Feature-Based Investment Cost Estimation Based on Modular Design of a Continuous Pharmaceutical Manufacturing System

By

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Abstract

Previous studies of continuous manufacturing processes have used equipment-factored cost estimation methods to predict savings in initial plant investment costs. In order to challenge and validate the existing methods of cost estimation, feature-based cost estimates were constructed based on a modular process design model. Synthesis of an existing chemical intermediate was selected as the model continuous process. A continuous process was designed that was a literal, step by step, translation of the batch process. Supporting design work included process flow diagrams and basic piping and instrumentation diagrams. Design parameters from the process model were combined with feature-based costs to develop a series of segmented cost estimates for the model continuous plant at several production scales.

Based on this analysis, the continuous facility seems to be intrinsically less expensive only at a relatively high production scale. Additionally, the distribution of cost areas for the continuous facility differs significantly from the distribution previous assumed for batch plants. This finding suggests that current models may not be appropriate for generating cost estimates for continuous plants. These results should not have a significant negative impact on the value proposition for the continuous manufacturing platform. The continuous process designed for this project was not optimized. Therefore, this work reiterates that the switch to continuous must be accompanied with optimization and innovation in the underlying continuous chemistry.

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Chapter 1. Introduction and Project Background

1.1 Introduction

The pharmaceutical industry is currently facing a number of challenges, including pricing pressure and an increase in regulatory scrutiny over product quality. In order to address these challenges, many firms have invested in innovative process technology. By implementing innovative technologies including process analytical technology (PAT), novel unit operations, advanced material handling systems, and real-time product release, firms hope to improve the performance and compliance of their manufacturing organizations.

Continuous manufacturing systems have the potential to be the next great leap forward in pharmaceutical manufacturing. In contrast to conventional manufacturing systems, in which large batches of chemical and drug product intermediates are produced, in continuous systems materials will flow continuously from operation to operation. Various economic studies have predicted continuous systems that will require less initial investment, lower operational expenses, and decreased throughput time relative to conventional batch manufacturing. The potential for order of magnitude improvements and savings has spurred investment in continuous manufacturing.

Once only conceptual, continuous systems now exist in various developmental stages across the industry. Fully integrated continuous manufacturing systems, though not yet a reality, can now be envisioned and designed in a more robust way. It is clear that these systems will operate completely differently from conventional plants. In order to justify additional investment in development of these systems, there is a need for development of financial models that are sensitive to the fundamental operational differences between batch and

continuous plants. This will identify the greatest opportunities to create value via the implementation of continuous processing.

This thesis proposes an alternative, feature-based, methodology for estimating capital investment costs for continuous manufacturing facilities. The methodology combines relatively detailed design work with cost estimates based on the outputs of the process design. In order to pilot the methodology, cost estimates are generated for a model continuous process and compared with estimates for a comparable batch plant. Total cost estimates are presented, as well as results segmented based on unit operation and cost area. Throughout the thesis, financial figures and design work has been disguised, but ratios and non-financial data are presented as found.

Based on this analysis, the continuous facility seems to be intrinsically less expensive only at a relatively high production scale. Additionally, the distribution of cost areas for the continuous facility differs significantly from the distribution assumed for batch plants. This finding suggests that current models may not be appropriate for generating cost estimates for continuous plants. Further work should therefore be done either to define and validate a more realistic cost estimation methodology, or to develop an alternative framework for evaluating investment decisions for this technology platform. To this end, several opportunities for further investigation are proposed.

1.2 Project Background

In 2007, MIT and Novartis entered into a research partnership to develop new continuously operated technologies for pharmaceutical drug substance and drug product manufacturing. Early work for this collaboration focused on the technical development of new continuous unit operations. Current work streams include ongoing work to develop individual unit

operations as well as the integration of sequential unit operations into a functioning continuous manufacturing system. In parallel with this development work, several studies have been issued comparing the economic benefit of continuous vs. batch processing. (Wilburn, 2010)[1] These studies have found continuous manufacturing to be favorable based on a variety of advantages, including reduced investment cost, improved yields, cheaper raw materials, and lower labor costs.

Previous studies report a 35%-40% decrease in continuous plant investment costs relative to batch. There is internal concern within Novartis that the cost estimation methods developed in previous studies may not be appropriate for justifying additional investment. These concerns stem largely from the fact that the equipment factors proposed were developed for batch plants based on many years of constructing batch plants. Continuous plants are expected to operate differently than batch plants, so the existing equipment factors may not be appropriate. Additionally, because many of the proposed continuous process equipment are newly available or unavailable at commercial sizes, there is significant uncertainty regarding their cost. This implies significant uncertainty in the resulting estimates even if accurate scaling factors are assumed.

In order to address these concerns, an alternative cost estimation methodology has been developed as part of a student internship project. The new methodology calculates investment costs based on design of the main process equipment as well as explicit estimates for various secondary cost areas. This study is conceptually similar to previous work in that it makes a financial comparison between a model batch and continuous

[1] Among others. Additional economic studies have been developed as part of this collaboration but are not in the public domain.

process. However, rather than test the economic benefit of continuous manufacturing, it has been designed to provide internally credible cost findings for a continuous system.

The model chemical process was not optimized for continuous manufacturing. In fact, an effort was made to model a continuous process that was a "direct translation" of the batch chemistry, which may not be the optimal process design strategy. Therefore, the results presented here should be interpreted as instructive primarily towards the development of more robust financial models.

1.3 Overview

The thesis is organized into several chapters. First, a brief literature review is presented, providing some technical context for this work. Next, a discussion of the problem statement and further project context is presented. Then, both the design model and cost model are described in detail. Results are then presented, followed by interpretation of these results, reflections on the process, and potential opportunities for further investigation.

Chapter 2. Technical Background and Literature Review

2.1 Manufacturing in the Pharmaceutical Industry

Production of pharmaceuticals comprises of upstream ("chemical") and downstream ("pharmaceutical") processing steps. During the chemical synthesis, raw materials are combined and purified via a series of chemical unit operations. This generally includes reaction steps, where chemicals are combined to form a new product, and isolation steps, in which the desired product is separated from unwanted solvents, catalysts, or impurities. Most unit operations are performed in large tank reactors. Materials are transferred between reactors via pumping or physical conveyance systems. In addition to tank reactors, isolation often requires filtration and drying, which are generally performed using a pressurized filter and agitated dryer. Although the primary batch equipment is generally multi-purpose, most process steps require extensive custom installations to provide the required inlet and outlet flows, level of agitation, heat transfer, pressure, or surface area.

The transition between upstream and downstream occurs following the final isolation step. The output of this step is the pure drug or active pharmaceutical ingredient (API). Following isolation and release of the API, it is combined with other inactive ingredients and processed into a suitable dosage form. Traditional downstream process equipment includes solid mixers, granulators, dosage forming and coating equipment. Downstream equipment is generally multi-purpose, although customization is often required to provide product containment and product flow.

2.2 Continuous Manufacturing

"Continuous manufacturing" refers generally to a process that is operated over an extended period of time, in contrast to batch processes which are operated intermittently. Continuous manufacturing is common in other industries, but rare in pharmaceuticals. This has been variously attributed to differences in regulatory standards, production scale, standards for quality control, and process equipment flexibility.

2.2.1 Expected Benefits

The economic benefits of continuous processing have been proposed both internally at Novartis and in the academic literature. (Thomas, Transforming the Pharma Industry: Lean Thinking Applied To Pharmaceutical Manufacturing, 2006) (Fletcher, 2010) Benefits are expected to be seen for both chemical and pharmaceutical processing, and should be seen at both system and unit-operation levels. (Thomas, Batch to Continuous: Coming of Age, 2008)

Shifting a single unit operation to a continuous process can often provide significant benefits. Chemical operations can benefit from "intensified chemistry". (Schwalbe, Autze, Hohmann, & Stirner, 2004) That is, in many cases continuous reactions can be operated at higher temperature and concentrations than corresponding batch reactions. This leads to shorter processing time, higher yield, or reduction in solvent waste. Additionally, continuous processing has the potential to reduce to standing concentrations of various intermediate products. For intermediates which are too hazardous to store in large quantities, continuous processing is the only option. Similarly, in pharmaceutical manufacturing continuous processing is occasionally required to produce a stable final product. (Lakshman, Cao, Kowalski, & Serajuddin, 2008)

Continuous manufacturing is also expected to provide benefit at the system-level. Integrated continuous systems are predicted to be intrinsically more efficient, due to reduced investment costs, reduced operating costs, increased quality, decreased in-process inventories, and decreased throughput time relative to batch. (Wilburn, 2010) On the pharmaceutical side, there is speculation that developing and implementing continuous manufacturing for pharmaceutical dosage forms would provide a number of additional benefits. These include accelerated development timelines, faster regulatory approvals, and flexible dosage forming. (Novartis, 2010)

2.2.2 Recent Trends

Interest in continuous pharmaceutical manufacturing has spurred an increase in continuous process development. The feasibility and advantages of various continuous unit operations have been studied, and there is general optimism that in many instances continuous processes can be implemented to demonstrate discrete benefits. (Roberge, Zimmermann, Rainone, Gottsponer, & Eyholzer, 2008) In addition to advances on the academic side, there has been a recent increase in the capabilities of 3rd party equipment manufacturers and engineering service providers to support implementation of continuous projects.

2.2.3 MIT-Novartis Collaboration

Novartis has made significant investments in developing continuous manufacturing technologies. A research collaboration was initiated with MIT in 2007 for the purpose of developing new continuous unit operations. In addition to this basic research, MIT has also constructed a pilot facility that will produce drug product. As of late 2010, various individual unit operations have been developed and tested, and the MIT team is in the process of linking unit operations and integrating various plant systems.

Responsibility for the implementation of continuous manufacturing technologies at Novartis falls primarily to the Technical Operations (TechOps) organization, Novartis' pharmaceutical manufacturing and supply network. Development of continuous capability is a key part of TechOps' long term strategic vision, as shown in Figure 1. Continuous manufacturing is positioned as the natural next step in the organization's transformation towards improved process excellence and operational efficiency.

There are several major work streams for continuous manufacturing at Novartis. Collaboration with MIT is ongoing. Modular equipment skids that control process feeds and reactions have been developed in collaboration with an outside vendor. Several continuous units have been purchased for development use. A commercially available continuous drug product processing line has been evaluated. Conceptual design of a new continuous manufacturing plant has been initiated.

2.3 Cost Engineering for New Technologies

2.3.1 Type of Cost Estimates

Investment in new production facilities will always require an initial financial justification. Generally, this involves estimates of the capital and ongoing expenses for operating the plant, weighed against estimates of the additional revenue generated. As projects advance from concept to design, the requirement for accuracy in cost estimates increases. (Christensen & Dysert, 2005) The utility of the cost estimates also shifts from financial justification to budgeting and control. (Humphreys, 2005) This increase in required accuracy mirrors the increase in available engineering design information, which can be used to construct more accurate estimates.

Roy offers a general framework for classifying various types of cost estimates. (Roy, 2003) During early development, very little is known about the product and a first sight estimate (FSE) is the only number that can be produced. The accuracy of FSEs depends on the experience of the estimator and the level of product definition. Later during the design process, costs can be estimated based on appropriate product parameters. Parameter based estimates (PBEs) associate product parameters such as product mass or annual plant production volume to a cost function based on exiting data. Similarly, as more design information is available, this data can be used to generate more robust estimates. Feature-based estimates (FBEs) associate specific product features, such as number of edges in a machined part or reactor volume in a production line, with cost functions for each feature.

