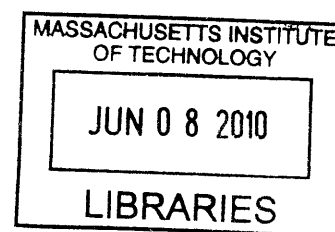
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Abstract

Manufacturing in the pharmaceutical industry is presently characterized as a batch production system, which has existed in its current form for decades. This structure is the result of historical regulatory policy as well as the conservative nature of the industry. Recent clarification by US and European regulatory bodies has opened the possibility to new approaches to the manufacturing process. This combined with changes in the market for the pharmaceutical industry has accelerated the rate at which new manufacturing technologies are explored. Continuous manufacturing is a paradigm shift in the pharmaceutical industry manufacturing structure, encompassing several new technologies and systems. The business impact of continuous manufacturing has not been well defined.

This assessment aims to compare a continuous manufacturing process to a batch manufacturing process for a particular Novartis product. The product has an established batch production process. Cost estimates and the continuous process cost is estimated using a four-step process: defining the process flow, performing the material balance, estimating the capital costs, and estimating the operating costs. This analysis shows that for the particular Novartis product considered, a continuous process is an improvement over the batch process in four performance characteristics: capital investment, operating cost, throughput time, and working capital requirement.

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Finally, I would like to dedicate this thesis to my lovely wife Michelle, for her support and patience throughout my two years as an MIT student. You are always there to listen to me and give me advice when I am challenged by the day to day requirements of class work, internship, and thesis writing. Thank you for being such a wonderful wife who makes my life better every day.

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1 Introduction

Efforts to improve operational performance within the pharmaceutical manufacturing industry include the application of Lean Manufacturing methodologies and Six Sigma quality techniques. These efforts have resulted in significant improvements in throughput times and production costs. Most efforts to improve the process have focused on working around the batch production system, which has been the method of production within the industry for decades (Van Arnum, 2007). The combination of industry regulation, familiarity with batch processes, and flexibility of batch production systems has limited efforts to adopt innovative continuous manufacturing technologies. Equipment makers and manufacturers have published results of continuous technologies replacing individual unit operations with a few process steps. This paper will explore the benefits of a truly integrated continuous chemical and pharmaceutical process for a specific Novartis product. The Novartis/MIT Center for Continuous Manufacturing has outlined the process flow for production of a Novartis product in a continuous flow process. By comparing this process to the actual batch production process, I will evaluate the benefits of an integrated continuous manufacturing process.

In the final section of the analysis I provide a methodology for estimating continuous production costs on a per kilogram of drug substance (DS) and process step level for a product similar in production scale to this product. This methodology is based on the four steps analyzed in detail in the first part of this thesis. These estimates are based on the integrated system approach of a continuous process and are not intended to be applied to cost estimates of individual process steps or unit operations run as a continuous step within an overall batch production system.

1.1 Project Motivation

The sponsor for the work contributing to this analysis is the Technical Operations group within the Novartis AG Pharmaceuticals division. In 2007 Novartis entered into a collaborative effort with the Massachusetts Institute of Technology (MIT) providing $65 million over ten years to develop continuous manufacturing technologies for the pharmaceutical industry. The research group is titled the Novartis – MIT Center for Continuous Manufacturing (CCM) and consists of several technical fellows from Novartis as well as 7-10 MIT faculty, graduate students, postdoctoral fellows, and staff scientists (Buderi, 2007). As research has progressed the CCM has developed a continuous process flow for a specific commercial Novartis product. The Novartis program manager for Continuous Manufacturing sponsored the Leaders for Global Operations project, which generated the hypothesis and analyses in this thesis, in order to answer the question "What is the business case of this specific Novartis product, manufactured at commercial scale using the continuous process flow developed by the CCM?"

1.2 Overview of Thesis

This thesis is organized as described below.

Chapter 1 outlines the general motivation for the thesis and provides an overview of the thesis contents.

Chapter 2 provides a brief discussion of the industry trends and company background as well as the collaboration between Novartis and MIT to develop continuous manufacturing technologies for pharmaceuticals.

Chapter 3 presents the hypothesis for the study undertaken.

Chapter 4 discusses the current state of manufacturing processes and supply chain at Novartis, which is common within the pharmaceutical industry.

Chapter 5 describes the general approach to the analysis and previous work that supports this approach.

Chapter 6 describes the existing total production cost (TPC) model used by Novartis.

Chapter 7 presents the results of the comparison of the continuous and batch production processes for total production costs, capital costs, working capital, and cycle time.

Chapter 8 discusses an overview of the business case and a summary of key findings.

2 Background

2.1 Trends in the Pharmaceutical Industry

The industry for patent protected pharmaceutical products is characterized by high-risk research activities that are rewarded by lucrative patent protection. The industry is also highly regulated with extensive requirements to prove efficacy and safety for a new product. Even after products are approved, changes to the formulation and manufacturing process often require new studies for safety and efficacy. Companies with a strong patented-product portfolio enjoy healthy margins and therefore manufacturing costs are typically a low percentage of the revenues. The combination of regulation and healthy margins has not put pressure on the industry to make advances in manufacturing technologies.

Two recent trends have placed more pressure on pharmaceutical companies with internal manufacturing organizations to improve the efficiencies of manufacturing operations. The first trend is the reduced productivity of research and development activities in generating new patent protected products. With the increased competition of generic pharmaceutical companies, margins of companies focused on patent protected products will face competitive pressures. The second trend facing internal manufacturing organizations is the increased capacity and capability of contract manufacturing organizations and forward integrating suppliers. The outside options are typically solely focused on manufacturing operations and often have cost advantages over internal organizations. The make/buy decision is one faced more frequently by the head of supply chain and operations groups.

2.2 Novartis

Novartis AG is an innovative healthcare products company headquartered in Basel Switzerland. Novartis AG consists of four business divisions: Pharmaceuticals, Vaccines and Diagnostics, Sandoz, and Consumer Health. In 2009 Novartis had approximately 100,000 employees and generated $44 billion in revenue (Novartis AG, 2010).

2.2.1 Pharmaceutical Technical Operations

The Pharmaceuticals business primarily develops and markets patent protected prescription drugs covering several therapeutic areas including cardiovascular, oncology, neuroscience, respiratory, and immunology. The Technical Operations group within the Pharmaceuticals business, or Pharma TechOps, is responsible for manufacturing the Pharmaceutical divisions 50+ products and delivering to a global market. The Pharma TechOps group operates approximately 23 sites worldwide with the majority of the sites in Europe, North and South America, and Asia. These sites fall into one of three operational groups: Chemical Operations, which is responsible for the production of small molecule drug substance; Biopharmaceutical Operations, which is responsible for the production of large molecule biologic drug substance; and Pharmaceutical Operations, which is responsible for converting drug substance from Chemical Operations and Pharmaceutical Operations into a dosage form suitable for the customer, called the drug product. Novartis Pharma TechOps is backwards integrated in the respect that they are producing the majority of the drug substance including early intermediates. With the trend toward increasing contract manufacturing capacity and capability in the industry, Pharma TechOps must consistently provide a cost competitive manufacturing option to the Pharmaceutical division.

