Implementation of the New FDA Quality by Design Guidance in Pharmaceutical Production

By

Stephanie Michelle Tozer

Bachelor of Science in Chemical Engineering, University of Colorado, Boulder, 2003

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

Master of Business Administration

AND

Master of Science in Chemical Engineering

In conjunction with the Leaders for Manufacturing Program at the

Massachusetts Institute of Technology

June 2008

Signature of Author_____
Department of Chemical Engineering &
MIT Sloan School of Management
May 9, 2008

Certified by_____
Charles Cooney, Thesis Supervisor
Professor of Chemical and Biochemical Engineering

Certified by_____
Roy Welsch, Thesis Supervisor
Professor of Statistics and Management Sciences

Accepted by_____
William Deen, Graduate Committee Chairman
Department of Chemical Engineering

Accepted by_____
Debbie Berechman, Executive Director of MBA Program
MIT Sloan School of Management

Implementation of the New FDA Quality by Design Guidance in Pharmaceutical Production

By

Stephanie Tozer

Submitted to the Sloan School of Management and the
Department of Chemical Engineering Division on May 9th, 2008 in Partial Fulfillment of the
Requirements for the Degrees of Master of Business Administration and
Master of Science in Chemical Engineering

ABSTRACT

Due to the highly regulated environment, it is difficult to implement changes to a pharmaceutical process. Even small change request approvals can require months of effort for pharmaceutical companies and regulatory agencies. This resource intensive process discourages continuous improvement and often results in outdated and inefficient manufacturing processes. In response to the growing need for improvement, the FDA issued a guidance to industry that provides a framework for acquiring improved process understanding and product quality in the manufacturing industry. The guidance is aimed at encouraging the use of process analytical technology (PAT) to monitor key quality attributes continuously during the process and enable early fault detection. The goal is to transition from the current method of quality through end of process testing to a new method of quality by design (QbD). In 2005 Novartis Pharma formed a unique collaboration with the FDA in an attempt to demonstrate the benefits and concepts of QbD. A cross-functional team was formed with the goal of developing a case study for one Novartis process that will serve as a model for future implementation of PAT and QbD.

During a six month internship, I worked with the Global PAT team members to help ensure the successful implementation of the QbD tools outlined in the FDA Guidance. The internship focused only on the drug substance manufacturing process. Specifically, I was responsible for collecting and analyzing process data during the manufacturing campaign, coordinating the commissioning of an on-line NIR probe and PSD analyzer, and identifying and

proposing future benefits of PAT applications to Novartis Pharma. I also conducted a throughput analysis after observing manufacturing operations and analyzing the process data collected during the campaign.

My thesis provides a background of the QbD/PAT initiative and includes a thorough literature search to benchmark the progress other pharmaceutical companies have made at applying QbD/PAT. I discuss in more detail the Novartis PAT project, and my specific contribution including the results of the NIR and PSD installation and validation, full scale Design of Experiment activities, Multivariate Data Analysis modeling, and process throughput analysis. I conclude with an analysis of barriers to implementation and provide recommendations for future implementation to other processes and plants at Novartis.

Thesis Supervisor: Charles Cooney
Title: Professor of Chemical and Biochemical Engineering

Thesis Supervisor: Roy Welsch
Title: Professor of Statistics and Management Sciences

Acknowledgments

I would like to acknowledge several individuals without whom I would not have been able to complete this project. I would first like to thank Marc Goeller and James Cheney for sponsoring the project and for their support and mentorship during my internship. They were always available to answer my questions and ensure that my time at Novartis was both rewarding and enjoyable. Additionally, I would like to acknowledge everyone who mentored me during my internship. These people include Jerh Collins, Richard Häefeli, Engelbert Schmid, and Martin Müeller. I appreciate all of the time that each one of you spent with me explaining the key concepts, introducing me to the plant personnel, helping me to obtain information that I needed, and frequently reviewing my progress. Also, thank you for introducing me to the Swiss culture by telling me where to get the best chocolate in town, taking me to my first football game, and giving me recommendations on where to visit in Basel. After 6.5 months I almost felt like a local!

There were several team members that helped with different aspects of my internship that I would like to thank- specifically Elias Ndzié (crystallization), Thorsten Roeder (NIR and MVDA), Michael Baysang (NIR), Michael Juhnke (milling) and Michel Foehrle (milling). I also would like to thank all employees at Novartis for being patient with me as I tried to learn Swiss German and for always taking the time to help translate for me when I did not understand. Everyone did an excellent job in ensuring that I felt included in the group and I enjoyed meeting each and every person I encountered during my internship. You all helped to make my internship an exciting and valuable learning experience for me.

I would also like to thank my MIT supervisors, Roy Welsch and Charles Cooney. You both provided invaluable support and advice to me during your visits to Switzerland.

Of course, I need to thank my classmates for being there for me when I had questions that I needed answered during my internship. I knew I could always count on you to point me in the right direction or at least make me laugh by sending an entertaining e-mail.

Finally, I would like to thank my parents for their continuous support. I know that during my internship I could count on you to listen to me, offer advice, and at least pretend to be interested in the work that I was doing. Thank you for being such wonderful parents who always believe in me and provide encouragement whenever I am faced with a challenge.

This page has been intentionally left blank

Table of Figures

Table of Tables

This page has been intentionally left blank

1. Introduction

1.1. Objective

Due to the highly regulated environment, it is difficult to implement changes to a pharmaceutical process. Even small change request approvals can require months of effort for pharmaceutical companies and regulatory agencies. This resource intensive process discourages continuous improvement and often results in outdated and inefficient manufacturing processes. In response to the growing need for improvement, the FDA issued a guidance to industry that provides a framework for acquiring improved process understanding and product quality in the manufacturing industry. The guidance is aimed at encouraging the use of process analytical technology (PAT) to monitor key quality attributes continuously during the process and enable early fault detection. The goal is to transition from the current method of quality through end of process testing to a new method of Quality by Design (QbD). Novartis would like to be an industry leader by being one of the first companies to implement the new FDA guidance on QbD. Competitors are also implementing similar programs, and Novartis knows that to remain competitive they need to be fast to react to the guidance and implement new Process Analytical Technologies to their manufacturing processes. Therefore, in 2005 Novartis Pharma formed a unique collaboration with the FDA in an attempt to demonstrate the benefits and concepts of QbD. Novartis formed a Cooperative Research and Development Agreement (CRADA) with the FDA, with the goal of submitting a revised New Drug Application (NDA) using the QbD principles by the end of 2007. A cross-functional team was formed with the goal of developing a case study for one Novartis process that will serve as a model for future implementation of PAT and QbD.

The goal of the project was to achieve real-time release and continuous improvement for drug product and drug substance manufacturing. This was to be achieved through the implementation of QbD and PAT principles as outlined in the FDA Guidance to Industry. The intention is to prove the concept of QbD and PAT by focusing on one pilot project that will create standards and set the path for implementation to other products in the future. The project ties into the overall corporate goals to be the "Toyota of Pharma" and achieve the overall lowest COGS in industry. The intent of my thesis is to summarize the key findings, both technical and

managerial, from my involvement on this project team and to offer recommendations for future implementation of QbD and PAT within the pharmaceutical industry.

1.2. Current state of pharmaceutical manufacturing

1.2.1. Manufacturing Process

Currently the majority of pharmaceutical manufacturing consists of batch processing with fixed manufacturing setpoints. A typical pharmaceutical process consists of four key steps: manufacturing of crude material (creation of active substance), intermediate product (purification), drug substance (preparing IP for final processing), and drug product (final processing, i.e. tablet formation). Each of these steps is broken down into a multitude of sub-steps such as crystallization, drying, milling, and wet-granulation. The process parameters, such as temperature, pressure, etc. are run at a specific set-point and must be controlled within a narrow, validated range. Statistical process control (SPC) methods are typically utilized to monitor the process (Kourti, 2006). Since only a few tablets out of several million are tested at the end, drug manufacturers are usually expected to conduct extensive in-process material testing. After each step, and in some instances sub-steps, samples are collected and analyzed offline to ensure that the product quality specifications have been met for that step. The batch will not proceed until the quality results are verified from the previous step. Generally, if any of the in-process or end of process testing is out of the specification, the entire batch is scrapped and typically not reworked (Yu, 2007). It could be said that the current strategy for pharmaceutical manufacturing is one of "quality-by-testing". The product quality is ensured by raw material testing, a fixed manufacturing process, in process material testing, and end product testing.