2.3.2 Cost Estimates for Pharmaceutical Plants

In the process industries, and in the pharmaceutical industry in particular, FBEs are commonly used to support project planning and cost control. (Hwang, 2006) To estimate the cost of a new plant, preliminary design work is done to identify unit operations, production volumes, and primary process equipment. Cost values for equipment are then calculated individually for each unit operation and multiplied by a scaling factor to account for other plant costs. (Perry & Green, 1997) The American Association for Cost Engineering (AACE) refers to such estimates as Equipment Factor Estimates, or EFEs. According to AACE, EFEs are accurate and appropriate "if the equipment factors are appropriate, if the correct adjustments have been applied, and if the list of process equipment is complete and accurate." (Dysert, 2003) It is unclear whether existing methods for continuous plants meet this general criterion.

Chapter 3. Problem Statement and Hypothesis

3.1 Detailed Problem Statement

Prior to significant expenditure on in a capital-intensive investment project, Novartis Engineering will typically construct an equipment-factored cost estimate. These EFEs are used for budgeting and for assessment of the business case for the project in question. Estimates for the primary equipment cost are based on an equipment list and standard cost information for each piece of equipment. To generate the total cost estimate, the primary equipment cost is adjusted by a series of scaling factors. Although costs are segmented into various cost areas, the total investment cost is a linear function of the primary equipment cost. To understand this, consider the primary equipment cost (PE), segmented costs areas (CA1 through CA7), and total investment cost (TC). The calculation method for each cost area is given as follows:

$$CA1 = 120\% * PE$$

$$CA2 = 206\% * CA1$$

$$CA3 = 78\% * CA1$$

$$CA4 = 19\% * (CA1 + CA2 + CA3)$$

$$CA5 = 15\% * (CA1 + CA2 + CA3 + CA4)$$

$$CA6 = 16\% * (CA1 + CA2 + CA3 + CA4 + CA5)$$

$$CA7 = 5\% * (CA1 + CA2 + CA3 + CA4 + CA5)$$

The total cost estimate is the sum of the individual cost areas, which can be reduced as follows:

$$TC = CA1 + CA2 + CA3 + CA4 + CA5 + CA6 + CA7$$

$$TC = 7.6 * PE$$

Accuracy of the total cost estimate is therefore extremely sensitive to uncertainty in the primary equipment cost, uncertainty in the assumed scaling factors, and to validity of the underlying model. This implies several clear drawbacks to applying this method to continuous plants. Because continuous plants are expected to operate differently than batch plants, the relative weight of each cost area may be different, and existing scaling factors may not be appropriate. Additionally, there is significant uncertainty in the cost of the main equipment, as the equipment for many continuous unit operations is less established on the commercial market. Finally, the relative sizes of each cost area may vary with production scale, making this type of model appropriate only across a narrow range of production scales.

Based on these reservations, there is a need for an alternative methodology for estimating investment costs. To this end, a model batch process was selected from Novartis' existing manufacturing portfolio. An analogous continuous process was designed, and cost estimates were prepared for both the batch and continuous processes. The primary goal for this project was to increase the credibility of estimates for the investment costs associated with continuous chemical plants. This is expected to remove a roadblock to the continued development of the continuous technology platform. This project is also expected to generate additional insights into the development strategy for continuous manufacturing.

3.2 Design Considerations

Because the goal of this exercise was to deliver an improved estimation methodology, rather than demonstrate the superiority of either batch or continuous scheme, care was taken to align the process and cost model design to be consistent with this goal.

3.2.1 Process Model Design

The continuous process was developed to be a literal translation of the batch chemistry. No new reactions, raw materials, or unit operations have been assumed. The project has not proposed any consolidation or elimination of unit operations. There has been no other optimization of the process chemistry. This design strategy is quite different from those proposed for previous studies. Historically, the shift from a batch to a continuous process has assumed numerous changes in the chemical synthesis in conjunction with the shift in operating method. The proposed approach isolates the intrinsic benefit of continuous processing.

Additionally, all unit operations have been reviewed to ensure that the analogous continuous process is feasible. For the final isolation step, no feasible analogous process could be identified, so that unit operation is designed to run in batch mode. Excluding unproven unit operations reduces model uncertainty and makes the cost estimates more credible.

Finally, care was taken to select the appropriate level of process design. The strategy for this exercise was to perform the process design at a greater level of detail and therefore provide more believable estimates. However, too much design work would deliver a model that was so process specific and labor intensive that it could not be easily applied to other systems. The work depicted here represents an appropriate balance between design depth and usability/transparency.

3.2.2 Cost Model Design

Project goals also influenced development of the cost model. A model was developed that would generate explicit estimates for various cost segments. These include direct

(equipment, installation, qualification) vs. indirect costs (building, infrastructure), and cost segmentation by unit operation, installation component, and equipment function. Flexible cost segmentation allows a broader range of analyses, as well as easier troubleshooting as underlying assumptions are refined.

Second, cost projections were developed to be collectively exhaustive of all potential investment costs. Each cost area was systematically reviewed to identify exactly what was spent so that all cost areas are at least nominally covered in the new model. This should avoid systematic errors associated with exclusion of key areas.

Finally, activity-based costing principles were used to develop directly comparable estimates for various cost areas. Indirect costs have been generated based on process requirements of a variety of common resources.

3.3 Hypothesis

We expect that if additional layers of process design are added to the basis for cost estimation, the resulting feature-based cost estimation methodology will provide robust, internally credible, and actionable cost estimates.

Chapter 4. Process Model Formulation

4.1 Process Model Structure

The model continuous process has been designed in a hierarchical, modular fashion, as shown in Figure 2. A process simulation is the fundamental design element, scales to an assumed production volume. The next element in the hierarchy is a series of process flow diagrams (PFDs). These PFDs detail the various continuous streams, secondary equipment, required utility connections, and basic control structure. The fundamental design element is a series of simple piping and instrumentation diagrams (P&IDs). These P&IDs specify the number of instruments and number of piping elements for each subunit. Each element in the process model provides design information that is fed into the process model.

4.2 Design of Primary Process Equipment

A series of analyses were performed to model the existing batch process and propose a new continuous process. Process parameters for the first reaction have been developed at Novartis. AspenPlus©, a commercially available software package, was used to model the initial reactions and calculate separation performance. Material flows, thermal loads, and reaction volumes were output from the process simulation and used to design and size individual primary process equipment.

4.2.1 Reaction 1

The first unit operation is a chemical reaction. One stream is a commercially available pre-mixed solution of a highly reactive compound. The second stream is an intermediate from upstream processing. The reaction is relatively rapid and exothermic, so good heat transfer is required to operate it safely.

For the continuous process, the unit residence time and composition of feed streams were optimized experimentally. These parameters were used along with an analysis of previously designed continuous equipment to specify the size and design of the required reaction system. Achieving precise stoichiometry for this reaction is critical, as small deviations in reactant concentration are expected to result in significant yield losses. Precise control is achieved through the use of metering pumps that supply each reactant solution at a tightly controlled flow rate. Additionally, a high reactor surface area is required in order to control the reaction temperature. The continuous reactor therefore includes internal baffling to achieve plug flow and good heat transfer.

In the batch process, this reaction is conducted in a jacketed stirred-tank reactor. The reactive reagent is charged over a period of several hours in order to control heat release and the formation of unwanted side products.

4.2.2 Reaction 2

In the second reaction, the reaction mass from the first reaction is mixed with a complex reactant solution. The second reaction is a multi-step dimerization of the reacting intermediate, requiring a long residence time and addition of a catalyst.

For the continuous process, the unit residence time and feed stoichiometry were determined experimentally. These parameters were used along with an analysis of previously designed continuous equipment to specify the size and design of the required reaction system. The column height and number of stages required is determined based on acceptable residence time distribution. Run continuously, this reaction is quite slow, requiring several hours of residence time to ensure completion. The reactant solutions are fed via metering pumps to a static mixer and then to an agitated vertical reaction column.

The column is relatively tall and requires a relatively large number of stage plates. There is vertical downward flow through the column, induced by gravity and by an axial pressure gradient. A baffled agitator provides radial mixing.

In the batch process, the second reaction is conducted in the same stirred-tank reactor as the first. The two reacting compounds are prepared as a solution and the catalyst is added at a controlled rate. Total process time is comparable to residence time of the continuous unit.

4.2.3 Quench

After the reaction mass leaves the reactor, it is quickly mixed with an acidic solution, quenching the reaction. After mixing, phase separation takes place rapidly, and the resulting phases are separated physically.

For the continuous process, the reaction mass is combined in a baffled tubular mixer with the quench solution. Residence time in the mixing unit is sufficient to achieve an emulsion. Phase separation is performed in an overflow-controlled settler tank with a residence time of around half an hour. Phase separation is rapid, with some impurities partitioning into the aqueous phase. Both the aqueous and organic phase are transferred from the settler tank at a metered rate.

In the batch process, the reaction mass is quickly transferred to a second jacketed stirred tank reactor. Acid is added under high agitation over a period of several hours. Agitation then stops and phase separation is allowed to occur. Complete phase separation takes approximately an hour, after which the organic phase is transferred out.

4.2.4 Wash

The wash step is similar to the quench. Water is added to the organic mass, mixed, and separated. Some residual impurities are removed in the aqueous phase.

The continuous train is similar to the quench train, with mixed feed streams, a static mixer, and a settler tank. The residence time for phase separation is again less than an hour.

In the batch process, the wash step takes place in the same reactor as the quench. Water is added, followed by agitation and phase separation.

4.2.5 Solvent Exchange

Following the quench, the product mass contains the crude product, process impurities, and a mix of solvents. Selective crystallization of the product requires a different solvent environment, so a solvent exchange is required. To achieve this, the reaction solvents are evaporated off, followed by addition of the crystallization solvents.

This solvent exchange is challenging to run continuously. Because the product mass must be continuously flowing, it must remain non-viscous and therefore total solvent concentrations must remain relatively high. In order to maintain this minimum solvent concentration, the solvent exchange is performed via a series of three falling-film evaporators. Each evaporator reduces the concentration to the minimum value, followed by mixing with heated crystallization solvent and an additional evaporation. The final outlet stream is the product mass in the crystallization solvent controlled at a high temperature to prevent premature crystallization. Total residence time of the evaporator system is estimated to be less than an hour.

Solvent exchange is significantly easier in the batch process. Because the solution does not need to be flowable at all times, there is no need for multiple additions of crystallization

solvent. To perform the batch process, the product mass is transferred to a third reactor, equipped with a top-mounted condenser. The product mass is heated until the process solvents are evaporated, and then mixed with a stream of crystallization solvent.

4.2.6 Crystallization

Selective crystallization of the product is the next isolation step. To achieve selective, quantitative crystallization of the product, the solution is cooled over a period of several hours using a linearly decreasing cooling gradient.

The continuous crystallization process replicates the batch cooling profile by passing the product mass through a series of stirred-tank reactors. This process has not been implemented experimentally, and there has been some internal debate as to whether it is technically feasible. We will assume so for the purpose of our analysis. There is a possibility that a quicker or more selective crystallization is possible due to improved process control, (Lawton, Steele, & Shering, 2009) but we will not make this assumption for our analysis. Transition between reactors is metered by control valves and does not require intermediate pumping. There are five reactors in total, all mounted on a single skid. The total residence time for the system is identical to residence time for the batch crystallization process.

The batch crystallization is conducted in a fourth reactor. The initial product temperature is relative high following the solvent exchange step, and the product solution is again cooled over a period of several hours.

4.2.7 Filtration & Drying

The cooled product slurry is then passed through a nutsche filter and dried in a paddle-drier. No continuous technology has been identified that will be able to operate this process, so for

the continuous system we assume this unit operation is conducted in a semi-batch fashion using identical equipment.