2.2.2 Toyota of Pharmaceutical Industry

As the industry trends have increased the competition for low cost, highly responsive manufacturing, Pharma TechOps has focused on improving operations along key metrics. The organization has been successful in improving customer service level, reducing cost of goods sold, and increasing flexibility of the last five to ten years. Pharma TechOps set the goal of being the Toyota of the Pharmaceutical Industry by adopting many of the lean philosophies and six-sigma techniques to eliminate waste within all aspects of the manufacturing supply chain. These continuous improvements have taken place within the structure of the traditional batch manufacturing process. The Pharma TechOps group believes that a step change in performance is possible by changing from batch to continuous process technologies. Figure 1 illustrates the operations performance vision for Pharma TechOps.
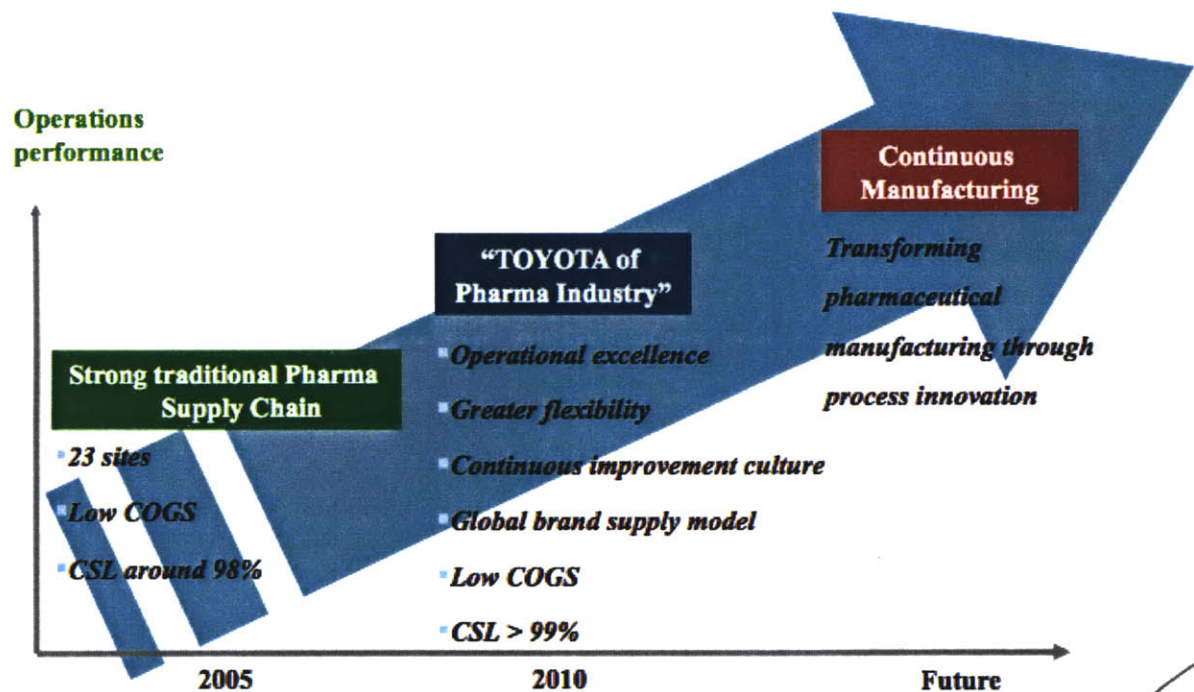

Figure 1 - Pharma TechOps Vision for Operations Performance.

2.3 Novartis MIT Collaboration

Novartis entered into the collaboration with MIT for several reasons. On one hand the faculty and graduate research programs are highly their technical expertise in healthcare related science and technology. Perhaps a bigger challenge to an organization such as Novartis is overcoming the internal resistance to radical new technologies. It is often advantageous to engage an outside expert when attempting to make paradigm-changing improvements within an organization. Novartis maintains a presence in the collaboration by matching internal experts with MIT researchers focused on specific topics. The collaboration faces certain challenges related to the nature of the partnership. First is the geographic challenge due to the physical locations of Novartis (Basel Switzerland) and MIT (Boston USA). The second challenge is related to the different priorities of for profit companies and research institutions. The Novartis – MIT CCM has addressed these challenges in part by altering how the CCM is organized and by developing a roadmap appropriate for both organizations.

The Novartis – MIT Center for Continuous Manufacturing is organized into small teams of six to eight individuals who are focused on a specific technical challenge. The center's roadmap is organized along two major efforts termed Blue Line and Red Line. The Blue Line research focuses on what Novartis describes as Blue Sky technologies. These technologies will enable the most aggressive vision of a continuous manufacturing process, but they also have a longer time horizon to possible commercial application. Figure 2 is an illustration of a Blue Sky vision for a continuous process. The Red Line research focuses on developing a bench scale process for a specific Novartis product using technologies available on a shorter horizon. The purpose of the Red Line is to create an opportunity for learning and to deliver a tangible result with commercial application on a shorter time scale.
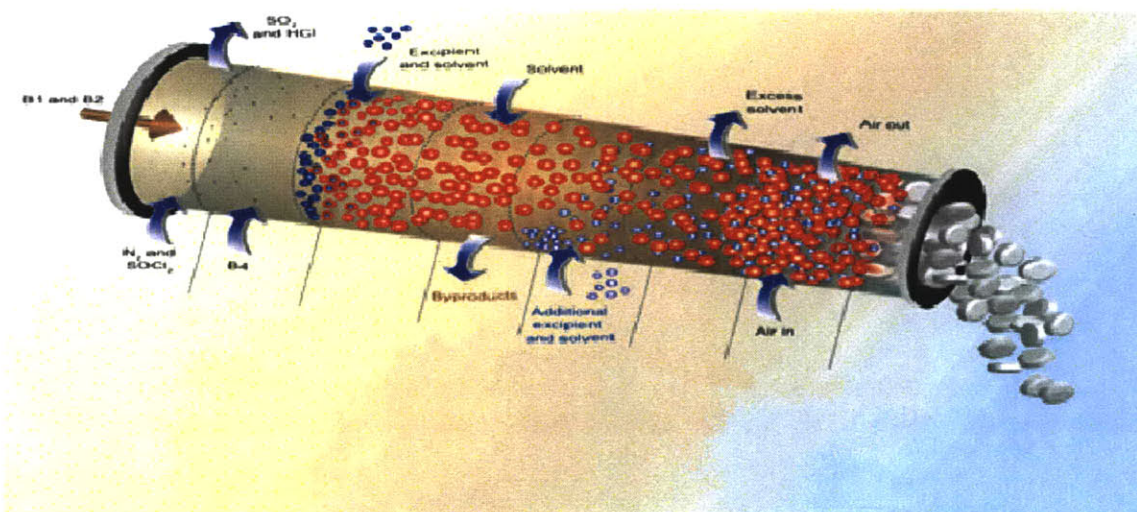
Figure 2 – Blue Sky Vision for a Continuous Process

2.3.1 Pilot Scale Continuous Process

Much of the basis for this thesis comes from the work done by the Novartis – MIT Center for

Continuous Manufacturing's developing a Red Line continuous process. Although the pilot

scale process has not yet been built, the lab scale reactions and separations have been validated

to the point where a material balance is available for the continuous process. In addition to the

material balance, a preliminary equipment configuration has been defined according to

throughput and the material balances requirements at the unit operation level. With this starting

point, it is possible to forecast a commercial scale continuous manufacturing process for the

purposes of comparison to the actual batch manufacturing process.