1.2.2. Validation Procedure

The traditional pharmaceutical validation requires that the manufacturing process be repeatable. This is typically demonstrated by testing three consecutive batches using offline analytical techniques. The requirements for validation are pre-determined before the validation runs based on the development and process scale-up data. The three validation batches must all

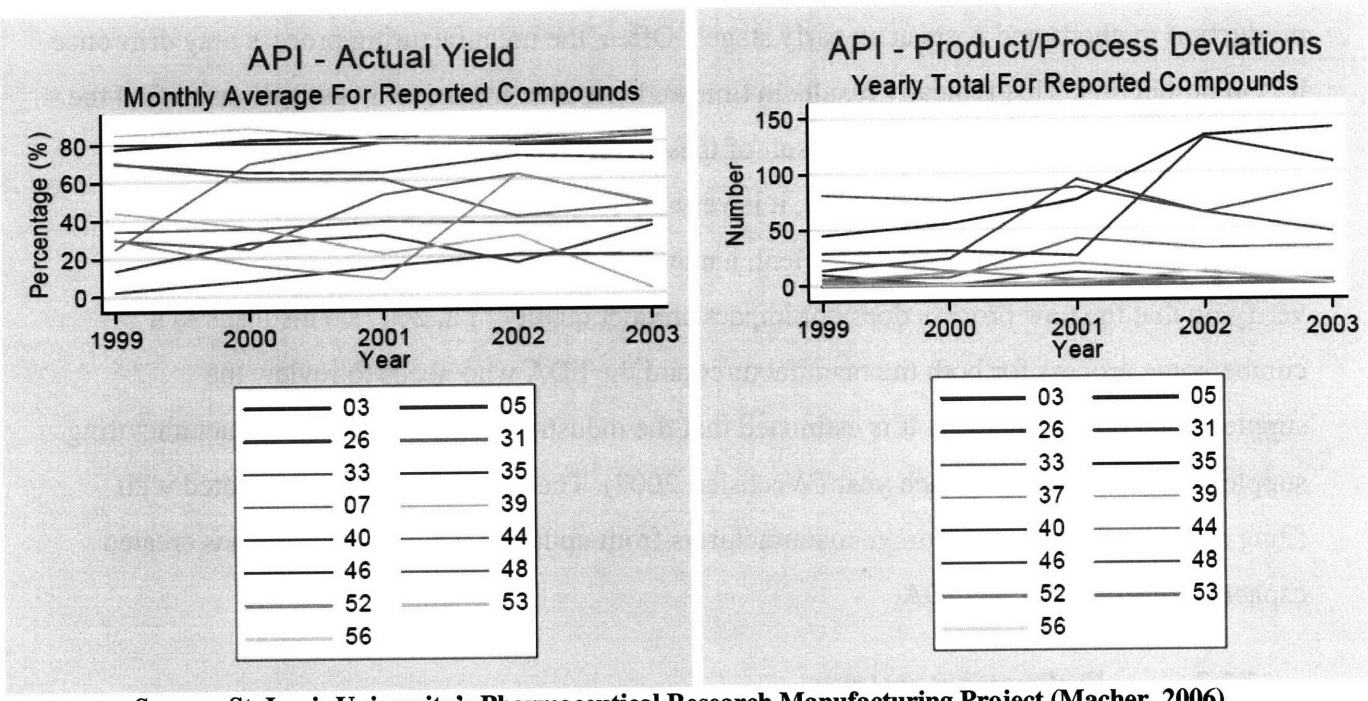
fall within these specifications. Once the validation has been completed, manufacturers are not permitted to make changes without filing supplements with the FDA. Drug manufacturers typically perform only limited characterization on the causes and effects of process variability outside of the validated range. As Hinz (2005) quotes "Because of the effort involved and the associated costs that are required to maintain compliance with government agency requirements, manufacturers avoid making any process changes after phase II clinical trials, thus locking in production methods and costs at an early stage". Often, the manufacturing process may drift once it is in production. This typically results in time and resource-intensive investigations to find the causes of the deviations. Even if the result of these investigations is that the manufacturing process or setpoints should be changed, it is very difficult to do so. Anytime a change is requested to make a process more efficient, a manufacturer must file data and documents verifying that the new process does not impact product quality (Yu, 2007). This leads to a cumbersome process for both the manufacturer and the FDA who needs to review the supplemental documentation. It is estimated that the industry submits about 4000 manufacturing supplements to the agency each year (Wechsler, 2002). The time and money associated with filing a process change discourage manufacturers from updating their process and has created capacity constraints at the FDA.

1.2.3. Performance metrics

The highly regulated environment ultimately results in inefficient manufacturing processes and the use of outdated methods and equipment. A KPMG study reported that 72% of drug recalls are a result of manufacturing defects (Cook, 2007). Capacity utilization levels have been estimated to be less than 15% and batch quality failures range from 5 to 15% (Scott, 2008). In some products, waste has been reported to be as high as 50% (Winkle, 2007). In comparison, the semiconductor industry maintains waste well below 1% (Femia, 2005). The average cycle time is 95 days, and the writing of non-conformance reports for batch failures can increase cycle time by 50% given that root causes for failure are usually not well understood. (Scott, 2008). Inventory turns in the pharmaceutical industry are 3-5 versus 50 for world class manufacturers in other industries (Femia, 2005). A benchmark analysis of the pharmaceutical industry was performed for St. Louis University's Pharmaceutical Research Manufacturing Project that was launched in 2002. Data were collected from 19 pharmaceutical manufacturers and 42 facilities

and is summarized in a 462 page report (Macher, 2006). As can be seen in Figure 1 the average monthly yield reported by the respondents varied between 20 to 80%, and the reported number of product or process deviations per compound varied between 0 and 150. It is clear that there is substantial room for improvement of pharmaceutical manufacturing processes.

Figure 1 Actual Yield and Process Deviations Reported by Pharmaceutical Companies



Source: St. Louis University's Pharmaceutical Research Manufacturing Project (Macher, 2006)

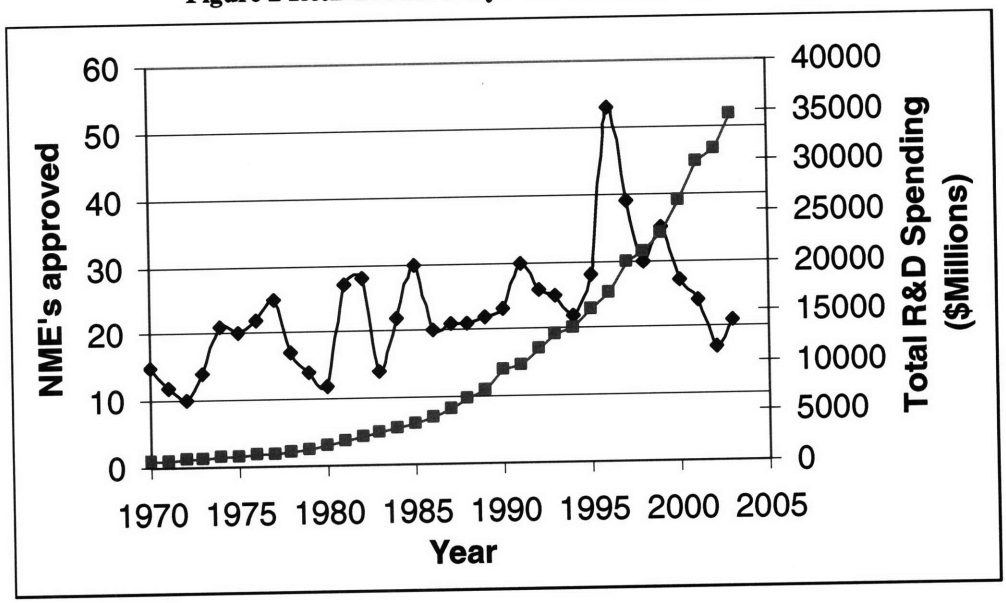
1.2.4. Why Change is Necessary

The profit margins in the pharmaceutical industry have historically been so high that there has been little incentive to invest in improving the manufacturing process. For example, in 2001, the pretax margins at the top 10 global pharmaceutical companies averaged over 26% (Sellars, 2002). However, the pharmaceutical industry is now facing increasing pressure to reduce costs. Neway (2003) describes these pressures as including:

Skyrocketing R&D costs: The pharmaceutical industry is one of the most research intensive industries in the world. Pharmaceutical industries invest approximately 3-4 times more into R&D, relative to sales, than traditional manufacturing companies (Cohen, 2005; NSF,2003). The cost to develop a new drug has increased substantially over the past 30 years, from $138 M in 1975 to $802 M in 2001 (PhRMA Industry Profile, 2008). The increased cost of developing a

new drug can be attributed to multiple factors, including higher failure rates, longer and larger clinical trials, and a shift towards development of more complex drugs. However, despite the increased spending on R&D, approvals of new innovative drugs (new molecular entities) have decreased dramatically. Figure2 shows the trends in pharmaceutical productivity from 1970 to 2005.