4.3 Process Simulation

With the primary process equipment designated, a process simulation was used to determine the flow rates and compositions of the various continuous streams. AspenPlus© was used as the simulation platform. The primary challenge of constructing the model is the assignment of physical properties to various non-standard compounds. The reactants and product are not present in Aspen's compound library. Therefore, physical properties from existing molecules deemed to be structurally or functionally analogous were used. We therefore expect some error in the simulated behavior of these species, specifically in their partitioning across various process solvents. Process information, including heating duties, stream sizes, pump duties, and requirements for heating and cooling fluids can be read directly off the Aspen sheet. The process model was constructed so that is was simple to calculate stream compositions for a variety of product output levels. This facilitated calculation of process requirements for various production scales. The process simulation is shown in Figure 3.

4.4 Process Flow Diagrams

In addition to the main equipment, secondary systems required to operate the process were identified. This included additional equipment for material handling, process control, and buffering, as well as requirements for heating and cooling utility connections, connections between equipment, and a basic strategy for process control. In order to specify these systems, process flow diagrams were constructed for each unit operation. The design

considerations for each secondary system were as follows. An example PFD is shown in Figure 4.

4.4.1 Material Handling Equipment

In order to run the process continuously, reactants must be staged and mixed prior to introduction into the continuous system. We assume raw material feeds are prepared daily and propose appropriately-sized tanks for this purpose. Additionally, scales and powder transfers systems are required for weigh and solid handling, respectively. Some reactants are stored off-site and pumped in to the process floor, which was not modeled explicitly.

4.4.2 Process Controlling Equipment

Various pumps and heat exchangers are required to maintain the appropriate flow rates, temperatures, and pressures. Duties and materials for each piece of equipment have been individually specified. The primary design considerations for this equipment are process material (corrosive streams require plastic, glass, or hastelloy) and precision (some functions reactions require equipment with a higher degree of precision than standard process equipment).

4.4.3 Buffering Equipment

A series of buffer tanks has been proposed for the continuous system. These are placed after the first reaction, following the wash step, and immediately prior to filtration and drying. The purpose of these buffers is to de-couple the various unit operations, which will reduce the effect of perturbations and allow units to keep running in the case of mechanical failure or out of expectation observations. It is unclear whether any or all of these buffers

will be optimal for a functional continuous system, but they have been included in order to provide a conservative, feasible proposal for the continuous system.

4.4.4 Heating and Cooling System

The number of unique heating & cooling connections were counted for each PFD. Each stream is assumed to be mixed and controlled locally.

4.4.5 Process Control Strategy

The number of process control loops are counted for each PFD. Control loops were defined qualitatively and are expected to be a reasonable surrogate for complexity and cost of automating the plant's control system.

4.5 Piping & Instrumentation Diagrams

In order to provide additional design information, each PFD has been further split into component sections. These sections represent combinations of equipment, piping, and instrumentation, and can be thought of as simple P&ID diagrams. For each of these drawings, process instrumentation and piping layout has been proposed based on analysis of existing continuous equipment. Common elements, such as feed systems or heat exchangers, appear many times throughout the continuous system. More specialized elements, such as the piping and instrumentation around the first reaction skid, occur only once. The P&IDs are used to estimate the number of instruments and piping components required for each section. In the final process model, there are close to 100 instances of the 15 modular P&IDs. The low number of unique P&IDs makes it relatively simple to apply this design concept to the entire system. An example P&ID is shown in Figure 5.

4.6 Plant Layout

In addition to the design elements mentioned above, a basic plant layout was proposed for the continuous process. This layout allows for a basic quantitative estimate of the production space occupied by the continuous process. To construct the plant layout, the footprint of each piece of large equipment, including all primary process equipment and tanks from the buffer system, was estimated based on design work. Each piece of equipment was lain out in a linear fashion, representing a model continuous line. Smaller equipment, including pumps, heat exchangers, and piping, was not explicitly included, as it can be installed in the space already reserved for the large equipment.

Chapter 5. Cost Model Formulation

5.1 Cost Model Structure

As stated previously, Novartis' established method for estimating investment costs involves design of the primary process equipment, construction of cost estimates for this equipment based on historical cost data, and the use of scaling factors to generate total cost estimates based on primary equipment cost. This is illustrated graphically in Figure 6.

In the new model, an alternative series of cost estimates was constructed based on design of the primary process equipment and supporting plant systems. This alternative structure is illustrated graphically in Figure 7.

The proposed cost model exists as a series of spreadsheets, each tabulating costs for an individual unit operation. Design information from the process model is entered into each spreadsheet. Additionally, design information from the process model and component unit operation spreadsheets is used to calculate indirect costs that should allocated to the continuous process, but cannot be assigned to any single unit operation. Costs have been segmented in various ways. This includes cost segmentation by unit operation, cost area, and direct/indirect.

5.2 Primary Process Equipment Costs

Main equipment is defined as reactors, mixers, and work up equipment. That is, any equipment responsible for modifying stream composition. For each piece of main equipment, calculation of the equipment cost was performed explicitly based on the process model. For conventional equipment, such as the falling film-evaporators, standard cost information for units of various sizes are available. Design information was used to

determine the size of the unit required. For the more novel continuous equipment, such as the tubular reactor, cost estimates were made based on a detailed design of the process equipment. Cost for individual components such as reaction tubes, hoses, skidding, instrumentation, and assembly were determined from vendor quotations.

5.3 Other Direct Investment Costs

5.3.1 Secondary Equipment

Secondary equipment has been defined as tanks, pumps, and heat exchangers. For each of these, equipment size was calculated based on process requirements from the process model. Internal standard cost data was used to price each piece of equipment based on its required size, material of construction, and design.

5.3.2 Installation

This cost area refers to the physical equipment installation, including skidding, anchoring, and secondary construction work. Installation costs were generated for each piece of equipment based on its weight and the likely complexity of the installation. Installation costs were formulated arbitrarily based on historical data. Accuracy for this cost area is likely to be low, but it is required to ensure the tabulated installation costs are collectively exhaustive. Installation costs are a small portion of the total direct investment costs.

5.3.3 Instrumentation

This cost area refers to the direct installation cost for the distributed control system. This includes probe hardware and installation, as well as connection to the distributed control system. This cost also includes the server, software, and GUIs for the distributed control

system. Standard instrumentation costs per instrument and per motor were assumed. The number of instruments and motors was counted based on the P&IDs.

5.3.4 Piping

This cost area refers to direct installation of process piping. This includes piping connections between the process equipment and distribution headers as wells as connections between equipment. Piping costs were based on required piping meterage. Meterage was determined by counting various design parameters from the simple P&ID diagrams. Each main equipment connection, t-junction, connection to an adjacent P&ID section, and dead end was counted as ½ an R-unit. Each R-unit was counted as 9m of piping. Piping diameter was then calculated based on flow rate and an assumed superficial velocity.

Piping costs per meter varies as a function of complexity and pipe diameter. Notably, because flow rates for the continuous system were significantly lower than for batch systems, process piping was calculated to be on the lower range (ID 10-15mm) for permanently installed rigid metal piping. Installation costs are essentially flat in this range, as they cover the welding, installation, and design work rather than the cost of the steel.

In practice, many of the piping installations proposed in this work would use temporary, flexible piping connections. This is expected to reduce the installation costs per meter below the figures calculated for this exercise.

5.3.5 Specialty Instrumentation

This cost area refers to any instrumentation beyond temperature, pressure, flow, or level gauges. All of the specialty instruments specified in this process were PAT units. Limited internal cost information is available for PAT implementation projects, so benchmark costs for hardware, automation, and method development were used. These benchmarks are

very rough estimates, as method development costs are expected to vary greatly by product. PAT costs are expected to decrease as Novartis becomes more experienced developing PAT applications. The proposed design contains three PAT elements, but it is still uncertain how many, if any, will be required in order to operate the continuous system.

5.3.6 Engineering

This cost area refers to process engineering costs associated with detailed equipment design and P&ID creation, as well as software engineering costs associated with programming and validating control automation. Standard costs per IO and per meter of piping were assumed. IOs and piping meterage were calculated as previously described. In order to account for more complex control required for continuous plants, an additional cost was applied for each primary control relationship, as defined in the PFDs.

5.3.7 Qualification

Qualification costs were calculated as 10% of the total direct investment costs. This factor was determined empirically in order to generate a qualification cost that was on the same order (4%-6% of the total investment cost) as that observed for batch plants.

5.4 Indirect Investment Costs

Prior to construction of the cost model, various indirect investment cost areas were considered. An assessment was made for whether each investment cost area would vary significantly based on the requirements of the continuous process. These areas were allocated based on process utilization of various plant resources (square meterage, heating and cooling capacity, and waste production). Areas for which no significant difference was

anticipated were bundled together and allocated to the continuous process based on the required plant footprint.

This cost allocation strategy is consistent with activity-based costing principles, and delivers an appropriate economic comparison between the batch and continuous processes. The cost charges for various resources assume a large plant, and therefore take advantage of economies of scale. The figures are therefore not representative of the costs for a standalone greenfield project. This modeling strategy was selected because the continuous system is expected to exist within the context of an existing facility or a new, large scale continuous facility. In the future, indirect cost allocations can be modified to fit the economic reality of specific investment projects.

5.4.1 Utilities

Heating and cooling utility consumption was modeled explicitly. Steady-state consumption is available for each heating/cooling operation based on the process simulation. Novartis has historical investment cost data for heating and cooling systems in its batch plants. However, there should be significant differences in actual utility consumption due to differences in usage profile, heat loss, and non-productive heat transfer (ie. heating/cooling of equipment between batches). Per-kW charges for the continuous system have been adjusted to reflect these differences.

Consumption of other utilities, including electricity, process air, other process gases, and cleaning solvents, is expected to be comparable to consumption in a batch plant. Investment costs for these additional utility systems have therefore been bundled together and allocated based on plant footprint.

5.4.2 Waste Treatment

Treatment of both organic and aqueous waste is the second indirect cost area. In the batch plant, aqueous waste is collected and transported to central wastewater treatment facilities. A portion of the organic waste is recovered, and the remainder is incinerated at a central incineration facility. For the model process, the waste streams for the batch and continuous processes are similar in composition, but not in volume. Therefore, investment costs associated with the waste treatment system of the batch plant have been determined on a per L/hr basis and allocated to the continuous system based on volume of waste generated. These standard allocations should not be used generically, as the investment cost for waste treatment depends greatly on the composition of the waste streams, the economic attractiveness of recovery, and the availability of local centralized treatment facilities.

5.4.3 Building

Building costs are available for the batch facility. The continuous process will require a similar facility in terms of capabilities, but is expected to occupy a different volume than the batch process. Therefore, investment costs associated with construction have been determine on a per m^2 basis and allocated to the continuous system based on process footprint. This charge is for "usable floor space" calculated by dividing the building cost for the batch plant by the space occupied by process equipment. This does not include walkways, storage space, airlocks, or offices. The building charge can be modified to reflect the economic reality of new projects.

Other building costs, including costs for the HVAC system, pilings, lighting, interior finishing, active safety systems, and power distribution, are expected to be fundamentally identical on a per m^2 basis. These costs have been bundled together with the building charge.

5.5 Batch Investment Costs

Batch investment costs are broken into direct and indirect costs similar to continuous. However, less rigorous process modeling and equipment design work has been done for the batch equipment. Therefore, the cost estimation methods used for the continuous costs could not be repeated for batch. Several secondary cost areas (procurement, direct installation, engineering, qualification) were calculated by multiplying batch costs by Novartis' standard scaling factors. Cost areas which could be calculated explicitly (utilities, building, and infrastructure) were calculated identical to the continuous plant.

This creates some concern that batch and continuous costs may not be constructed on the same basis. However, cost estimation based on scaling factors is expected to be more accurate for batch than for continuous because equipment cost benchmarks and scaling factors are more established for batch.