3 Hypothesis

A continuous manufacturing process for pharmaceutical products has the potential to reduce overall production costs. Using the case study of a commercial Novartis product with a given annual demand requirement, known batch production cost estimates, and a high level proposal for a continuous production process, I will show that the following improvements can be expected:

- Lower capital investment costs and facility footprint.
- Lower operating costs.
- Lower total product cost
- Shorter throughput times.
- Lower working capital requirements.

4 Current State of the Production Process and Supply Chain

4.1 Overview of the Current Structure

The supply chain structure of Novartis Pharma TechOps consists of multiple facilities located across multiple geographic regions. The supply chain path for a product depends on the production volume, the process technology, and the number of steps required. An example product may require Drug Substance synthesis steps taking place across two or three facilities followed by the Drug Product formulation steps at another facility. The final process step could be a packaging operation taking place at yet another location. Most products also pass through a safety stock location in a warehouse at the interface of the Drug Substance and the Drug Product steps.

4.1.1 Batch Production

An integral aspect to the current production system is defining a batch of material. Process steps, which may consist of a series of unit operations, have a defined recipe stating the quantity of starting materials and targeted output materials. The individual unit operations follow a recipe that controls the process conditions applied to a specific batch of material. After processing is completed, quality control checks are performed according to specifications. By this approach, the integrity of a batch is verified and documented. This allows for traceability of materials in the event that a product is found to be contaminated or have adverse effects to customers. The paradigm of batch production and post production quality control is common to the industry in large part due to the fact that pharmaceutical products are regulated by government agencies.

The batch model does have some additional advantages. In an innovative company such as Novartis, the flexibility in process steps that a batch mode provides is important as new drugs are

being continuously developed. New drugs often require unique processing pathways, which can be simply accommodated by careful selection and ordering of the batch processing equipment already in place. Thus, no large structural rearrangement is necessary, which cuts down on equipment costs. These batch processes are also well understood, currently well optimized for the operations they perform and readily available for use as the equipment is already in place. Also, the scale up from lab scale is relatively straightforward conceptually, in that the batch processing equipment resembles the equipment used in the lab.

4.1.2 Chemical and Pharmaceutical Operation Split

As described in the overview of the supply chain structure, there is a physical split in the supply chain between the chemical and biopharmaceutical operations that produce the active pharmaceutical ingredient or drug substance, and the pharmaceutical operations that produce the drug product. In addition to the physical separation of facilities, these are also separate organizations within a firm such as Novartis. One reason for the separation is the nature of the physical processes taking place in each facility. A chemical operations facility consists of equipment designed to perform the unit operations required in chemical synthesis including reactions and separations. A pharmaceutical operations facility typically consists of equipment designed to perform the unit operations required in creating a drug product formulation including powder mixing and tableting. In addition to the different unit operation requirements, there is also a difference in the complexity of market requirements in a chemical operations facility as compared to a pharmaceutical operations facility. Drug substance produced in a single chemical operations site may satisfy the requirements for multiple pharmaceutical operations because the drug substance is essentially a raw material. Pharmaceutical operations must produce multiple dosage sizes, multiple combinations therapies, and serve multiple markets with different

packaging requirements due to language and labeling needs. For this reason the chemical operations facilities can typically take advantage of economies of scale in production that the pharmaceutical operations cannot. This complexity in the pharmaceutical operation also means that the pharmaceutical operations are typically more labor intensive from a direct labor and overhead perspective than are the chemical operations facilities in the same supply chain. Conversely the chemical operations facilities typically have higher fixed costs and are more capital intensive than the pharmaceutical operations.

In addition to the internal reasons for this structure, it is important to note that the regulatory environment also contributes to this structure. As the product flows through the supply chain, the level of quality control requested by the regulatory bodies increases. This means that the type of analytical equipment and support staff required onsite is often different for a pharmaceutical operation facility than for a chemical operation facility.

5 Approach

The approach taken in this thesis to estimate the costs of both systems, and consists of four basic steps.

1. Calculate the annual demand of drug substance required based on the forecasted annual demand of doses. For the batch process, translate the annual demand into a daily capacity requirement. For the continuous process, translate the annual demand into flow-rates requirements based on 24 hours by 7 days per week operation.

2. Perform a material balance based on the unit operation yields, process inputs, and waste streams. Combine this with the annual demand to determine batch sizes and unit operation flow-rates.

3. Size equipment at the unit operation level based on the batch size or flow rate and the residence time. At this point one should characterize the ideal throughput time for the batch and/or continuous process. Estimate the price for the unit operations equipment and support equipment. Estimate the total capital investment costs based on all costs required to design, build, and qualify all required facilities.

4. Estimate the operating components of the Total Product Cost. Estimate the annual material, ecology, and utility costs based on the material balance information. Estimate the direct labor cost based on the operating requirements of the facilities. Estimate the material handling cost based on the number of facilities required, warehousing requirements, and incoming material inspection requirements. Estimate the quality assurance cost based on the level of offline labor-intensive analytical requirements and documentation requirements. Estimate the overhead costs based on the organizational structure of the overall supply chain as well as the number of products produced in the

facility. The accuracy of these estimates is largely dependent on the level of detail available with respect to the facility process design.

5.1 Previous Work by MIT Practice School

Two previous business case analyses for comparison of a continuous process versus a batch process were performed by teams of students from the MIT Practice School within the Chemical Engineering department. These groups used the same approach described above, but did not include the Total Product Cost operating components such as overhead, quality assurance, and material handling. The previous groups also did not have the benefit of a defined continuous process with validated yields and a preliminary material balance. The results of this thesis are generally consistent with the work of the MIT Practice School (Alf, Barr, & Couling, 2008). One component explored by the Practice School reports is the comparison of a multipurpose batch facility with multiple dedicated continuous lines (Barr, Musolino, & Xu, 2008). From a practical perspective the multiproduct case is overly general and a better comparison requires a detailed understanding of the process requirements for each product.

6. Total Production Cost Model

The cost categories included in this comparison are based on the standard cost categories used by Novartis Pharma TechOps' internal cost accounting system (Brennan & Goerke, TechOps Finance Product Costing Overview, 2008). Novartis uses a calculation called Total Product Cost to set a cost on what they intend to produce. The Total Product Cost consists of Materials Costs and Processing Product Costs. Material Costs consist of price of materials from vendors and toll manufacturing fees. For this product Novartis did not charge any toll manufacturing fees; hence this is not included in the analysis. The Processing Product Costs include several costs categories associated with converting the materials from raw materials to finished goods. Table 1 list the Processing Product Cost categories and describes whether these are fixed or variable and direct of overhead costs.

Category	Direct or Overhead	Variable or Fixed
Utilities	Direct	Variable
Ecology	Direct	Variable
Material Handling	Direct	Variable
Direct Labor	Direct	Variable
Quality Assurance	Direct	Variable
Production Area Overhead	Indirect	Fixed
General Factory Overhead	Indirect	Fixed
Building and Equipment Depreciation	Direct	Fixed

Table 1 – Total Product Cost Categories

7 Business Case Analysis

The results of my analysis indicate that switching to a continuous process for the last four steps of a fifteen step process results in a 36% reduction on total production costs for the steps analyzed, which results in a 14% reduction in the total cost per tablet. Furthermore the throughput time of the four steps decreases by 90% and working capital requirements decreases by 90%. All absolute product costs in this analysis have been normalized in order to protect the confidentiality of Novartis' product cost information. The percentage improvements are based on the calculations made during the project utilizing actual Novartis product cost information. The cost components are broken down by the operational components and the capital investment requirements. The drivers of each cost category are discussed in more detail below.