Figure 2 R&D Productivity in Pharmaceutical Industry



Source: NME approval data adapted from FDA Center for Drug Evaluation and Research; R&D spending data adapted from PhRMA Industry Profile, 2008.

Decreased periods of patent exclusivity: In June 2003 President Bush signed a bill that limited patent extensions to pharmaceutical companies. The "Greater Access to Affordable Pharmaceuticals Act" limits the number of 30-month patent extensions that pharmaceutical companies can receive to only 1 (U.S. Congress, 2003). This closes a loophole in the 1984 Hatch-Waxman Act that allowed companies to receive multiple extensions to their initial pharmaceutical patents.

Increasing generics market: Patents of several blockbuster drugs have recently lost, or will soon lose, patent protection. Between 2007 and 2012 more than three dozen drugs, equating to combined revenues of over $67 billion, will lose patent protection (Martinez, 2007). When a drug comes off patent, generic manufacturers can produce the drug at a fraction of the cost. In

general, once the first generic enters the market the price for the drug falls by 20%, and then can drop by as much as 90% as other generics enter the market (Nocera, 2006).

The industry is finally realizing that in order to remain competitive, they need to start investing in their manufacturing process. They can no longer afford to lose revenue from their products because of long start-up and scale-up times, lost batches, process instability, and product recalls. Ajaz Hussain, the Deputy Director of the FDA's Office of Pharmaceutical Science, states that "In the current state, innovation and continuous improvement in pharmaceutical manufacturing is discouraged to a large extent by uncertainty"(Hussain, 2005). Janet Woodcock MD, the Chief Medical Officer of the FDA, has said "What we need to do is to start modernizing everything. That's the way out" (Woodcock, 2007).

1.3. PAT Initiative

In August 2002, recognizing the need to improve the manufacturing processes in the pharmaceutical industry, the FDA launched a new initiative entitled "Pharma cGMP's for the 21st Century: A Risk-Based Approach." The goal of this initiative is to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. The FDA also hoped that the initiative would help change the perception that the FDA is resistant to change and hence stifles innovation and continuous improvement. The overall theme is that the FDA is proposing a move from the current state of quality by testing, to a "desired state" of quality by design. In the words of W. Edwards Deming, "Quality comes not from inspection, but from improvement of the process".

Quality-by-design is defined as a "systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development" (Winkle, 2007). It begins with predefined objectives and emphasizes product and process understanding. Product and process performance characteristics are scientifically designed to meet specific objectives, not derived from performance of test batches. During QbD development of a product, the development team seeks to determine the multivariate relationships among material, manufacturing process, and environmental variables that affect the product quality. The increased process knowledge allows for the scientists to define the "design space", i.e. ranges within which the process will consistently ensure a predefined quality at the end of the process. Once the relationship between

process variables and product quality is understood, the product quality can be controlled in real-time by adjusting process variables. This will allow for the elimination of offline testing and real-time release will be possible.

Table 1 highlights the differences between the current state of pharmaceutical manufacturing and the desired state once Quality-by-Design has been implemented.

Table 1 Comparison of Current state and Desired State

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, supported by robust quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release

Source: Presentation by Helen Winkle (2007)

1.3.1. PAT Framework

Process Analytical Technology (PAT) has been defined by the FDA as a system to design, analyze, and control pharmaceutical manufacturing processes through the measurement of critical process parameters and quality attributes (FDA, 2004). PAT is a tool that can be used to achieve quality by design, and is an "enabler of the real goal: the understanding, variation reduction, and control of critical process parameters in the business context of maximizing value" (McCormick, 2006) .

The pharmaceutical community was asked to take on responsibility of drafting a guide to assist companies with the implementation of QbD. In 2004, the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) issued the "Guidance for Industry PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality

Assurance." (FDA, 2004) This guidance was intended to create a framework that would assist industry with practical application of PAT in order to achieve quality-by-design. The guidance was not intended to be mandating, but rather attempt to create a regulatory environment that fosters innovation. The framework consists of four main components- multivariate tools, process analyzers, process control tools, and knowledge management IT systems. Implementation of these tools will allow scientists and engineers to develop the scientific and mechanistic basis of process understanding, and move away from the current method of purely correlative models.

Multivariate tools for design, data acquisition and analysis enable the identification and evaluation of product and process variables that may be critical to product quality and performance. Instead of performing traditional one-factor-at-a-time experiments, multivariate methods allow for efficient identification of critical interactions of product and process variables. These multivariate methods include statistical design of experiments (DoE), response surface methodologies, and multilinear regression analysis.

Process analyzers measure the physical, chemical, and biological properties of materials. Data collection using online or inline process analyzers can be nondestructive, require minimal sample preparation, and have rapid or real-time response when compared to traditional methods. Although many forms of process analyzer exist, the most common forms of process analyzers are Near Infrared Spectroscopy, X-ray diffraction, FT-IR Process Analyzers, Particle Size Analyzers, and Light-Induced Fluorescence. The process analyzers can either be implemented at-line, online, inline, or offline:

> ***At line***: sample removed from process stream and then analyzed in close proximity to process equipment
>
> ***Online***: sample diverted from the process, analyzed, and returned to process stream
>
> ***Inline***: sample is not removed from process stream and can be invasive or noninvasive
>
> ***Offline:*** sample is removed, isolated, and analyzed away from process in laboratory

Process control tools are used to monitor and actively manipulate a process to ensure control. Process analyzers can be integrated into a process control application to measure critical process

parameters and product attributes and adjust accordingly in real-time in order to achieve desired in-process and finished quality specifications.

Continuous improvement and knowledge management tools – Integration of PAT (process analyzers, multivariate analysis, and process control tools) results in the generation of a large volume of data which must be converted from data to knowledge. These tools collect, analyze and present data in a manner that can be easily understood by process operators and engineers.

1.3.2. Benefits of QbD and PAT

The obvious main benefit of PAT is the increase in process understanding and control. However, strategic implementation of QbD and PAT can also offer substantial benefits to a company in terms of reduced operating and quality costs. Although difficult to quantify how these translate into cost savings, a recent estimate of potential worldwide cost savings from efficiency improvements is suggested to be as high as $90 billion (Benson, 2004).

- **Reduced Cost of Quality**

As mentioned above, average batch failure rates in the pharmaceutical industry are around 15% (2.5 sigma). Product quality inspections bring the defect rate of product introduced to the market to approximately .003% (5.5 sigma). The cost of these quality programs is significant and therefore brings the cost of quality, on average, to 25% of sales (Schneider, 2006). The cost of quality is significant due to a multitude of variables including time-based endpoints, process variability, raw material variability, sampling time, sampling errors, and sample preparation (Scott, 2008). G.K. Raju, director of the MIT Pharma Manufacturing Initiative, has said that manufacturers often spend more time on quality control testing than on actual manufacturing (Weschler, 2002). Improved process understanding and control can greatly reduce this cost of quality by reducing the rates of defects in the process. One estimate is that the potential savings from PAT-driven reduced cost of quality will be over $1 billion for each of the top 10 pharmaceutical companies (Schneider, 2006).

- **Decreased cycle time:**

Replacement of offline testing with online methods would reduce production cycle time by eliminating the long lag period between steps waiting for offline analytical results. It has been reported that only 3 days, out of an average 35 day cycle time, consist of value-added activities (Dean, 2001). Another report estimated that only about 2% of a typical quality control check time is spent testing the material (Raju, 2001). A cycle time reduction to the industry best practice of six days would decrease inventory in the system and save inventory carrying costs, which average $76 million for each of the top ten pharmaceutical companies (Schneider, 2006).

- **Enabler of Continuous Manufacturing**

Additionally, this move from reliance on end-point testing to real-time analysis is a necessary pre-cursor for achieving continuous manufacturing, a goal that Novartis is aggressively pursuing. In continuous manufacturing, the process is run start to finish with no intermediate stops between process steps. Continuous manufacturing requires significantly less square footage and equipment to produce the same volume of product, which translates to substantial CAPEX savings. It has been proposed that continuous manufacturing will reduce the building volumes from new facilities by up to 65% from current levels (Crosby, 2008). It is estimated that even a 50% reduction in CAPEX at each of the top ten pharmaceutical companies would translate to $0.8-1.6 billion per year (Schneider, 2006). Continuous manufacturing also allows for enhanced manufacturing flexibility to respond to rapidly evolving market needs.

- **Decreased process development time**

For new products, a benefit of PAT is the ability to use multivariate methods and online analyzers to reduce the time required to scale-up a process and perform validation. This translates to decreased time to market which is highly valuable in the competitive pharmaceutical industry.