5.5.1 Main Equipment Costs

Main equipment was taken from the installed batch equipment train. Standard costs for all equipment are available internally at Novartis and are based on recent vendor estimates on a local (Swiss) cost basis.

5.5.2 Procurement

An addition 20% of the main equipment cost was figured to account for procurement of equipment not represented in the initial process design. This initial scaling factor is referred to as CA1.

5.5.3 Installation

The direct installation costs (CA2) were calculated to be 206% of CA1.

5.5.4 Engineering

Engineering costs (CA4) were calculated to be 73% of CA1.

5.5.5 Qualification

Qualification costs (CA7) were calculated to be 26% of CA1.

5.5.6 Indirect Costs

Indirect costs (CA3 - utilities, CA5 - building, CA6 - infrastructure) were calculated identically to the continuous process, based on resource allocation.

Chapter 6. Results

Investment costs were calculated for the continuous and batch plants at a series of production scales. These cost estimates were determined in aggregate and segmented across a variety of categories.

Additionally, because the work depicted here involved the design of feasible, operating continuous systems, various unanticipated findings resulted from these analyses. These can be generally associated with operation and design of the continuous manufacturing systems. The results are presented below and should be considered a starting point for planning around these issues.

Finally, it should be noted that design of the continuous process was conservative, having assumed no improvements in process performance or optimization of the process to run continuously. Segmented cost data has been used to quantify and rank the cost savings associated with various process improvements that could potentially be realized in the continuous system.

6.1 Investment Costs

6.1.1 Scaling of Total Investment Costs

Total plant investment costs as a function of installed capacity are shown in Figure 8. Based on this analysis, the batch process appears to be favorable at installed capacities below 800 tpy, and continuous appears to be favorable at capacities above 1200 tpy. The primary driver for the difference between batch and continuous is doubling up of the batch equipment at scales beyond 700 tpy. At 1400 tpy, the 700 tpy line has been fully duplicated and the plant will comprise of two lines operating independently.

6.1.2 Direct Cost Areas

Direct investment costs are costs that are needed to construct a continuous system, assuming the building, utilities, and infrastructure are already present. These costs are shown in Figure 9. Notably, different scaling behavior is observed for each cost area. The cost of the main equipment increases with the production scale, as the size and complexity of the equipment increases. Installation and piping costs also appear to scale less steeply than costs for the main equipment. Costs associated with instrumentation, PAT, and engineering remain constant across the three model production scales.

6.1.3 Other Cost Areas

In addition to the direct cost for the continuous plant, the model accounts for indirect costs and the cost of the filtration and drying system. These are shown in Figure 10. Charges for the utility installations double along with the doubling of production scale, as the process requires twice as many resources. The building costs also increase, but not linearly, as the continuous equipment increases in size. The filtration and drying system, for which a continuous unit operation could not be identified, is a significant portion of the overall investment cost.

6.1.4 Fixed vs. Variable Investment Costs

In Figure 11, investment costs have been aggregated as either fixed, variable with production scale, or related to filtration and drying. Filtration and drying costs are segregated because this unit operation will be run batch-wise in the model continuous system. There appears to be a significant fixed cost associated with installation of a continuous process. Qualitatively, process engineering, method development, instrumentation, and automation will have to be performed for any plant, and are not

expected to change significantly with the installed capacity. In addition to these fixed cost, there is a variable element with cost related to the volume of material flow, resource utilization, change in equipment size, and minor duplication of equipment.

6.1.5 Cost Segmentation By Unit Operation

Direct investment costs can be segmented by unit operation as shown in Figure 12. These values are for an installed capacity of 700 tpy. As shown in this figure, consolidation of unit operations in the batch plant leads to more equipment, and therefore a greater investment cost, for the continuous plant.

For individual unit operations, there is variability in terms of the economic benefit relative to batch. Extraction and solvent exchange are roughly equivalent in cost, while reaction and crystallization seem to be slightly more favorable in batch. The filtration and drying step is significantly more expensive than other unit operations.

6.1.6 Apparent Scaling Factors

Cost ratios and apparent scaling factors have been derived from the continuous cost estimates. These are shown in Figure 13. In general, the continuous factors are on the same order as the existing batch factors. However, the apparent scaling factors vary significantly with production capacity, as different cost areas scale at different rates. The ratio of main equipment to installation cost decreases with increasing production scale, while the charge for utilities increases linearly. These factors are instructive, and comparable enough to the batch factors that they seem credible.

6.2 Continuous Plant Operation

In addition to investment cost modeling, the process design was used to derive some information about how the continuous plant would operate. Simple estimates for various operation expenses areas were made. Additionally, several key operational challenges were identified. These are presented here, along with analysis for the system in question, and a general framework for modeling these areas in the future.

6.2.1 Operating Costs

Based on work from previous MIT projects, the ongoing operating costs for continuous plants have been identified as raw material costs, labor, depreciation of capital, QA/release, waste disposal, and overhead are the primary operational costs. Rough estimates of several operating cost areas were constructed based on past work. These values, based on annual production of 700 tpy, are shown in Figure 14. It is important to note that these estimates have not been constructed as rigorously as the figures for investment cost. They should, however, be representative enough to give a sense of the relative value of each cost area.

The operating costs are similar for both processes, with relatively small variations that can be qualitatively explained. However, even though the predicted differences are small relative to the absolute costs, they are large relative to the investment cost, and particularly a yearly allocation of the investment cost. This suggests that for the model process, investment cost alone is not sufficient to evaluate the business cast for batch vs. continuous.

6.2.2 Raw Material Costs

Raw materials costs are driven by raw material consumption and process yield. The batch and continuous processes have an identical yield, so the costs are almost equal. The

continuous process can be run at a lower concentration of catalyst concentration than batch. This results in a significant yearly savings because the catalyst is expensive and not recoverable. The solvent exchange produces more solvent waste when run continuously, increasing the operating cost.

6.2.3 Waste Treatment Costs

Waste treatment costs are calculated as a function of the total waste produced. Again, the solvent exchange is less efficient when run continuously, resulting in a small additional cost.

6.2.4 Heating and Cooling

Heating and cooling costs are calculated as a function of the various unit operations. Based on this analysis, costs for the continuous process will be slightly higher than for the batch. This has not been validated, and may be incorrect due to greater ambient heat loss for the batch process.

6.2.5 Low Utilization Performance

For products ramping up in demand, or for products where initial demand projects are not realized, capacity utilization will be significantly less than 100%. This will lead to idle capacity for both batch and continuous systems. While batch systems can respond to idleness by reducing the number of campaigns or batches, continuous systems are restricted by the minimum system throughput.

For continuous systems, the minimum throughput is the minimum throughput of the least flexible piece of equipment. Stated mathematically, the minimum system throughput (V) for a system containing i integrated unit operations is

$$V_{system} = \min (V_i)$$

The continuous system we have proposed has a minimum throughput of approximately 33% of maximum. Therefore, when demand is less than 33%, the continuous system must be run in campaigns to avoid significant accumulation of inventory. This will result in some inventory accumulation over the course of each campaign, as well as additional costs incurred for startup, shutdown, and changeover. Individual component capacities and inventory profiles for levels of product demand are shown in Figure 15.

6.2.6 Equipment Reliability

The continuous system would optimally run throughout the year, with only a single annual stoppage for maintenance. However, reliability of the continuous equipment is unclear, and there is potential for continual equipment stoppages due to component failure, process drift, external disruptions, or variability in raw material quality. The frequency of equipment stoppages is a function of both the reliability of the individual components and of the number of integrated continuous unit operations. The number of system stoppages (S) in a given period of time for a system containing i integrated unit operations, each with an expected number of unplanned stoppages S_i is

$$S_{system} = \sum_i S_i$$

In case of failure, some product would have to be discarded as waste due to being potentially out of spec. For the model process, we assume that for every failure, the material in the reactors would be discarded, but the material in the workup equipment could be isolated and retained. After line stoppage, we assume 3 residence time equivalents of raw material would be discarded as the system returns to equilibrium.

There is clearly the potential for significant product losses if we assume a low system reliability. One option to mitigate these losses is the installation of a buffer system that would allow the reaction system to run in case of stoppages in other sections. The cost of this buffer system and the range of potential savings are shown in Figure 16. One of the challenges of developing the capability for continuous manufacturing will be to deliver a stable, highly reliable system that is robust to external disruptions.

6.2.7 Salvage Value

Based on a technical assessment of the continuous equipment, no equipment is so specialized that it could not be adapted for another process in case of product failure. Therefore, the salvageable costs for continuous equipment should be the same as those for batch, assuming there are a sufficient number of continuous projects available. Salvageable costs are defined as equipment, building, and supporting infrastructure, and exclude process-specific automation and design. Based on this assumption, salvageable batch investment costs are 88% of total, and 83% of total for continuous. The difference is driven by PAT implementation costs for continuous, which are not recoverable. Recovering this equipment value is only feasible if there is sufficient demand for used process equipment (ie. sufficient continuous projects available internally or an external market for continuous equipment and facilities).

Chapter 7. Conclusions and Opportunities for Further Investigation

Based on this work, various conclusions can be drawn regarding the technology described here, and about the use of equipment-factored cost estimation in general.

7.1 Cost Advantages of Continuous Manufacturing Systems

For the model process, the continuous facility will only be cheaper at relatively high production scales, ie. greater than 1000 tpy. This is at the high end of expected production requirements, suggesting that without any optimization of the batch chemistry, continuous should only be beneficial at the highest production volumes. Investment in continuous is intrinsically more expensive at lower scales because unit operations cannot be consolidated, process automation is more expensive, and equipment is more expensive on a cost/volume basis. Continuous becomes favorable at higher scales because multiple trains become required for the batch process, and investment costs for the batch system begin to scale linearly with production scale.

These results should not imply a significant negative impact on the potential value of continuous manufacturing systems. Instead, this work reiterates that to deliver continuous systems that require a reduced capital investment, the switch to continuous must be accompanied with innovations in the underlying chemistry. This could include alternative synthetic pathways, consolidation of unit operations, accelerated processing times, elimination of isolation steps, improvements to process yield, or the implementation of lower-cost reactants. Value on the unit operation level will be driven by the feasibility of implementing these improvements for continuous processing.

In additional to more efficient unit operations, continuous manufacturing systems are expected to provide benefits at the system level. This was explored in some detail in this analysis, but results were inconclusive. The greatest drivers for value on the system-level are expected to be reduction in labor costs, an order-of magnitude decrease of in-process inventory, and elimination of most ongoing costs associated with quality control. (Wilburn, 2010) Our system is expected to deliver an in-process inventory reduction of 70%. However, the key driver for lower operating costs will be reduction in direct labor and in costs associated with QC and product release. Based on the experience of operations experts at Novartis, reductions in labor cost on the order of 50% seem possible. However, a quantitative justification for this assumption could not be constructed. Until a functioning commercial system is in place, these assumptions cannot be validated.

7.2 Robustness of Cost Estimates

This work is based on the premise that if process modeling could be performed in greater detail, the resulting cost estimates would be more robust. The only way to truly confirm this assumption would be to build the physical plant and compare each set of estimates with validated cost figures. Technological and financial constraints make this impractical. Therefore, it is impossible to determine whether the new estimates are truly more reliable. This limitation is a fundamental drawback of new methodology for cost estimation in an industry with a low clockspeed and slow iteration cycle. In this case, it is probably wisest to rely on the indicator I have referred to as internal credibility. That is, if after review by a cross-functional team of internal experts, there is a consensus that financial estimates were generated in an appropriate manner, they should be accepted. Future projects should focus

on assembling the appropriate team of internal experts and communicating results and methodology in a clear way so that they can be easily reviewed.