In addition, the total production cost is estimated for the product assuming a continuous process is developed for a full fifteen step process. A methodology is developed from the more detailed analysis of the last four process steps and applied to the early process steps for a more complete comparison of a continuous versus a batch production process.

7.1 Continuous versus Batch Process

The primary structural change to the supply chain is a result of combining the chemical and pharmaceutical operations, which operate in separate facilities for the current batch process supply chain, into a single facility. In addition all unit operations are linked to allow for a continuous flow of material from beginning to the end of the process. Figure 3 illustrates the change to the supply chain for an integrated continuous manufacturing process.
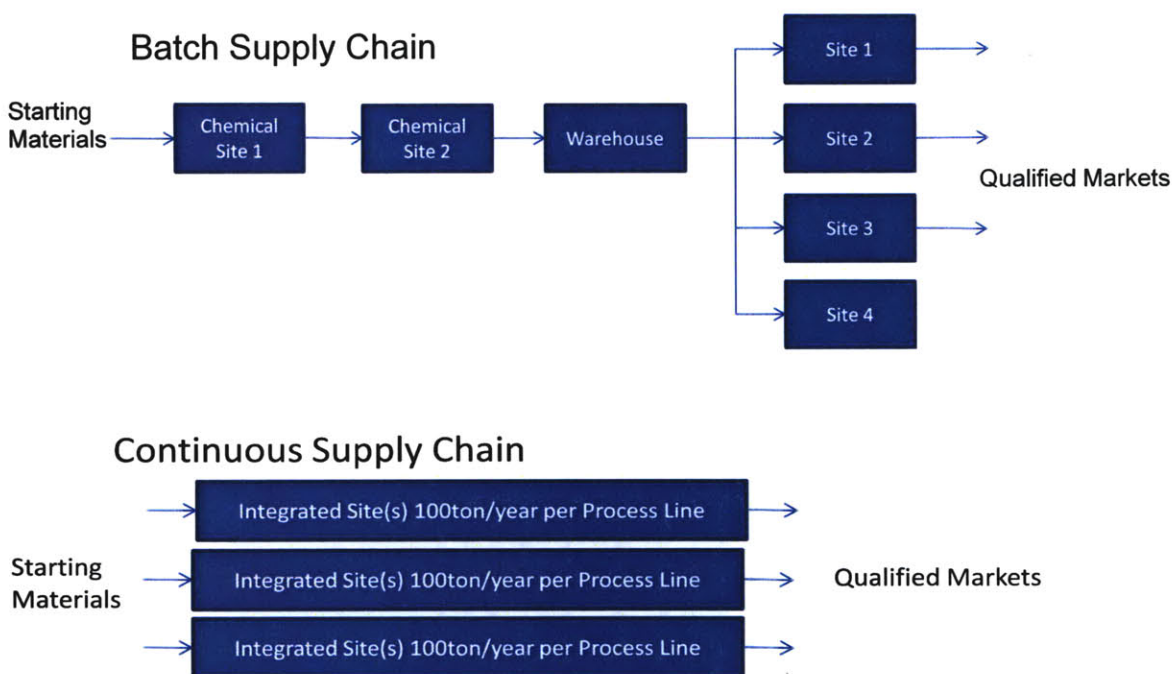
Figure 3 - Comparison of Batch and Continuous Supply Chain

Figure 4 is a high-level process flow diagram for the current batch manufacturing process. The chemical synthesis of the active pharmaceutical ingredient (API) involves three chemical reactions. The three reactions will be referred to as C10, C11, and C13 and they take place in a Novartis Chemical Operations site. Each reaction step also requires processing in addition to the reaction step in order to purify the desired product streams for the subsequent step. Additionally, the C14 step is a mechanical milling of the C13 intermediate product in order to obtain the

official API.   Once the desired API is created, it is converted to a coated tablet as the drug

product (DP) form. This takes place at one of multiple Novartis Pharmaceutical Operations sites.
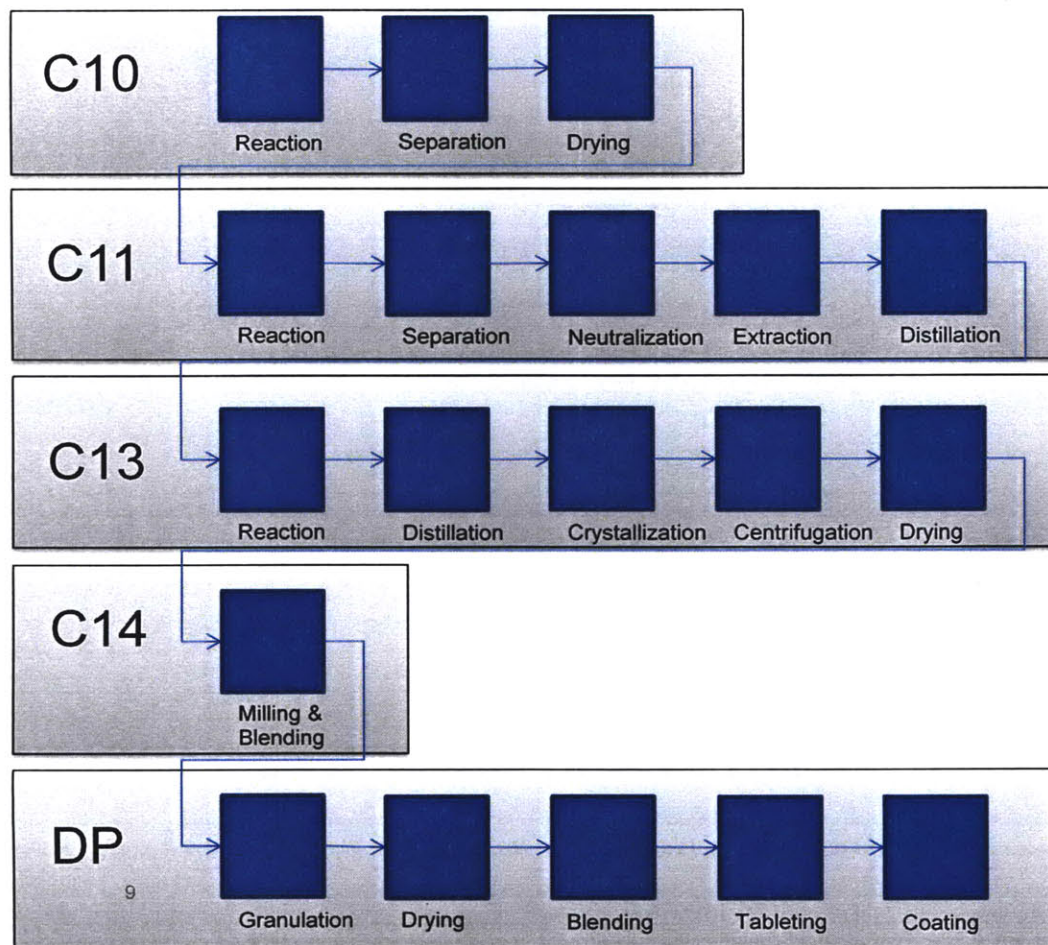
Figure 4 - Batch Process Flow Block Diagram

The C10 step involves a reaction step, which takes place in an agitated vessel. This is followed

by a solid/liquid separation step, which takes place in a nutsche. The final step is a drying

process that takes place in a paddle dryer to store the intermediate product as a dry powder

(Messer, Novartis Product X Base Suspension, 2009) (Messer, Novartis Product X Base, 2009).