- **Increased ability to make process change**

A flexible process will reduce the number of manufacturing supplements required for post market changes, as companies will begin to rely on process and risk understanding. This

will remove one of the hurdles that companies faced when trying to improve their manufacturing processes.

- **Decreased regulatory agency burden**

Additionally, implementation of QbD and PAT will benefit the FDA and other regulatory agencies as the time spent on reviewing applications and supplements will decrease and therefore free up resources. Nasr from the FDA has said that "Resource requirements will go down because the QbD approach and regulatory flexibility will result in a reduction in the number of supplements. So the resources that we currently use to review supplements will be available for new applications" (McCormick, 2006).

1.4. Levels of QbD Implementation

I propose a 5 level classification system of Quality-by-Design implementation. This classification is my own and most likely not used in other sources. However, for the remainder of my thesis I will refer to the five levels of QbD implementation as proposed and described below:

Level 1. Online monitoring of process data using online sensors. This is typically referring to process inputs (or control variables), such as temperature, pressure, and speed.

Level 2. Replacing offline quality measurement with online measurement using process analyzers that measure product quality in real time. Implementation of this step is independent of step 1. Therefore, you can have online process analyzers that measure product quality without monitoring the input process parameters online.

Level 3. Understanding relationship of input parameters on output parameters by performing DoE at the laboratory scale, pilot scale, and/or full scale. This step is necessary in order to establish a design space in which the process can operate robustly and consistently produce quality product. This step can be performed independent of step 1 and 2, however it is necessary to use either online or offline process analyzers to measure the product quality.

Level 4. Incorporating online process data into multi-variate model that will predict product quality. Once this is model is validated, the majority of product testing (either online or offline) can be eliminated. The multi-variate model incorporates input variables from the very beginning of the process (i.e. crude material) to the end. Therefore, incoming raw material specifications and process data are used to predict the final product quality for each step. The product quality data are then carried into the subsequent step as an input variable to the model. Achieving this level of implementation is highly dependent on steps 1 as the online data are needed for incorporation into the model. Additionally, if the multi-variate model is going to be used to trend a process and real-time, then an understanding of acceptable operating ranges for the key variables must be determined through DoE (step 3). Achieving real-time release requires extensive model validation and monitoring of all measurement devices.

Level 5. Controlling process in real-time using MVDA and feed-back loops. This is the ultimate goal of QbD as it minimizes deviations by employing immediate corrective action when a process in abnormal. Achieving this level is dependent on steps 1, 3, and 4. In order to implement feedback control loops, an in-depth understanding of the relationship between input and output variables must first be determined through DoE.

1.5. Literature search

1.5.1. Demonstrated use in other industries

Process analysis, monitoring, and control have been in use for over 40 years in several industries including the petrochemical, polymer, and chemical industries. These industries all followed the path that the pharmaceutical industry is starting out on now. They saw the need for real-time quality measurements and developed real-time analyzers. The Universal Oil Products first analytical and control instrument group was formed in 1959, and given the mission of developing on-line analyzers (Kourti, 2006). After the industry became capable of collecting real-time measurements of quality properties and of other process variables, automatic process control techniques were developed. In 1961, a paper was published in *Applied Statistics* suggesting that computers could allow for multivariate analysis of variables in industrial

applications (Thomas, 1961). However, it wasn't until about 15 years ago that industries really started to incorporate multivariate statistical analysis to monitor and trend the process performance in real-time. Over the last 15 years, several industries have managed to improve process performance and reduce cost through multi-variate-statistical analysis.

1.5.2. Pharmaceutical industry

The pharmaceutical industry lags far behind these other industries in implementing PAT and QbD principles to production. A Wall Street Journal article (Aboud, 2003) quotes that *"the pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing technology lag far behind those of potato-chip and laundry-soap makers".* The industry understanding of PAT is quite varied. Some view it as only a way to measure quality by replacing offline analysis with online analysis and many companies are just focusing on applications of technology such as NIR. A literature review of over 80 articles focused on applications of process analyzers in the pharmaceutical sector, 58 focused on the application of NIR to processes such as granulation, compression, and milling (Scott, 2008). There is one review article by Yu (2003) does offer a very in-depth overview of examples of PAT applications, including sensor technologies, experimental design, and MVDA to crystallization processes. Often literature reflects the benefits of a particular piece of technology without any emphasis on or referral to the 'broader' goals that are at the heart of PAT initiative. It is this narrow focus within the industry that led Ajaz S. Hussain, deputy director of the Office of Pharmaceutical Science at the FDA to say "you've got to remember that PAT is not about just throwing in-line sensors at a production line. It is more about understanding the sources of product variability during production and controlling your processes in a flexible way to allow you always to produce a quality product" (Maes, 2006).

In the summer of 2004, Pharmaceutical Technology posted a brief on-line survey to better understand the awareness and attitudes of PAT within the pharmaceutical industry (McCormick, 2005). The 65 responses demonstrated only a moderate understanding of PAT concepts and implementation. Over 60% of respondents believed that PAT would yield improvements in quality, reduce rejects and increase equipment efficiency. However, 49% said that their organization does not have an awareness of the FDA PAT guidance or an established

PAT team. This survey clearly shows that there is a disconnect between the perceived benefits and implementation efforts within pharmaceutical companies.

The majority of pharmaceutical companies are currently only at phase 1 or phase 2. The focus of most PAT implementation has been on replacing offline testing with online testing (Yu, 2004; Maes, 2007). However, the future vision of the FDA quality-by-design initiative is to have quality built into the process. The pharmaceutical industry has a long way to go before it will be at the level achieved by many other industries. There is a need for increased communication between the FDA to close the gap between the high-level guidance and practical, validatable implementations in the factory.

2. Pilot QbD Project

2.1. CRADA and CMC Pilot Applicants

The FDA instituted a pilot program, managed by the Office of Drug Quality Assessment in July 2005. Twelve large pharmaceutical companies were asked to volunteer to demonstrate their "quality-by-design, product knowledge, and process understanding of the drug substance and drug product in a new drug application" (FDA, 2005). The goal is for industry to help shape the FDA guidelines on future QbD submissions. Although not part of this program, Novartis did enter a similar CRADA with the FDA in order to demonstrate the feasibility of applying QbD principles to a manufacturing process.

2.2. Team Composition

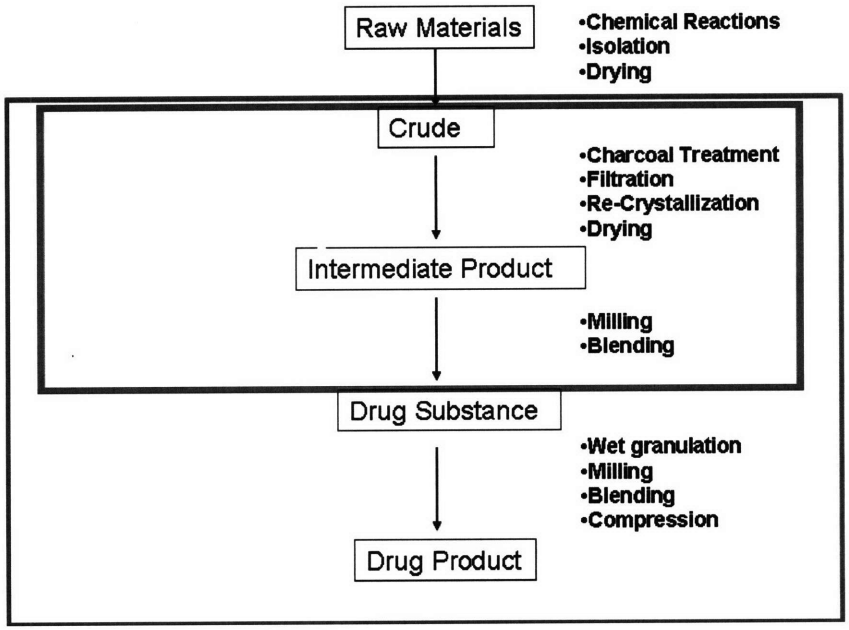
The project leader realized early on that it was critical to have a multi-functional team in order to successfully implement PAT. Therefore, the team consisted of members from Research and Development, Process Engineering, Manufacturing, IT, Quality Assurance, and Regulatory. Additionally, outside vendors and consultants were involved with the equipment installation and validation. There were over 30 key team members, spread across multiple sites in Switzerland, New Jersey, and France. The team leader was the director of the Global PAT division, and reporting directly to him were two senior scientists- one in charge of the PAT drug substance team (Chemical Operations) and the other in charge of the PAT drug product team (Pharmaceutical Operations). I believe that the team composition was critical to the success of PAT implementation as it involves cross-functional teamwork and support from upper management.