7.3 Utility of Cost Estimates

This thesis has proposed an alternative method equipment-factored cost estimation. However, equipment-factored estimates remain attractive for because they require relatively little upfront design work to construct. In future work it will be critical to identify a cost modeling strategy that is appropriate for the task at hand. Should simple back of the envelope cost estimates be needed, equipment-factored estimates could be constructed using the scaling factors derived from this project. Alternately, a cost estimate could be constructed using only a process simulation, derived scaling factors for the direct investment costs, and consumption-based cost allocations for indirect cost areas. Either choice will result in more credible estimates, but require relatively modest design work.

The newly proposed methodology, even if it is more robust, will require between 5x and 10x the investment in design and modeling time due to the higher level of process design and manual data entry required. This makes it poorly-suited for early conceptual-stage estimation tasks. However, if estimates are require to support implementation of a specific investment, preliminary design work will have to be done in any case, and it would be reasonable to develop the process design and cost model concurrently. Similarly, if there are other new technologies for which conventional cost factors do not seem to be appropriate, revising the estimation methodology to reflect more in-depth design work is a good strategy. In either case, it is important to balance the level of apparent robustness with the effort required to produce these estimates.

7.4 Alternative Frameworks for Evaluating Investment Costs

Equipment-factored estimates and design-based estimates can both be used for the purposes of initial cost estimation and budgeting. However, if the task at hand is to compare two alternative technologies at a very early conceptual stage (ie. batch vs. continuous), these estimates can often be misleading. Consider the following scenario.

Conventional wisdom at Novartis is that uncertainty for conceptual-stage estimates is at least ±35%. Suppose this implies the true cost is a normal random variable with a mean of μ and a standard deviation of 0.175μ. Consider cost estimates for two alternative facilities, one of CHF 50M, one of CHF 40M. If we compare two estimates, C_1 and C_2, we see:

$$C_1 = N(50,8.5)$$

$$C_2 = N(40,7)$$

The difference between the two estimates can be thought of as economic benefit of one versus the other:

$$B = C_1 - C_2$$

With an assumed correlation coefficient ρ between the two estimates, the benefit can be expected to be distributed as follows:

$$B = N(10, ((8.5)^2 + (7)^2 - 120\rho\ )^{0.5})$$

Although the expected savings for the C_2 investment are CHF 10M, the economic benefit is uncertain, as illustrated in Figure 17. With relatively low estimated cost differences (10-20%) high uncertainty in the underlying estimates (35% or more) and low correlation between the two outcomes (unclear, but 0.5 seems like a reasonable high end estimate), it is challenging to compare two model processes with any degree of accuracy.

The practical implication of this exercise is that relatively small estimated cost differences do not rigorously prove that one investment is the superior option. Instead, these differences suggest that one method is likely to be better, and that there is a potential economic benefit associated with the option to use continuous processing. If two competing technologies are to be evaluated against each other, it would be wise to consider an alternative framework for evaluating this dilemma.

7.4.1 Option Valuation

One alternative for evaluating risky investment decisions is an option valuation model. This model seeks to quantify the expected benefit from investment in a new project based on the potential economic benefit and the probability of success. (McGrath & Nerkar, 2004) In the previous example, assume the firm has the capability of implementing the C_1 process, but would have to invest to develop the capability of implementing the C_2 process. In this case, the value of the option to implement C_2, V, is average value of the lower investment costs.

$$V = \overline{C_1} - \overline{min(C_1, C_2)}$$

I ran a simple Monte Carlo simulation for the probabilistic scenario described in the previous section, yielding an option value of CHF 12M – CHF 10M for values of ρ ranging from 0 to 1. The firm should be willing to pay around this value to develop the option to build a facility with the C_2 technology.

This type of option-based valuation is preferable to simply comparing equipment-factored estimates because it takes into account the uncertainty in the underlying estimates and can be directly related to development expenses. Future work that seeks to evaluate the economic benefit of emerging continuous technology should incorporate these considerations into the financial model.

7.4.2 Value of Potential Process Innovations

The process design and cost model described in this work can also be used to inform decisions surrounding development of new continuous capabilities. There is optimism that continuous processing will yield benefits through a host of potential process innovations. These include reduction in the number of unit operations, process intensification, use of cheaper reactants, and various other innovations.

In order to understand the relative impact of these potential innovations, I used the segmented cost results to make a rough estimate of the impact of each innovation in the context of the fully designed continuous system. As an example, to determine the impact of eliminating a single unit operation, I found the average direct cost incurred by each unit operation. Similarly, to determine the impact of an increase in yield, I took the value of 5% of the primary raw material costs. Figure 18 shows the value of selected potential process improvements in the context of the model continuous system.

While the exact value of each potential cost savings bears significant uncertainty, their relative magnitude is instructive. Based on this analysis, dramatic changes in the cost structure will only be achieved through significant improvements to the chemistry – more efficient synthetic pathways, cheaper reactants, increased yields, or significant consolidation of unit operations. There appears to be less economic value associated with thermal recycle or waste reduction. These insights can be used to focus development efforts on continuous capabilities that will provide the most value in their implementation.

7.5 Other Opportunities for Further Investigation

The models documented here could be expanded upon in a variety of ways. In the context of continuous manufacturing, validation of the standard costs associated with individual cost

areas should be the main area of focus. Additionally, this study has raised a number of questions concerning the operational capabilities of continuous systems. These areas should be concurrently investigated alongside the ongoing design and implementation of continuous systems.

Beyond these immediate applications, I see an opportunity to integrate modular design work with feature-based cost estimation in other fields. The methodology documented here could be repeated for batch pharmaceutical plants, and could also be extended other capital-intensive industries. The capability to assemble quick, relatively accurate cost estimates based on initial design work is probably most valuable to engineering firms or other organizations that routinely construct such estimates.