The C11 step consists of a gas/liquid reaction step, which again takes place in an agitated vessel.

This is followed by a separation in a nutsche. Then an additional reaction and liquid/liquid

separation take place in an agitated vessel. The solution is then distilled and solvent is added to store the intermediate product stream in a solution (Messer, Novartis Product X Base Sol, 2009).

The C13 step consists of a reaction step, which takes place in an agitated vessel. This is followed by a crystallization step to purify the product stream, which takes place in a stirred vessel. The next step is a solid/liquid separation that takes place in a centrifuge. The final step is a drying process that takes place in a paddle dryer to store the intermediate as a dry powder (Neville, Novartis Product X Salt, 2008).

The C14 step consists of a mechanical milling of the C13 intermediate dry powder in order to achieve a rough powder size distribution prior to the DP step. This step takes place at a different Novartis Chemical Operations site from the C10, C11 and C13 steps (Clausen).

The DP steps consist of a series of mixing steps, which combine the API with the remaining formulation ingredients. The primary ingredients are first mixed in a wet granulation vessel. The mixture is then dried in a fluidized bed drier and sieved to obtain a targeted particle size distribution. The remaining formulation ingredients are then added in a blending vessel. The formulation is then converted to a tablet using a tablet press. The final step for the bulk drug product is a coating step, which takes place in a pan coater (Desset-Brethes & Leboulanger, PHAD000160A).

Figure 5 is a high-level process flow diagram for the new continuous manufacturing process. The process flow is grouped with highlighted chemical reaction steps as they correspond to the batch process in terms of chemical reactions. The process equipment is completely different and the C14 step is eliminated in the new process flow. The DP is still a coated tablet, however the core of the tablet is now based on a thin film polymer material rather than a compressed powder.
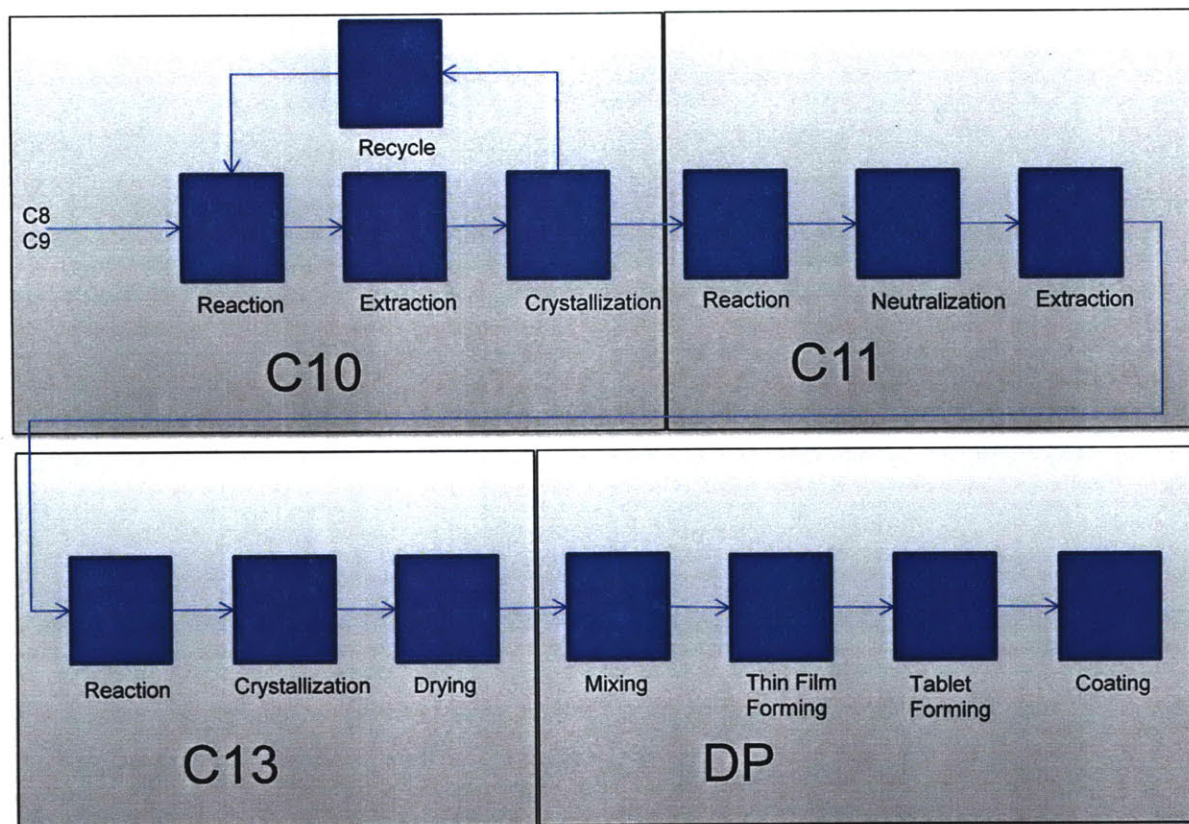
Figure 5 - Continuous Process Flow Block Diagram

The C10 step utilizes new reaction chemistry with a shortened reaction time. This allows for a reasonable residence time and reactor volume for the flow chemistry. The reactor is a combination of glass plate micro-reactors for efficient mixing and a static mixer tube to achieve the required residence time for the reaction to reach completion (Foley & Heider, 2009). A countercurrent liquid/liquid separation is used to split one of the excess starting materials. The other excess starting material is recovered during a continuous crystallization process. The crystallization process is carried out in a series of agitated vessels. One recycle loop is required in this process segment in order to improve the overall material yield and process economics. The recycle loops primary equipment is a falling film evaporator used to separate the solvent material.

The C11 step involves a similar chemistry as the batch process, but replaces a gas phase acid reactant with an aqueous phase acid reactant. This short reaction can be accomplished in a tube reactor with sufficient volume to achieve the target yield. A neutralization process follows with an aqueous base mixed in a micro-mixer reactor with short reaction time limited by mass transfer. The product stream is then purified by separating the salt in aqueous phase from the product with an organic solvent. This separation occurs in a countercurrent liquid/liquid extraction column.

The C13 step involves the salt formation step, which takes place in an agitated vessel running in a continuous mode. The agitated vessel is a relatively small sized based on the product stream flow-rate and the residence time requirement. The next steps are a continuous crystallization, filtration, and drying required to achieve a pure product stream. All of this equipment is based on standard designs but adapted for continuous flow and lower throughput rates of a continuous system.

The DP steps result in a coated tablet, but use a very different process and materials to achieve the end product. The dry powder is dissolved and blended with a soluble medical grade polymer material. This mixing takes place in extruder type equipment capable of achieving high uniformity with a low internal volume. The liquid is then transformed into a tablet and coated using a continuous coating process.