2.3. Scope

A product was chosen that was relatively simple with a well understood process. The rational, as explained by Cook (2007), is that by starting with a simple, relatively easy to understand process, QbD implementation is more manageable. The product had already been approved and on the market, therefore a supplemental filing is required. The manufacturing process involves both drug substance and drug product manufacturing. Drug substance

manufacturing, which consists of crystallization and milling, purifies the crude material and prepares it for further processing. The Drug Product process transforms the drug substance into the final tableted form sold to consumers. Figure 3 shows a high-level breakdown of the process.

Figure 3 Overview of Manufacturing Process



It was decided by the process team to not include crude (primary synthesis) manufacturing into the project scope. This is because crude manufacturing is a more basic process that is currently performed on older equipment onto which would have been difficult to install new technologies. Therefore, only drug substance and drug product manufacturing were included in the scope of the project (small box in Figure 3). My specific involvement included only drug substance manufacturing (large box) and therefore I will only be discussing these process steps throughout the thesis. However, many of the challenges of implementing QbD and PAT to drug substance manufacturing were also present in drug product manufacturing. Therefore, the recommendations that I make are not unique only to drug substance manufacturing, but to the entire process.

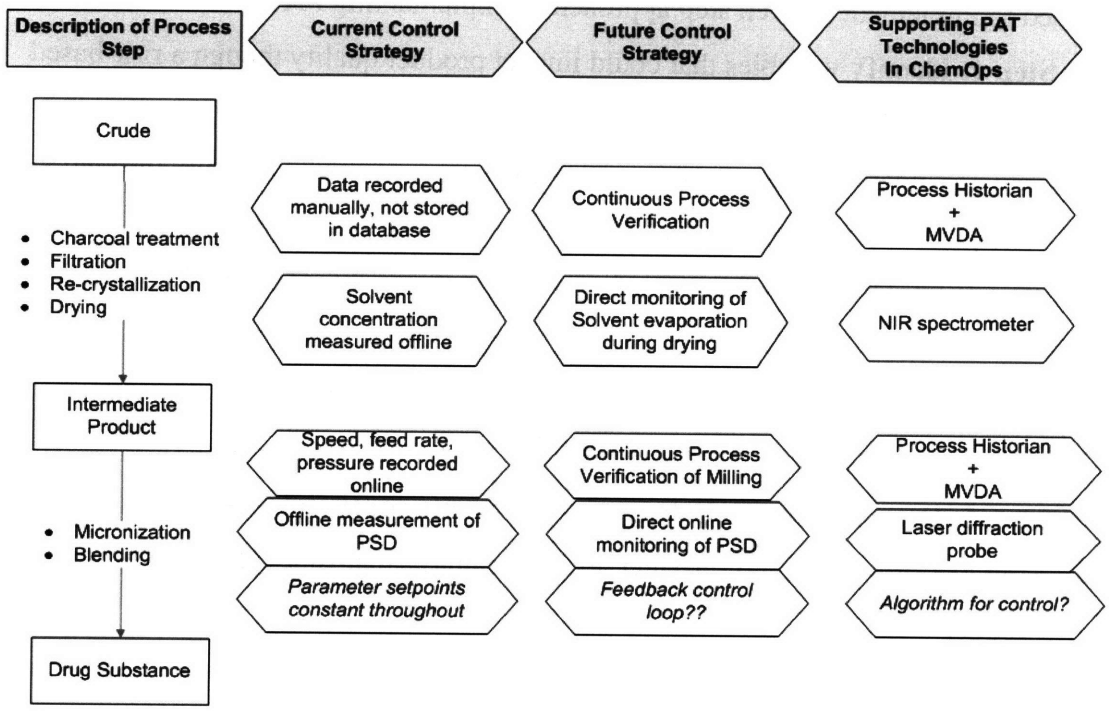
2.4. Team Approach

The team decided to implement a seven step approach to implementing PAT:

- **Step 1:** Identify variables that could impact product quality though a risk-based analysis (FMEA)
- **Step 2:** Understand relationship of these variables to product quality through systematic experiments (DOE) at lab scale to define design space
- **Step 3:** Implement PAT in manufacturing to monitor process variables in real time
- **Step 4:** Use Multi-Variate Data Analysis to build a model that will predict product quality based on the process data
- **Step 5:** Develop control strategy that will ensure consistent product quality
- **Step 6:** Eliminate end of product testing and have real-time release of drug product
- **Step 7**: Encourage continuous learning through data collection and analysis

The team approach encompasses all five QbD layers. Figure 4 outlines the current control strategy and future control strategy envisioned for intermediate and drug substance manufacturing. In order to achieve the future control strategy, supporting PAT technologies need to be implemented. Additionally, in order to have continuous process verification and continuous release, it is necessary to have a well characterized process and defined design space. Therefore, for each process step an FMEA and design of experiment must be performed at the laboratory and pilot scales in order to propose the acceptable operating parameters at the commercial scale.

Figure 4 Overview of Manufacturing Control Strategy



In order to achieve the ultimate goal of continuous process verification, Levels 1-5 of QbD need to be implemented. The first step required the added capability for the process data to be recorded electronically and stored in a database. Although not a simple task to move a plant from being manual to automated and to connect all process data in a process historian database, this was not within the scope of my internship or thesis as it was completed before I arrived. In the following chapters, I will however discuss the specific procedures and challenges faced by Novartis in attempting to implement levels 2-4 of QbD.

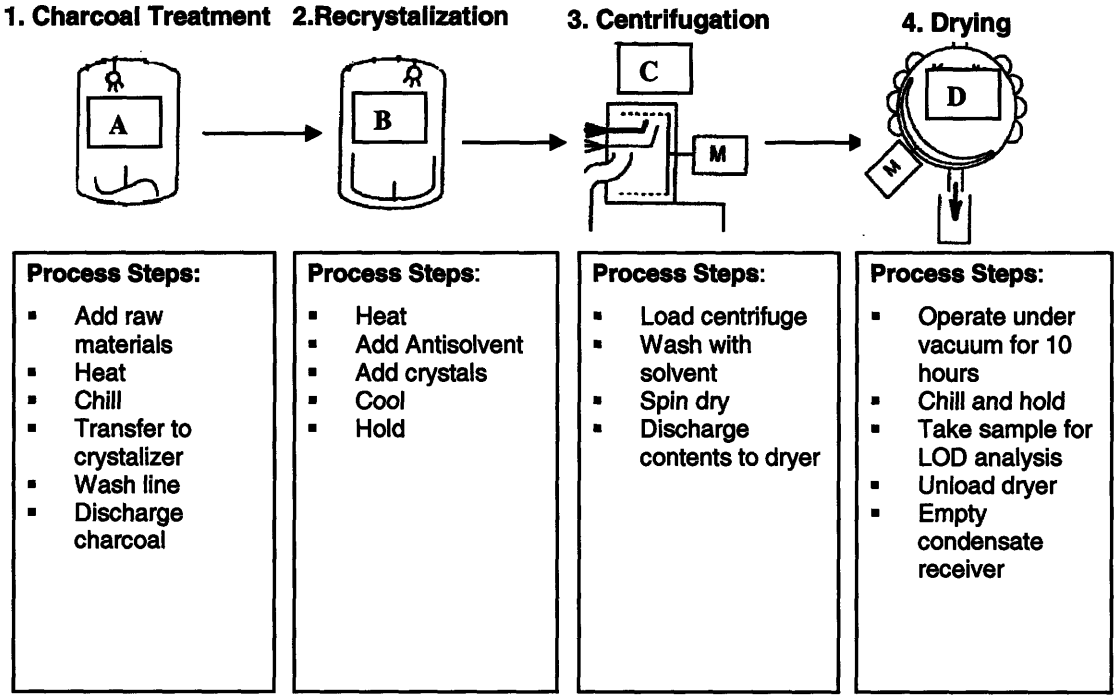
3. Level 2 Implementation - NIR

3.1. Current Process

3.1.1. Process Description

The intermediate product is produced in Switzerland at a Multi-Purpose Production facility. The purpose of this step is to purify the crude material using an activated charcoal treatment. The IP production consists of four primary unit operations: Charcoal treatment, recrystallization, centrifugation, and drying. Each unit operation is further broken down into a series of steps, which are described in Figure 5.

Figure 5 Overview of Intermediate Production Process



3.1.2. Control strategy

The process, before implementation of PAT, was controlled in a rather manual fashion. The equipment that was used was the same that had been used when the plant was built in the early 1960's. The current control strategy is to set a parameter, such as temperature, through manual valve adjustments. The process parameters are manually recorded in a batch record. At the end of the batch, a printout of the process trends is

obtained and analyzed to ensure no process deviations occurred during the process. However, no electronic data are recorded or stored and therefore cannot be retrieved at a later time. Parameters that are deemed "quality critical" in the initial filing and therefore necessary to control throughout the process include pressure, temperature, stir speed, and amount of raw materials added.