Figure 1. Novartis TechOps' Strategic Vision

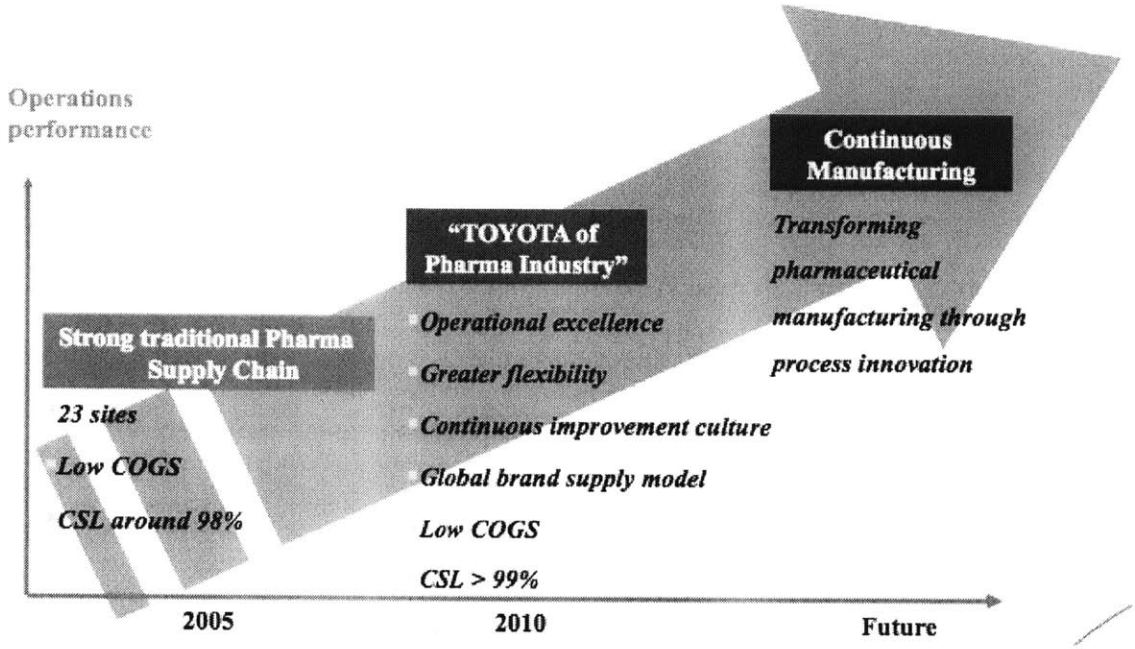


Figure 2. Process Model Structure

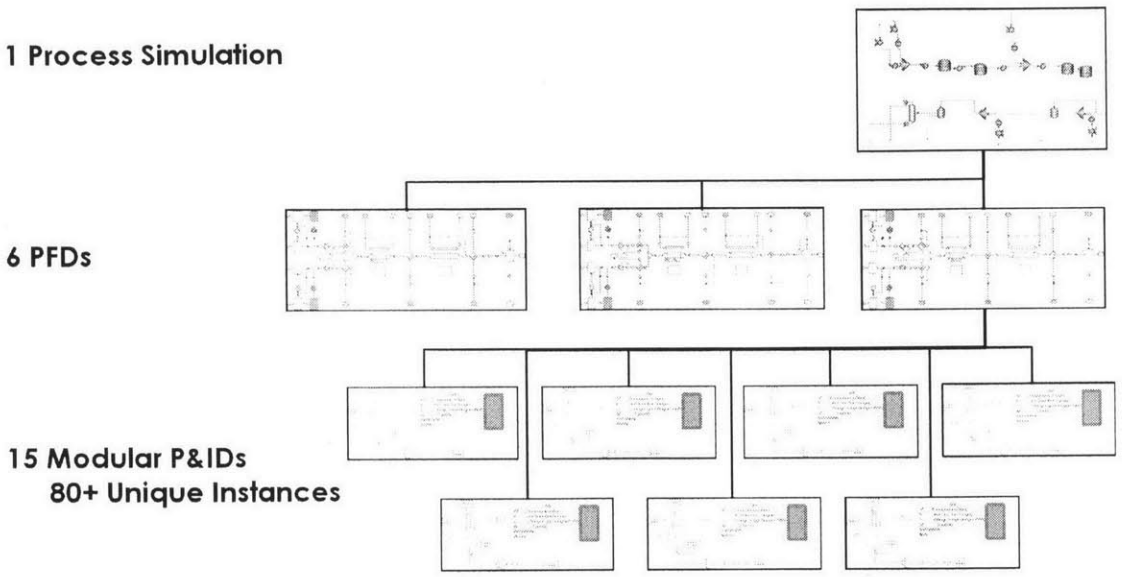


Figure 3. Design Element: Process Simulation

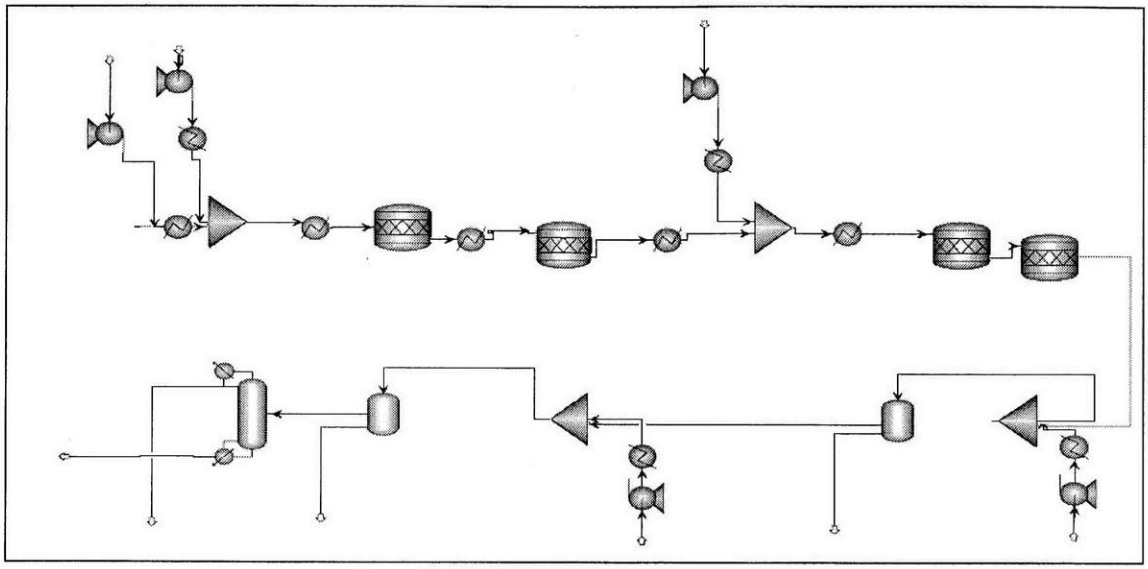


Figure 4. Design Element: Process Flow Diagram

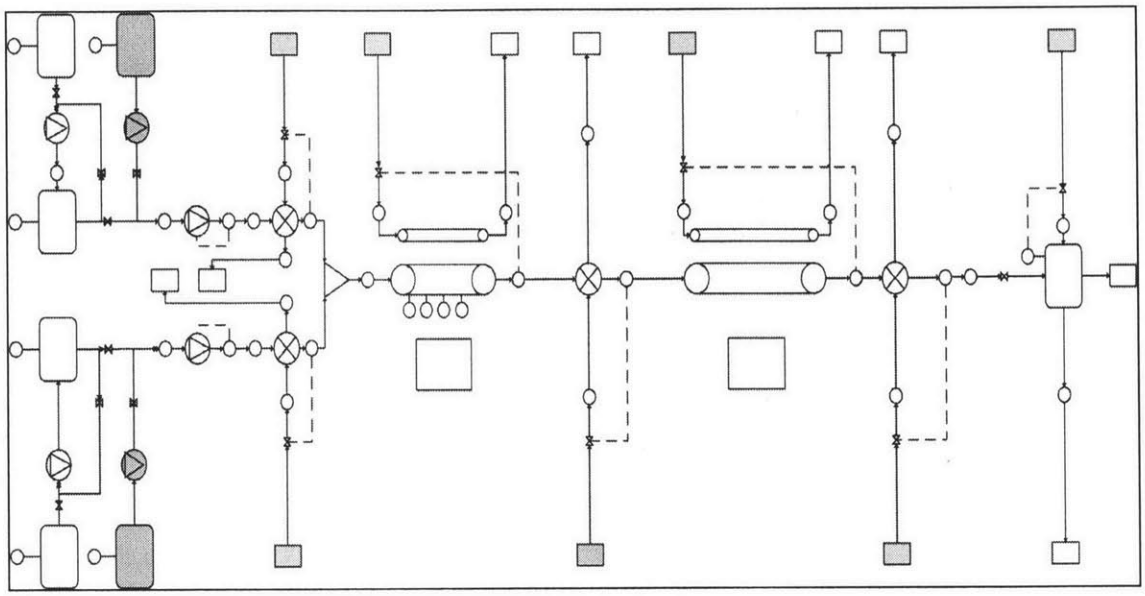


Figure 5. Design Element: Piping & Instrumentation Diagram

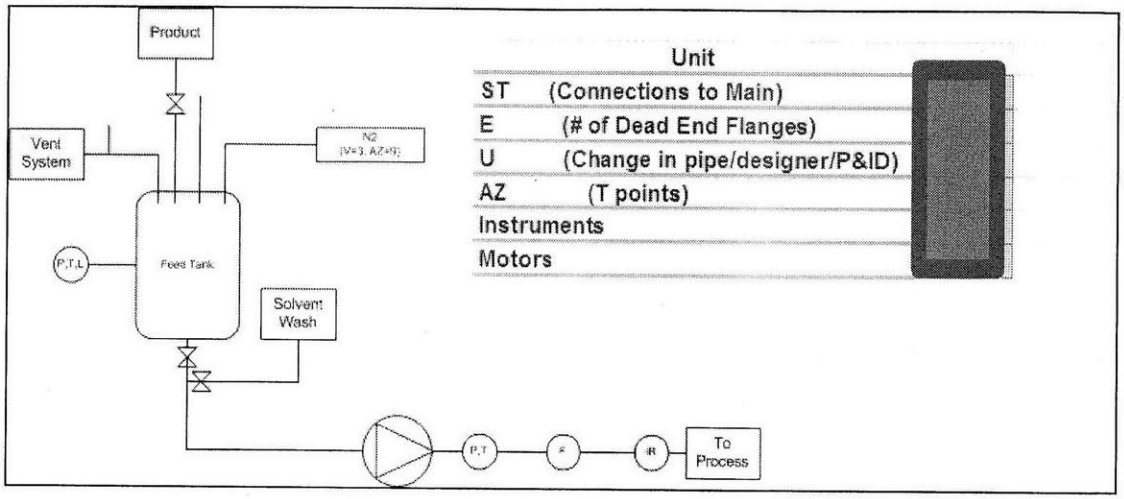
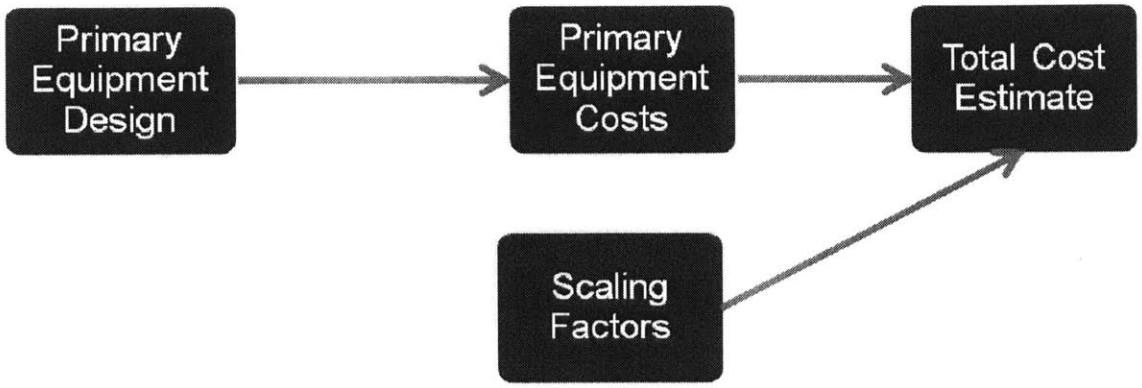


Figure 6. Existing Methodology for Cost Estimation

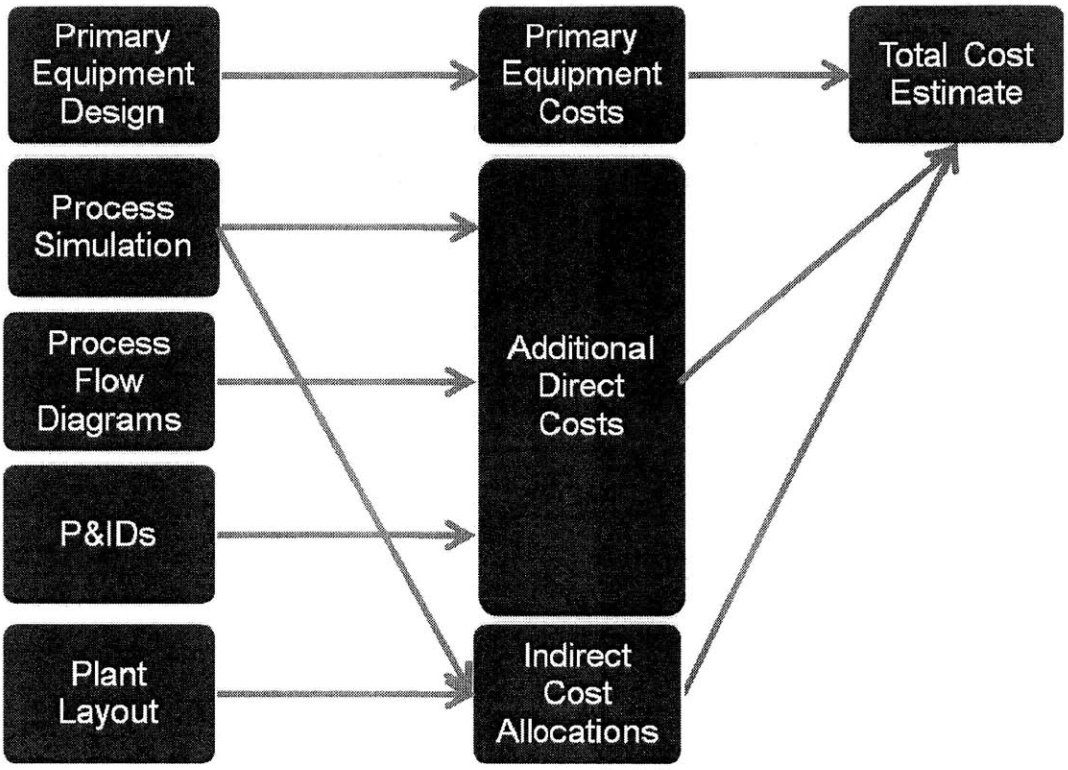


Primary Equipment Design = f(process model)

Primary Equipment Costs (PE) = f(primary equipment design, historical equipment costs)

Total Cost (TC) = f(primary equipment costs, scaling factors)

Figure 7. Proposed Methodology for Cost Estimation



Primary Equipment Design = f(process model)

Process Simulation = f(process model)

Process Flow Diagrams = f(process model)

P&IDs = f(process model)

Plant Layout = f(process model)

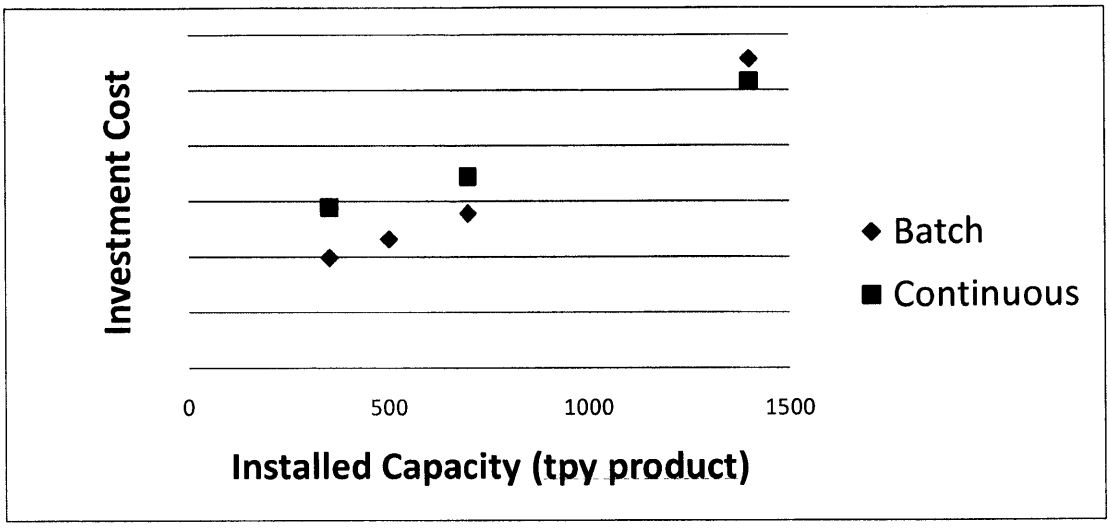
Additional Direct Costs = f(process simulation, process flow diagrams, P&IDs)

Indirect Costs Allocations = f(process simulation, plant layout)

Primary Equipment Costs = f(primary equipment design, historical equipment costs)