The analysis compares both the operational and investment costs for the Novartis standard

product costing categories. In addition the analysis examines the impact on throughput time and

working capital. In order to estimate costs I use an annual demand of 300 Tonnes of active

pharmaceutical ingredient with a 50% drug loading. This annual demand is based on actual

demand requirements for this product and the capacity for the primary batch chemical production

facility. (Brennan, Novartis Product X Demand Forecast, 2009) (Neville & Roland, ChemOps

CH - PU WSH, 2009) The batch sizes were taken from the actual production process and used

to calculate the number of batches per year at each step in the process. For the continuous

process, the annual demand is translated into an hourly volume flow-rate through each unit

operation. This calculation assumes around the clock operation with four weeks of shutdown

during the year. The last three chemical synthesis steps of a fifteen-step synthesis and the bulk

drug product formation are the steps that are considered for the continuous flow analysis. Table

2 describes how the annual demand translates to batch sizes and the number of batches as well as

continuous material flow-rates at multiple stages of the process.

	Batch Size	Number of Batches	Continuous Flowrate
C10	943 kg	406	19 kg/hr
C11	1115 kg	274	12.6 kg/hr
C13	707 kg	431	12.5 kg/hr
DP	257 kg	2334	25 kg/hr

Table 2 - Comparison of Batch Size and Continuous Flow-rate

The continuous process as described in the previous section was sized based on some of the

commercially available equipment and the annual demand. For this case the current batch

production capacity was replaced by three parallel continuous lines, which are capable of 100

metric tons per year of drug substance equivalent production. It is possible that further

reductions in building footprint and equipment investment costs are possible by scaling up the equipment. Three reasons to keep the continuous process lines this size are avoiding scale-up issues from development to production, risk mitigation with parallel production lines, and potential for a distributed production network. Section 7.3, which discusses capital investment costs, is based on three parallel lines for the continuous production process.

7.2 Analysis of Operational Costs

The operational costs of the continuous process are driven by the material balance of the process, the layout of the plant, and the operating strategy of the plant. The material balance and process conditions drive the material, ecology, and energy costs. The integrated structure of a continuous process and the control strategy drives the labor, material handling, QA, and overhead costs. All costs reported refer to the cost per kg of DS equivalent in a 50% drug load coated tablet form.

The comparison of the batch and continuous process operation costs are outlined in Table 3. The absolute costs are a normalized to a 300 mg tablet that cost CHF 1.00 to produce in the current batch process.

Category	Batch Process (CHF/kg DS)	Continuous Process (CHF/kg DS)	Percent Improvement Batch to Continuous
Material	426	309	27%
Utilities	19	13	31%
Ecology	26	19	25%
Material Handling	82	36	56%
Direct Labor	178	89	50%
Overhead	171	137	20%
Quality Assurance	115	32	72%

Table 3 - Summary of Operation Costs for Batch and Continuous Processes

7.2.1 Material Costs

When comparing the material costs of a continuous process versus a batch process there are two primary drivers of cost reductions. The first is an improved reaction pathway that is enabled by the continuous process and the second is an improvement in reaction yields due to tighter process control from improved heat and mass transfer (Weiler & Junkers, 2009) (Lavric & Woehl, 2009). In this case the continuous process achieves a 24% reduction in material cost through a new reaction pathway in the C10 through DP steps. The new pathway achieves a higher overall yield than the batch process. This pathway reduces cost by elimination, reduction, or replacement of solvents. Pilot scale production will be required to validate the improvement in yields due to improved heat and mass transfer properties and better control of reaction conditions. Tighter control of reaction conditions can yield fewer side products thereby simplifying or eliminating separation and purification steps. Companies developing continuous flow micro-reactors have tested several reaction types with demonstrated improvements in reaction yields (Braune, et al., 2008).

7.2.2 Ecology and Utilities

The ecology cost is calculated based on the material balance and category of waste stream produced. The primary drivers of ecology costs for this product are water treatment and incinerated waste. The continuous synthesis pathway eliminates or replaces some solvent requirements. This combined with an improvement in yield reduces the waste streams that require treatment. For this product and process the reduction in ecology cost is 25%. The utilities costs are driven by three main components; the unit operation process temperatures, the unit operation mass flow-rates, and the building footprint HVAC. As the footprint requirement is decreased by 60%, the reduction in HVAC energy requirements represents the largest decrease

in the utility costs. The improved reaction pathway does, however, require different process temperatures during two of the process steps. In the first step the chemistry is run at a higher temperature but with less solvent mass to heat and with a reaction time that is $1/10^{th}$ of the batch process. In the second step the chemistry is run at ambient conditions in a very short reaction time. The overall decrease in utilities cost is 30%.

7.2.3 Labor Costs, Material Handling, and Overhead Costs

These four operational costs were grouped together because the improvements are largely due to the structure of a fully integrated continuous process. If individual steps in a process are transformed to continuous operation, then, with the exception of QA, these cost are not expected to decrease, and in some cases may increase.

To model the labor costs I first determined that the primary tasks for the new plant are control room operations, equipment repair, and preventative maintenance (Roberge, Zimmermann, Rainone, Gottsponer, Eyholzer, & Kockmann, 2008). Based on the projected number of technicians required to support a continuous line and the need to support 24x7 operations, I calculated a total headcount requirement to be 50% less than batch for the continuous process.

The material handling activities between process steps and between sites will be eliminated. Purchasing, receiving raw materials, and shipping finished product would be the only remaining material handling steps in the process. This results in a 55% decrease in material handling costs.

Overhead costs cannot be predicted with an exact model due in large part to unknowns regarding how much support staff and site services would be required for an integrated process. At a high level, the reduction of plant footprint and a reduction in the number of facilities in the supply chain should reduce overhead costs. On the other hand a company's supply chain strategy will

largely influence the potential for overhead gains. The footprint and scalability of a continuous process gives a company the flexibility to have multiple smaller regional plants or fewer larger centralized plants. For this process comparison I projected a 20% decrease in overhead costs.

7.2.4 QA Costs

A continuous manufacturing process running at steady state requires a process characterization and a robust process control system utilizing PAT in order to meet all regulatory requirements. The traditional post process testing currently in place for most products is highly labor intensive and insufficient to control a continuous process (Swaminathan & Zega, 2005). Real time release of a Novartis product manufactured in batch processes has been demonstrated by application of PAT tools with a demonstrated elimination of 90% of labor costs. The total QA costs for the continuous process are estimated to be 72% less than the current batch process.

7.3 Analysis of Capital Costs

In this example a supply chain network consisting of one chemical plant and four pharmaceutical process lines is replaced by a single production facility. In the chemical synthesis steps, large vessels used for reactions, separations, and crystallizations, are replaced by micro reactors, continuous extraction, and continuous crystallization equipment. In the pharmaceutical steps, blenders, fluidized bed dryers, and tablet presses are replaced by new equipment such as thin film forming coaters and thin film cutting and forming equipment. This equipment is able to meet the annual output requirements with a 60% reduction in building footprint. The continuous process does require additional investment in process analytical technologies (PAT) in line with Quality by Design (QbD) principles in order to achieve real time product release. The investment costs were annualized according to Novartis cost accounting practices in which equipment investments are depreciated with a 15 year straight line method (Brennan & Goerke, TechOps Finance Product Costing Overview, 2008). Again, the absolute costs in this section are normalized to a 300 mg tablet that cost CHF 1.00 to produce in the batch process.