3.1.3. Testing

The only IPC that occurs during for drug substance manufacturing is the loss on drying test at the end of the cycle. It specifies that the loss on drying at the end of the drying cycle must be below 0.2%. Loss on drying is a measurement of how much liquid (water+solvents) evaporation there is when the sample is dried for a set amount of time in a dryer. The equation for calculating LOD is: LOD= (weight before-weight after)/ (weight before). LOD does not measure the actual water and ethanol concentrations; it is only an indicator of the actual concentrations. Previous studies had shown that when the LOD was less than 0.2%, that the actual water and solvent concentrations were within the acceptable product quality limits. The drying process endpoint is time-based. Only after ten hours is a sample withdrawn from the dryer and analyzed. If the LOD is within specification then the dryer is emptied into containers and shipped to the milling facility. As only one sample is taken, the water and solvent evaporation trend is not measured or known during the drying process. At the end of the drying process, a sample is taken and tested for product impurities and actual solvent concentration using Karl Fischer and HPLC.

3.2. NIR Description

3.2.1. Technology

Near-infrared spectroscopy (NIR) instruments are some of the most widely utilized Process Analytical Technologies in pharmaceutical manufacturing. NIR has historically been widely used in the laboratory as an analytical technique to identify material composition. It has also been used to monitor particle size changes, moisture content, blending homogeneity, and completeness of reactions. The specific application described here is to monitor liquid (water +

solvent) concentration during the drying operation. NIR can be used to measure liquid in either the solid or the vapor phase.

The technology is based on measuring the intensity of the absorption of near infra-red light by a sample. A near infrared light beam is pointed at the sample using a fiber optic probe and the reflected signal is processed for reflective characteristics. The NIR absorption spectrum is due to the vibrations that each functional group generates in the NIR spectrum (780-2500 nm). NIR offers a distinct advantage over other spectroscopy techniques in that it allows analytical measurements to be made without the need to perform any sample preparation and is non-invasive, and therefore is ideal for on-line and at-line measurements. The apparatus contains a probe that is connected to a spectrometer. The spectrometer transforms the raw spectral data using chemometrics (Fourier Transform) to identify the exact composition of the raw material. Then, a model is built that predicts the water and solvent concentration based on the transformation of the raw spectral data. A paper by Reich (2005) explains the technology in great detail, including the basic principles, theory, and practice of chemometric data processing.

For this process, the NIR probe was installed at the bottom of a spherical dryer for measurement of liquid in the bulk. The probe is not in direct contact with the material, but instead the infrared light beam shines through a sight glass. In order to prevent build-up of material onto the sight glass, an N_2 purge was implemented to remove material from the sight glass after every spectral measurement.

3.2.2. Benefits

This technology offers substantial benefits both in terms of quality, safety, and cost. On-line dryer monitoring has the potential to eliminate the need for multiple in-process sampling during drying because the end of drying can be determined automatically through the online analysis. Because the drying endpoint is determined through online measurements, the need for offline sampling is eliminated. This improves quality because the potential for over-drying and under-drying is minimized. Over-drying can cause loss of desired hydrate forms, a change in polymorphic form, as well as processing complications such as fracturing of crystals leading to smaller-than-desired particle sizes (Parris, 2005). Under-drying can result in an excess of solvent that could have potential safety implications for the patient. Manually collected samples are

susceptible to changes in physical conditions like humidity and segregation, which will lead to inaccurate moisture analysis.

Often, the vapors are hazardous and physical handling of wet samples can raise safety and hygiene issues for the operators. Secondly, when the sample is taken at the Novartis facility, it typically takes between 30-60 minutes to run the sample to the lab and analyze it using the LOD method. Since the drying operation is not completed until the offline analysis results show that the solvents are below the acceptable limit, processing delays occur as operators wait for the results from the offline analysis.

Online monitoring significantly reduces the overall required testing time. Han and Faulkner (1996) reported that the traditional method required 15 minutes to measure moisture content (LOD) and an additional 30 minutes for the analysis of the active ingredient. However, the NIR reflectance method required less than a minute for moisture content, identification, and assay analysis. This reduced time translates to direct cost savings through decreased cycle time and expensive laboratory analysis.

3.3. Use of NIR by other companies

Inline or online NIR has been implemented by many companies for use in several process steps including granulation, blending, drying, crystallization, and compression. NIR can be used to analyze a multitude of attributes such as moisture content, particle size, blend homogeneity, and chemical composition.

A specific example of a company using NIR to monitor drying operations is GlaxoSmithKline (Parris, 2005). They used NIR to monitor the composition of the vapor-phase gases that are drawn from the dryer. The product was wetted with two solvents, dichloromethane and n-heptane. They used Simca P+ software to perform the following data analysis: 1) Correct spectra for baseline shift using 1st order derivatives, 2) Apply principle component analysis (PCA) to reduce dimensionality of dataset, 3) Plot the scores of first principle component to create the overall-all drying profile over time. After successfully monitoring several batches, GSK realized that the drying was actually completed in less than six hours, significantly less time than the 12 hours that they had previously been drying the product. GSK was able to eliminate sampling for off-line testing and rely only on the online data. Additionally, the process engineers were able to see the immediate effects of agitation on the drying process. This

increased process knowledge provided by the online data enabled them to optimize the drying process.

3.4. Validation

Much literature exists on what key elements need to be considered when validating NIR spectroscopy for PAT application. An article by Scott and Wilcock (2008) summarizes in great detail the findings from 5 different papers relating to NIR validation. In the following section, the specific approach that Novartis used to validate the online NIR method is discussed.

3.4.1. Validation Procedure

The installation and subsequent validation of the NIR probe into the dryer was a collaboration between the process engineers, manufacturing personnel, and the equipment vendors. In order to replace offline testing with the online method, it had to be proven that the online method could consistently and reliably measure both the water concentration and the solvent concentration during the drying process. In order to do this, a cross-validation between the online and offline method had to be performed. There were a total of 11 dryer batches. It was decided to use the first eight batches to calibrate the model, and the last three batches to validate the model. The project team decided to take a three step approach to accomplish the validation:

1. Acquisition of calibration samples

   In order to calibrate the model, multiple offline samples were collected during the entire drying process. Samples were collected before drying, and at 30 minutes, 1 hour, 1.5 hours, 2 hours, 5 hours, and 10 hours. Because samples were to be measured in the probe manufacturer's laboratory, the samples were held in sealed containers until the validation runs were completed. All samples were analyzed at the same time, so some samples were held for up to three weeks before being measured. The samples were then measured for water and ethanol concentration using the approved offline HPLC and gas chromatography methods.

2. Model Development

The raw NIR data had to be converted into a model that would predict both water and solvent concentration. To do this, the equipment vendor used multiple calibration standards to develop a model. This model was then used to predict water and solvent concentration based on the raw NIR data obtained during the calibration runs.