Total Cost Estimate = f(primary equipment costs, additional direct costs, indirect cost allocations)

Figure 8. Investment Cost Scaling With Installed Capacity



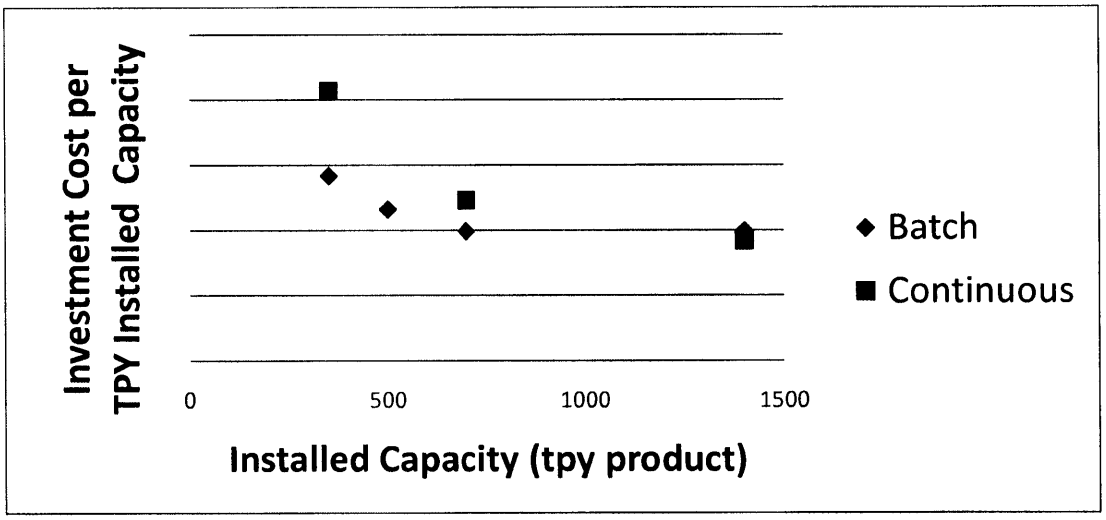


Figure 9. Direct Investment Costs for Continuous Plant

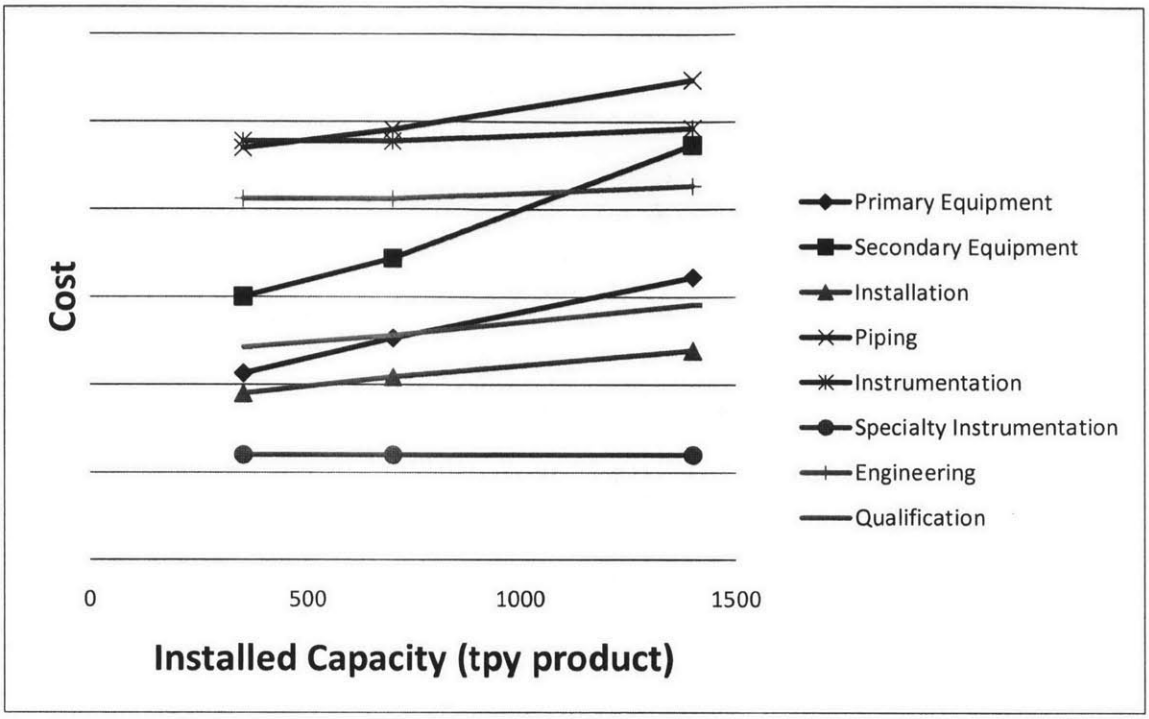


Figure 10. Other Investment Costs for Continuous Plant

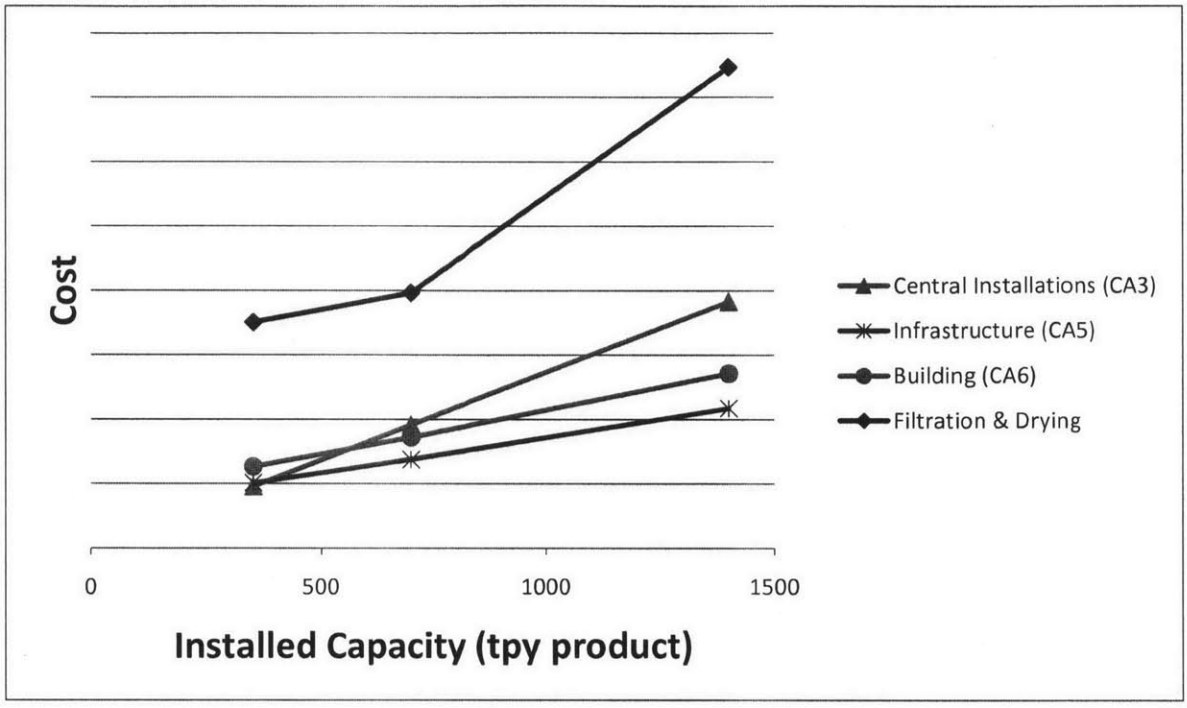


Figure 11. Total Costs for Continuous Plant

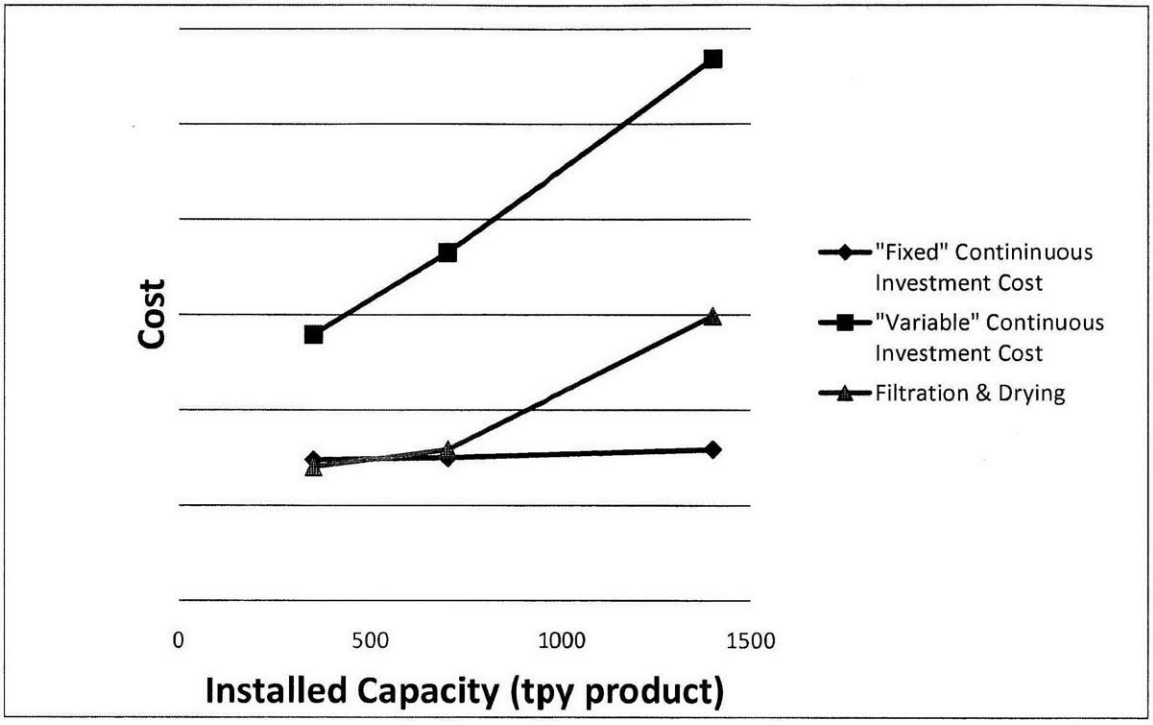


Figure 12. Direct Investment Costs by Unit Operation

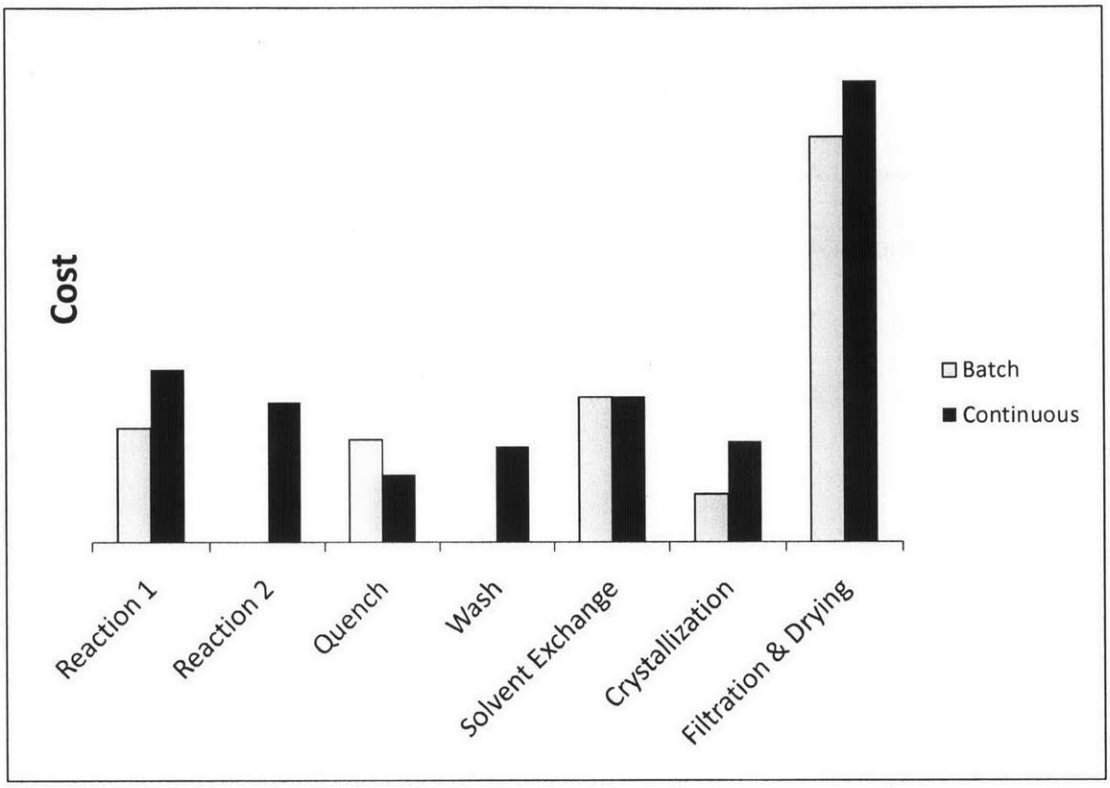


Figure 13. Relative Costs and Scaling Factors for Continuous Plant

	% of Total			
	Continuous 1400 tpy	Continuous 700 tpy	Continuous 350 tpy	Standard Batch
Main Equipment (CA1)	16%	15%	16%	16%
Installation (CA2)	33%	35%	39%	32%
Central Installations (CA3)	15%	11%	7%	12%
Engineering (CA4)	12%	14%	17%	11%
Infrastructure (CA5)	8%	8%	7%	11%
Building (CA6)	10%	10%	9%	13%
Qualification (CA7)	6%	6%	7%	4%

	Scaling Factors			
	Continuous 1400 tpy	Continuous 700 tpy	Continuous 350 tpy	Standard Batch
Main Equipment (CA1)	100%	100%	100%	120%
Installation (CA2)	207%	231%	246%	206%
Central Installations (CA3)	93%	73%	42%	78%
Engineering (CA4)	20%	24%	27%	19%
Infrastructure (CA5)	11%	10%	9%	15%
Building (CA6)	12%	12%	10%	16%
Qualification (CA7)	7%	7%	8%	5%

Figure 14. Running Costs for Batch vs. Continuous Production

	Batch Cost	Continuous Cost	Savings
Operating Cost - Raw Materials			
Reactive Compounds	CHF 25,090,200	CHF 27,628,636	-CHF 2,538,436
Catalyst	CHF 26,401,150	CHF 20,250,288	CHF 6,150,862
Solvents	CHF 15,251,171	CHF 15,913,793	-CHF 662,622
Operating Cost - Waste Treatment			
Reaction	CHF 0	CHF 0	CHF 0
Isolation	CHF 1,173,958	CHF 1,211,523	-CHF 37,565