The equipment costs are driven by three main factors: equipment sizing, number of process operations, and process equipment complexity. The equipment is dramatically smaller than batch equipment required to achieve the same annual output. The primary equipment components such as micro-reactors have a relatively high cost to equipment space ratio compared to standard batch equipment. The larger equipment cost decrease comes from a decrease of support equipment costs due to smaller pumps, heat exchangers, and makeup tanks (Achermann, 2009). The continuous process in this example reduces the number of process unit operations from 19 to 14. This is achieved by elimination of some steps required for separation and drying of intermediates. The continuous process also eliminates unit operations at the

interface between chemical synthesis and pharmaceutical formulation steps. The process does require additional analytical and control system investments in order to fulfill all requirements for real-time release consistent with QbD strategies (Pellek & Van Arnum, 2008). A large number of these costs would also be required to achieve real time release goals for a batch process; however I observe these are required for the continuous process. Table 4 outlines the basic equipment and support equipment requirements by process step.

Step	Batch Equipment and Support Costs		Continuous Equipment and Support Costs	
C10	CHF	6,918,000	CHF	10,393,200
C11	CHF	8,201,700	CHF	5,352,000
C13	CHF	19,561,200	CHF	11,116,500
DP	CHF	22,624,808	CHF	15,060,000
Total	CHF	57,305,708	CHF	41,921,700

Table 4 - Batch and Continuous Primary and Support Equipment Costs

Costs for installation, engineering design and qualification are expected to remain similar to the batch process as a percentage of the total investment costs. The costs due to additional complexity are offset by the smaller equipment size. In addition, I expect some economies of scale due to parallel scale-up. The cost for central facilities and HVAC are reduced relative to the cost of the primary equipment due to the lower peak demand requirements and small footprint of the facility. The operational and performance qualification is expected to double as a percentage of the total investment costs due to the increased complexity of control systems and testing of integrated equipment.

Table 5 and Table 6 show the additional equipment related and building related costs. Table 5 details the equipment installation and qualification costs as a percentage of the basic equipment and support equipment costs. For example, to calculate the piping cost for the C10 process one would multiply the C10 Batch Equipment and Support Cost (CHF 6,918,000) by the Piping

Factor in Table 5 (50%) for CHF 3,459,000. Table 6 details the building and facilities related costs as a percentage of the Equipment and Support Equipment costs. The same method is used to calculate the Additional Building Related Capital Costs. The total Capital Costs for the process are calculated by summing the Additional Building Related Capital Costs and the Additional Equipment Related Capital Costs.

Additional Equipment Related Capital Cost Factors

Cost Area	Batch	Continuous
1. Erection	5%	5%
2. Piping	50%	50%
3. Electrical	15%	15%
4. Automation HW + Instruments	25%	40%
5. Automation SW + Tests	40%	60%
6. Engineering	87%	87%
Total	222%	257%

Table 5 – Additional Equipment-Related Capital Cost Factors

Additional Building Related Capital Cost Factors

Cost Area	Batch	Continuous
1. Building	150%	50%
2. HVAC	60%	30%
3. Process Infrastructure	45%	45%
4. Other	50%	50%
Total	305%	175%

Table 6 - Additional Building and Other Capital Cost Factors

The most significant cost difference from the batch to the continuous process from Table 6 is the building related space costs. The building footprint requirements of a continuous plant are 60% less than that of the batch process. This is driven by a reduction in the space required by the primary process equipment and the support equipment as well as an elimination of warehouse space required for intermediate material storage. The total office space requirement remained constant for this analysis. Table 7 outlines the building space requirements by category.

	Combined Batch Footprint (m^2)		Continuous Footprint (m^2)	
Process Equipment	5,940	49%	1,000	25%
Infrastructure Space	2,454	20%	1,000	25%
Walk Areas	1,360	11%	400	10%
Warehousing/Storage	1,282	10%	422	11%
Office	1,188	10%	1,188	23%
Total	12,224		3,950	

Table 7 - Batch and Continuous Building Footprint Summary

Table 8 shows the overall comparison of the capital investment requirements for the batch manufacturing process and the continuous manufacturing process.

Total Capital Investment Batch Process	Total Capital Investment Continuous Process	Percent Improvement
CHF 572,541,329	CHF 338,203,315	41%

Table 8 – Total Capital Investment Requirement and Improvement

7.3 Analysis of Working Capital

The continuous process achieves a dramatic reduction in throughput time from intermediate starting material to bulk drug product. This directly reduces the level of working capital required. In addition a safety stock inventory location can be eliminated further reducing overall working capital. The Throughput Time and Working capital improvements are highlighted in Table 9 and Table 10.

Throughput Time	Residence Time	QA + Storage Time	Transport Time
Batch	17 Days	30 Days	5 Days
Continuous	3 Days	2 Days	1 Days

Table 9 - Batch and Continuous Throughput Time

Working Capital	Pipeline Inventory (Days of Inventory)	Safety Stock (Days of Inventory)	Total
Batch	52	49	101
Continuous	6	6	12

Table 10 - Batch and Continuous Working Capital

The continuous process developed for this product achieves shorter throughput times for three reasons. The first is a decrease in reaction times and separation step residence times. This is in part due to the reaction chemistry that is chosen and in part due to the improved heat and mass-transfer characteristics, which allows for shorter process times within unit operations. The second reason is the elimination of process steps. One example is the elimination of a drying step required to store an intermediate in a stable condition. The final factor is the elimination of material holdups between process steps and transportation requirements between sites. Each process step has a buffer to hold batches between process steps. For the product considered here,

this buffer time is low because the production takes place in a plant dedicated to this product. Two site-to-site shipping steps as well as a warehousing operation are eliminated by integrating the chemical synthesis and drug product formation,. The throughput time improvement for this process is a decrease from 52 days (Hafeli, 2008) to 6 days.

The throughput time improvement has a corresponding impact on the working capital required at a steady state production level. With the steady state production assumption one can use Little's Law (I= R*T, I-Inventory in the System R-Steady State Demand T-Throughput Time) to calculate the inventory in the system. Reducing the throughput time from 52 to 6 days would lead to a decrease in working inventory of 90%. In addition to the decrease in working inventory, a benefit of the continuous process is the elimination of a safety stock step at the interface of chemical synthesis and drug product formation. In order to achieve desired customer service levels, Novartis includes safety stock in the manufacturing supply chain. The customer service level goal, process lead-time, and demand variability determine how much safety stock is held at certain steps in the process. For the batch process there is a safety stock target of 49 days of inventory at the interface between chemical synthesis and drug product formation. This safety stock inventory is shifted to finished product inventory. Because the lead-time is reduced by the continuous process, the level of the safety stock added to finished product inventory would be reduced to 6 days of inventory.

7.4 Application of Cost Model to Additional Process Steps

The in depth analysis in the previous sections provides a framework for estimating the total production costs of future products. This methodology applies to an integrated continuous process as outlined in the introduction. The following stepwise approach is not significantly different from cost estimation for a batch process, however general cost estimation factors derived from the detailed case example are applied to the stepwise approach.

1. Perform a mass balance to derive the material costs. The continuous process may allow for improved synthesis paths or better yields, but these must be validated at the lab or pilot scale.