3. Model Validation

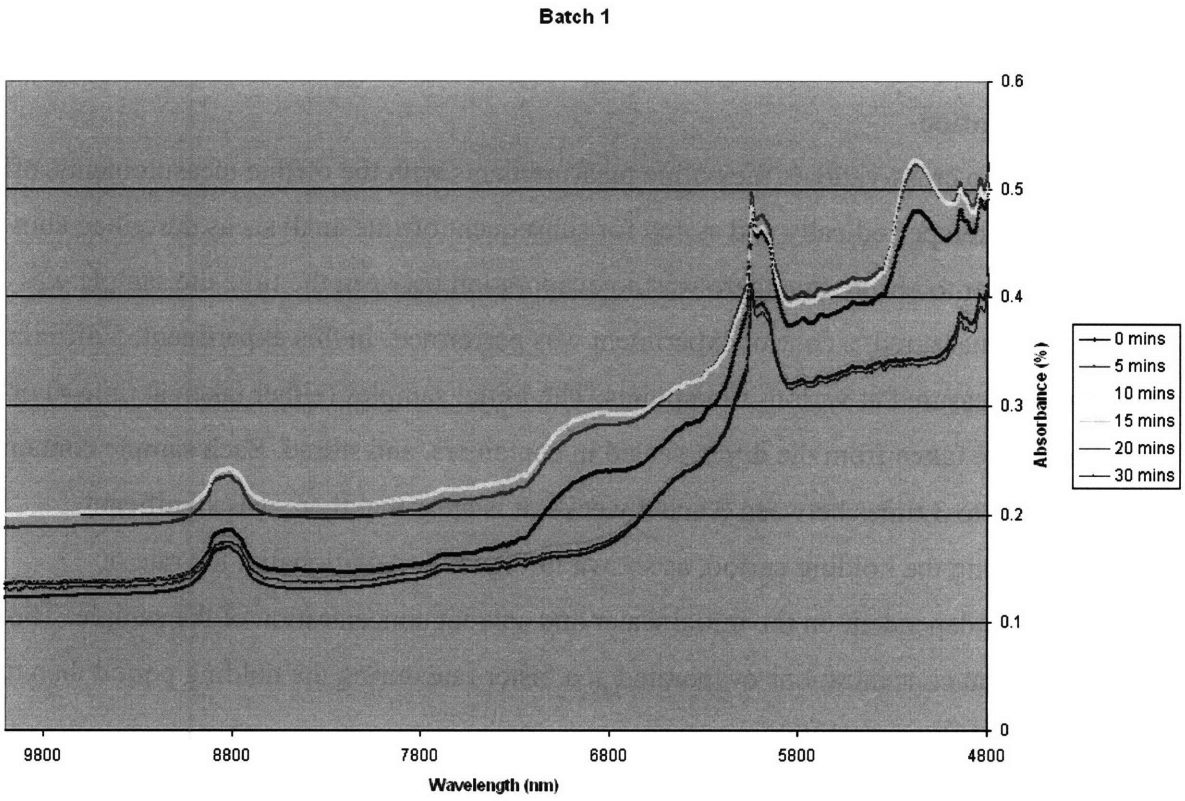
The validation was to be deemed successful if the offline and online measurement were statistically equivalent. Determining how to set the acceptance criteria proved to be rather challenging as there was not a standard protocol for cross-validating the method. The sensitivity of both the online and offline methods was taken into account. We referred to the validation protocol of the offline method to find the sensitivity of the offline method. There is a higher sensitivity at lower solvent concentrations, meaning that the offline method is more accurate when the solvent concentration is lower. Therefore, it was decided to break the validation into two parts, during the initial drying when the water and ethanol concentrations are greater than 0.7% and during the end of drying when they are less than 0.7%. The validation would be deemed successful if the difference between the online and offline method was less than 3x the sensitivity of the offline test, as determined during the initial method validation test. The sensitivity of the offline was calculated to be 0.5% when the actual concentration is greater than 0.7% and 0.1% when the actual concentration is less than 0.7%.

3.4.2. Validation Results

The method validation was initially unsuccessful for two reasons, the mechanical issues with the probe installation and the sample storage conditions. These two issues are described in more detail below.

Probe Installation: Careful monitoring of the raw NIR data revealed that the raw spectral data did not change after the first 15 minutes of the drying process. Figure 6 shows a sample of the raw data from one of the first several model calibration runs.

Figure 6 Raw NIR spectra from Drying Process



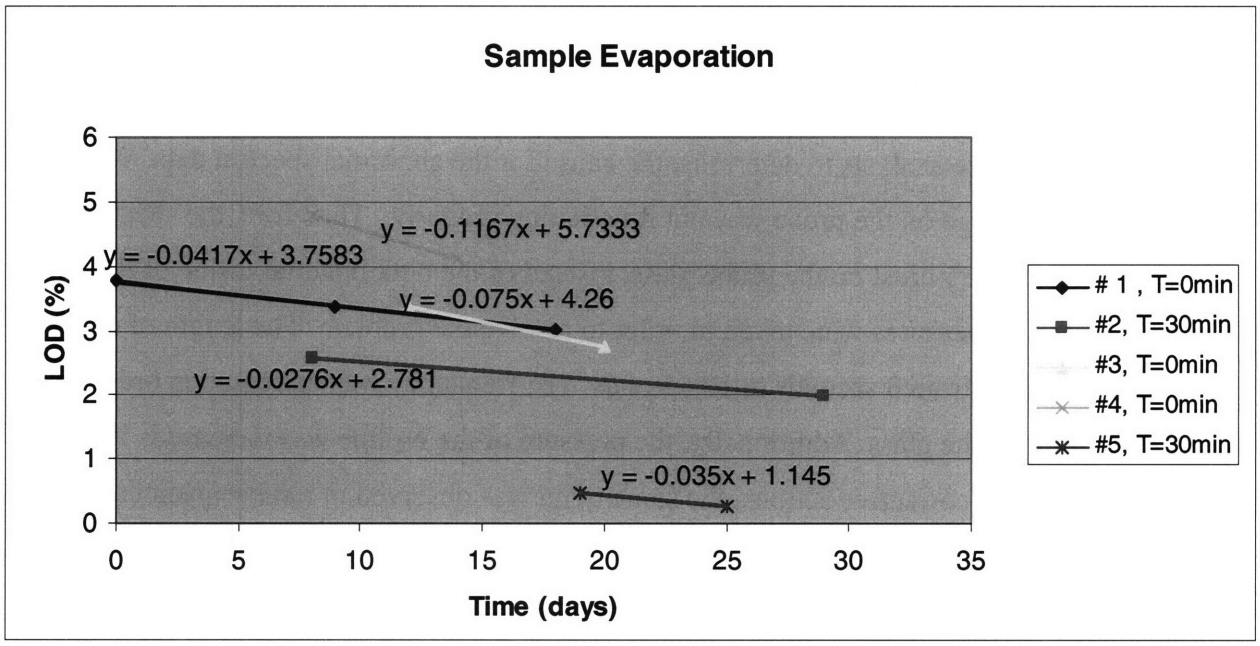
As can be seen, the OH and H_20 peaks (7000nm and 5200 nm wavelength) do not change at all during the first 10 minutes and have disappeared completely after approximately 15 minutes, indicating that the material was dry at this time. The scientific experts knew that it was impossible for all of the water and solvents to evaporate after such a short time. Therefore, we had to do a root cause analysis to determine the cause for the abnormal spectral data. We realized that the nitrogen purge on the probe was not functioning properly. Therefore, the spectrometer was measuring the dry crust on the probe glass, instead of the bulk material inside of the dryer. Several corrective measures were taken in order to resolve the problem. The length of each N_2 flush was increased from 3 seconds to 10 seconds. The frequency was increased in order to prevent buildup on the glass. Additionally, the pressure of the N_2 line was increased. After implementing these corrective actions, the same trend was observed in a subsequent calibration run. It was determined that the purge line was clogged again. While the dryer was loading, back pressure on the dryer pushes material into the flush line. We can't change the pressure differential in the dryer, but we were able to add a constant positive pressure on the line by having a continuous nitrogen flow during the dryer loading period. These three corrective

measures- increased flush time, increased flush pressure, and constant positive pressure on the line during loading eliminated the line clogging.

Sample Evaporation

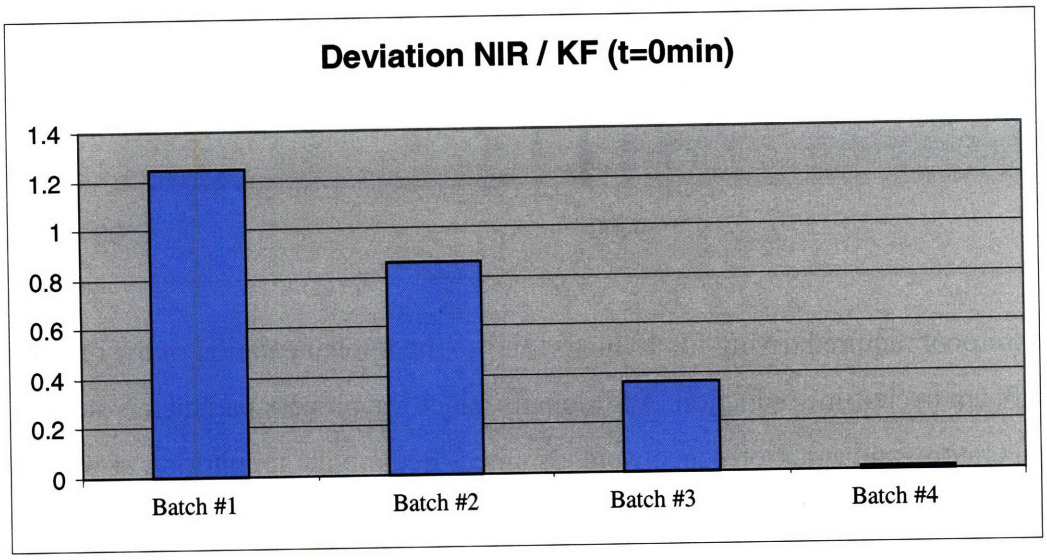
In order to cross-validate the online measurements with the offline measurements, offline samples were taken periodically and stored for subsequent offline analysis as described above. However, in order to ensure that there was no evaporation between the time the sample was withdrawn and measured, a control experiment was performed. In this experiment, 5 different samples were measured at various time points. The initial samples (either taken at time=0 or after 30 minutes) were taken from the dryer, sealed in containers, and stored. Each sample container was measured 2 to 3 times between 0 and 4 weeks. It is clear that there was significant evaporation during the holding period, as shown in Figure 7. Additionally, the rate of evaporation was dependent on the initial water and solvent concentration of the sample. Those with higher initial concentrations evaporated at a faster rate during the holding period than those with lower initial concentrations.