Operating Cost - Heating & Cooling			
Reaction	CHF 51,862	CHF 48,037	CHF 3,825
Isolation	CHF 109,021	CHF 205,723	-CHF 96,702

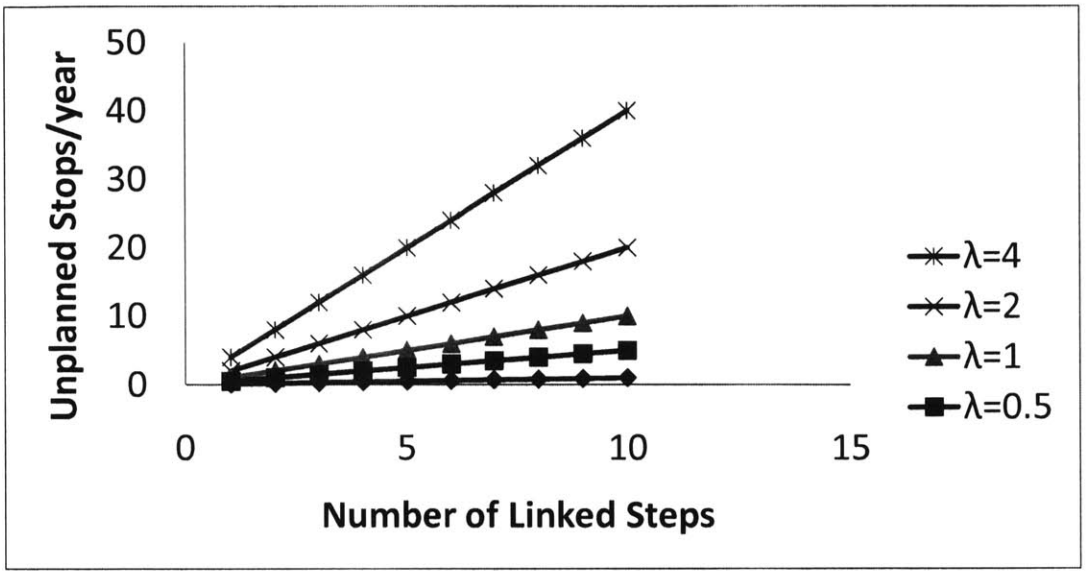
Note: Values have been disguised

Figure 15. Low Utilization Performance

	Minimum Annual Product Throughput (base = 700 tpy product)	
	Batch	**Continuous**
Reaction 1	1 batch (1.4 t/year)	10% of max (70 t/y)
Reaction 2	1 batch (1.4 t/year)	10% of max (70 t/y)
Quench	1 batch (1.4 t/year)	<5% of max (35 t/y)
Extraction	1 batch (1.4 t/year)	<5% of max (35 t/y)
Solvent Exchange	1 batch (1.4 t/year)	10% of max (70 t/y)
Crystallization	1 batch (1.4 t/year)	33% of max (233 t/y)
Filtration & Drying	1 batch (1.4 t/year)	1 batch (1.4 t/y)
System	**1 batch (1.4 t/year)**	**33% of max (233 t/y)**

	Continuous System Performance			
Product Demand	**50 tpy**	**100 tpy**	**150 tpy**	**200 tpy**
Optimal Campaigns/year	2	2	2	2
Avg. Product Inventory (tons)	10.3	15.3	15.4	10.6

Figure 16. Operational Reliability



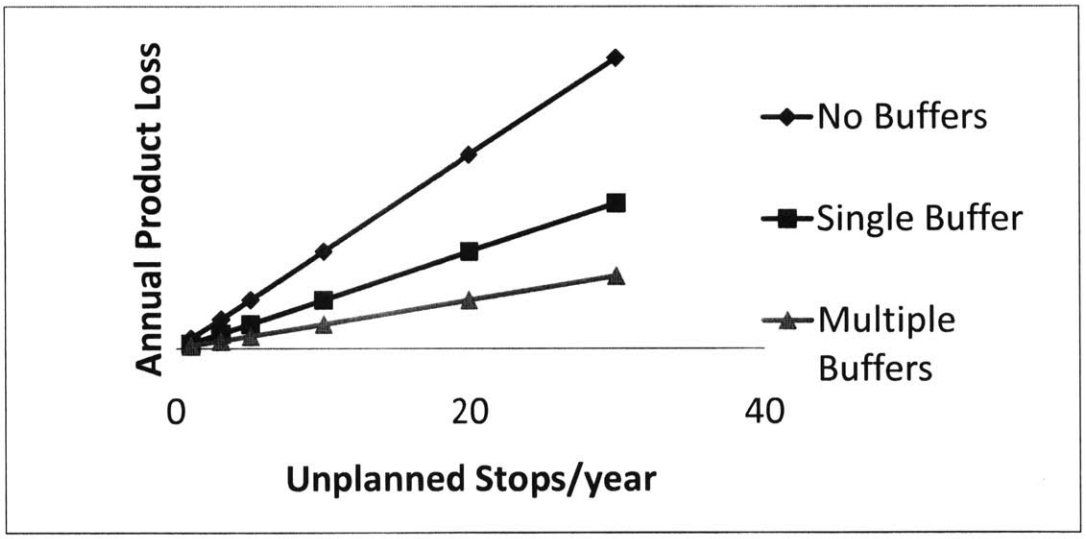


Figure 17. Relative Economic Benefit of Batch vs Continuous

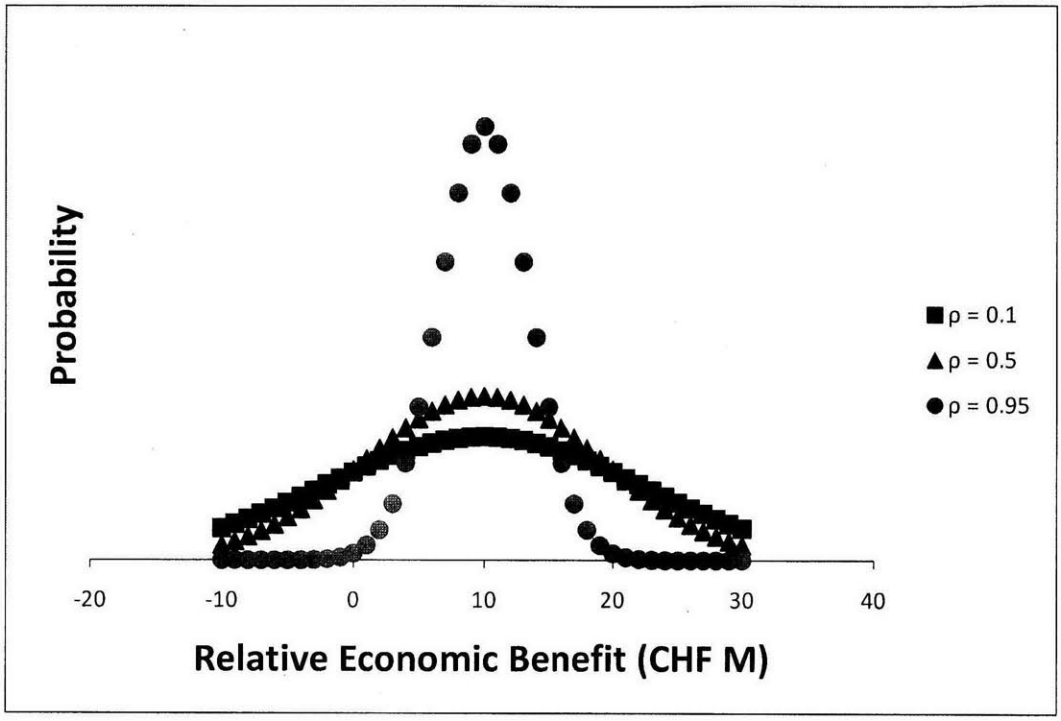


Figure 18. Cost Savings Associated With Various Process Improvements

Process Innovation	CapEx Savings	OpEx Savings
Enable use of cheaper reactant	-	CHF 12M/y
Increase reaction yield 5%	-	CHF 4M/y
Eliminate filtration and drying	CHF 8M	CHF 3M/y
Reduce catalyst consumption by 10%	-	CHF 3M/y
Develop more efficient solvent exchange	CHF 2M	CHF 2M/y
Eliminate single unit operation	CHF 2M	-
Consolidate extraction steps	CHF 1M	-
Reduce aqueous waste 25%	-	CHF 0.10M/y
Reduce energy use 25%	-	CHF 0.05M/y

Note: Values have been disguised

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