2. Estimate the equipment and building depreciation costs. This should be done in detail based on a process flow diagram when possible. If the detailed equipment list for a continuous process in unknown, one can use a general approximation method to calculate the equipment cost. A simple approach is taking the number of process steps (defined as chemical conversion steps) and multiplying by a general factor.

3. Determine the labor headcount required to run a continuous process line. The labor model utilized in this approach is having a dedicated control room headcount and headcount used for equipment maintenance and rapid equipment failure response. The total headcount per shift can be estimated at a minimum of 4 per process line and adding an additional headcount for every two process steps worth of equipment. The plant is expected to run in a 4 shift operation model for 24x7 production. The local labor rate is applied as appropriate.

4. Material handling, QA, utilities, and ecology were each largely derived from the material balance and factory footprint. Based on the case example, these costs did not change

significantly as a percentage of the total costs versus a batch process with the exception of QA

costs, which are reduced by a half. Table 11 gives the percentage of total TPC for each

component. Also included here are the overheads. These are difficult to estimate and are

dependent on overall operational strategy of the organization.

Category	Percentage of TPC
Material Handling	1.7%
Quality Assurance	2.0%
Utilities	2.5%
Ecology	4.8%
Production Area Overhead	4.2%
General Factory Overhead	4.0%

Table 11 - Continuous Cost Estimation Factors

Summing each component can give a high level approximation of the product TPC when using a

continuous manufacturing process. This estimate is at best in the ± 30% accuracy range as

determined by a sensitivity analysis of key factors that drive cost. Chemical yield accuracy,

equipment cost accuracy, and equipment installation cost accuracy are the factors that contribute

to the overall cost estimate accuracy. The overall benefits come from the opportunity to pursue a

more efficient overall chemical synthesis, elimination of intermediate steps and material

handling, a less labor-intensive process, better QA systems, and a smaller factory footprint.

By using this approach I have estimated the total product cost by extending a continuous process
to the previous 10 production steps. The material costs are estimated to decrease by 5%, which
is a conservative estimate based on the detailed analysis in the previous section. The additional
total production cost components are estimated using the table of factors described above. For
this product material costs are higher than average, even for the early synthesis steps and

therefore the overall gains are limited by the improvement in material costs due to yield improvement or alternate synthesis pathways.

Table 12 provides a summary of the total product cost per kg of DS in a 50% drug load of a coated table assuming a continuous production system for the 14 step chemical synthesis and drug product formation.

Category	Improvement
Material	21%
Direct Labor	50%
Bldg & Equip	33%
Material Handling	56%
Quality Assurance	64%
Utilities	21%
Ecology	29%
Production Area Overhead	20%
General Factory Overhead	20%
Total	29%

Table 12 - Batch and Continuous Total Production Costs for Full Process Flow

8 Conclusions

8.1 Key Findings and Specific Recommendations

When considering a product that has an annual production level of 300 tons of drug substance

per year and a 50% drug load, continuous manufacturing presents an advantage over batch

manufacturing in several areas. Table 13 highlights the comparison results for the conditions

presented in this analysis. The total production cost incorporates an annualized capital

investment as well as all operating costs. The working capital improvement also reflects the

throughput time of the process. These results support the hypothesis that there is a positive

business case for continuous manufacturing processes based on an improvement in capital

investment costs and facility footprint, operating costs, Total Product Cost, throughput times, and

working capital requirements.

	Percent Improvement C10 – DP	Percent Improvement Full Process
Total Production Cost 150mg Tablet	21%	30%
Total Production Cost 300mg Tablet	19%	28%
Capital Investment	50%	42%
Working Capital	91%	90%

Table 13 – Key Parameters for Continuous versus Batch Comparison

8.2 Questions for Further Research

Additional research should consider the case for other products with different annual production volumes and number of products. **Error! Reference source not found.**highlights the fact that for a company such as Novartis, product volumes requirements vary widely. The advantage often cited for batch manufacturing is the flexibility to handle low volume products by running campaigns for many products using the same equipment. Further research could examine the business case of a multipurpose batch facility with a facility producing multiple products on low volume dedicated continuous process lines.
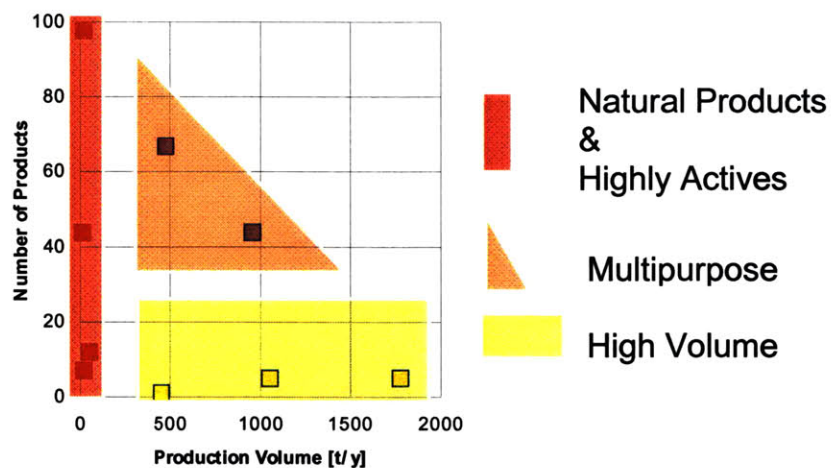

Figure 6 – Annual Production Volume for Novartis Product Portfolio

8.3 Limitations of Analysis

The conclusions of this thesis are limited to volume range and greater accuracy of estimates can be obtained by a refinement of the cost estimations. This analysis covers a range of active pharmaceutical ingredient volume of 100 – 300 tons per year. Furthermore, both the batch and continuous processes were defined as dedicated to one product. As the volume of production scales to less than 100 tons per year, the conclusions of this thesis may not apply. Dedicated batch equipment is expected to lose economies of scale more quickly than continuous equipment. On the other hand, products with lower annual production volumes are typically produced in a plant with mixed use equipment.

The accuracy of cost estimates for continuous equipment and a plant designed for continuous will improve as equipment design requirements are refined and plant automation and infrastructure is designed in detail. Collaboration with equipment vendors is required to refine equipment designs and obtain better cost estimates. A detailed engineering plant design is required with piping requirements, automation and instrumentation requirements, and support infrastructure.

8.4 Final Comments

The outlook for continuous manufacturing of pharmaceuticals is quite positive despite some barriers to implementation. Many of the process equipment technologies described in this business case are available today. Close partnerships between pharmaceutical manufacturers and equipment suppliers should be able to close the gap on remaining technologies. Replacing existing capital investments with new technologies is perhaps the largest barrier to implementation. This requires more than a simple business case for the new investment. It requires a change to the skills and structure of the current manufacturing organization. Furthermore, for wider transition to continuous manufacturing as the standard for the supply chain, a toolbox of process technologies and reaction chemistries must be developed to support a wide variety of active pharmaceutical ingredients and drug product formulations.

It is likely that a pilot line process could be running in three to five years based on one to two years of additional technology development for the process described in this report. Most capital projects require two years from start of design work to process qualification. This line should provide valuable learning for additional process lines. Novartis should focus on developing a continuous process for new, higher volume products first and then converting existing high volume products where the business case makes sense. A realistic time horizon for implementation of new of products and processes to continuous production in five to ten years is envisaged. The business case supports this transition as technology, regulatory understanding, and organizational skills evolve.

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