Figure 7 Sample Container Evaporation



This obviously affected the model calibration results since the samples were not measured offline until completion of all validation batches (holding period ranging from 1-4 weeks). As can be seen in Figure 8, the longer the sample was held, the larger the deviation between online (NIR) and offline (Karl-Fischer, KF) measurements. The sample from Batch #1 was held for multiple weeks, whereas the sample from Batch #4 was held for less than a week before offline measurement. The data in Figure 8 were generated by Solvias.

Figure 8 Comparison of Online to Offline Results

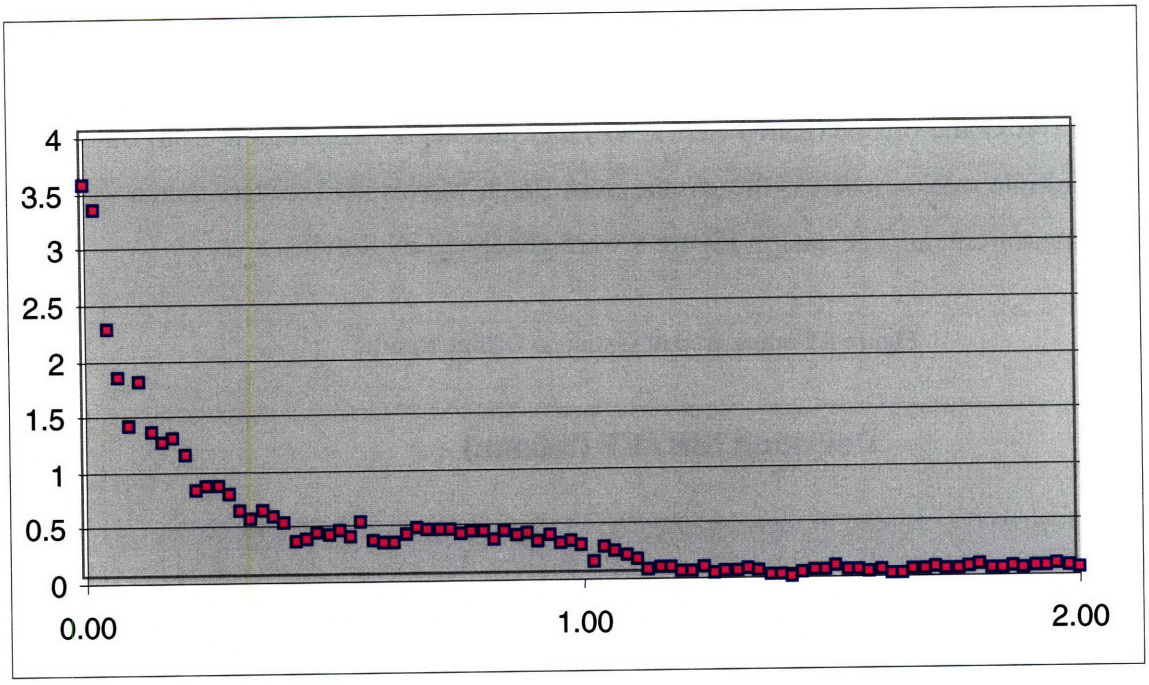


Therefore, due to evaporation, the offline values were lower than the online values measured by the NIR probe and the model validation was unsuccessful.

3.5. Increased Process Knowledge

Through real-time monitoring of the dryer, we were able to determine that the bulk material was dry within 1 hour. Figure 9 shows the model prediction of water concentration as a function of time based on the NIR data for one of the completed batches. The data in this figure were generated by Solvias.

Figure 9 NIR Model Prediction for H_20



The process protocol required drying for 10 hours, and so the implementation of the online probe enabled significant cycle-time reduction. Additionally, since the process parameters such as pressure, temperature, and agitation speed were also measured, online monitoring of water and solvent concentration will allow for further optimization of the drying process.

3.6. Feasibility of Use in Production

The NIR is a valid tool that should be implemented in to production runs. Several factors need to be considered when validating an online NIR method to replace an offline measurement. First of all, the optimal position of the probe within the dryer must be researched. Measuring the vapor concentration instead of the bulk concentration of liquid offers substantial benefits. As seen in our case, direct contact with the API can coat or foul the probe or sight glass with a small amount of material that is not representative of the bulk, which leads to unrepresentative results. The solvents in the vapor phase are present in inert N_2, which is not present in the spectral data. When monitoring the bulk material, the API spectra are present which can complicate the analysis. However, it may be desirable to monitor the bulk material for a number of reasons. There might be scientific reason for measuring the API, for instance if the NIR method is replacing the test to measure product quality. If measuring the solid-phase, preventative

measures must be taken in order to ensure that the probe is indeed measuring the bulk concentration. The probe should be placed in an area of the dryer where there is unlikely to be material build-up. A purge should be implemented to clear the sight glass of excess material, and finally a positive pressure should be applied at all times to the purge line to prevent material from clogging.

When performing the cross-validation, care must be taken to ensure that there is no evaporation of the samples taken for offline analysis. In order to prevent this, ideally the offline analysis should be performed immediately after the sample is withdrawn from the reactor. If this is not feasible, then it is critical that the samples be stored in airtight containers preferably in a refrigerator. Both of these issues are discussed by Moffet et al. (2000), who noted that the sample containers and probe installation are important factors to be considered when validating an online NIR probe.

This page has been intentionally left blank

4. Level 2 Implementation- Laser Diffraction Probe

4.1. Current Process

Achieving the correct particle size is critical as the particle size affects both the manufacturing process and performance of the final product. Attributes such as ease of compaction and drug dissolution profile are often impacted by the particle size dissolution of the intermediate product. Therefore, the last step of Drug Substance Manufacturing is to reduce the particle size through micronization in an opposed jet fluidized bed mill. After micronization is complete, the batch is blended before being filled into multiple containers. The resulting X_{50} and X_{90} values after micronization and blending must be within the specified limits of ≤ 6 μm and ≤ 15 μm). X_{50} and X_{90} refer to the values at which 50% and 90%, respectively, of the particles measured are smaller than the value. The current process control procedure is to monitor the key operating parameters: classifier speed, feed dosing rate, and nozzle pressure continuously and automatically during the entire milling operation. The current quality control procedure is to take a representative sample from the containers and measure the particle size offline in a separate laboratory facility.

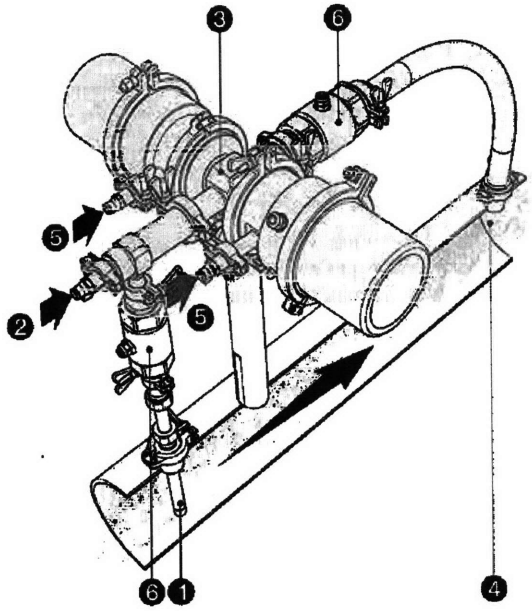
4.2. PSD

4.2.1. Technology

Because of the criticality of accurately controlling the particle size, online monitoring and control using PAT technologies is desirable. In February of 2007, a Malvern Insitec D Online Particle Size Analyzer was installed. The motivation for installing the online PSD probe is to replace the offline measurement method to achieve real-time release and ultimately use the process knowledge gained through the online PSD to eliminate the PSD testing completely. The technology applied by the Insitec Probe to measure particle size is known as laser light diffraction. Light from a laser is shone into a cloud of particles which are suspended in a transparent gas (true only for dry dispersion). The particles scatter the light, with smaller particles scattering the light at wider angles than the larger particles. The scattered light is measured by a series of photodetectors, and the diffraction pattern can be correlated to the

particle size based on light Mie's theory of diffraction. Figure 10 shows a detailed picture of the instrument.

Figure 10 Malvern Insitec Particle Size Analyzer



Source: Malvern User Manual

The following is a description from Malvern Instruments explaining how the system works. The tip flute, or sampling accessory, (1) is located in the process powder stream. The powder from the process stream is aspirated by the air venturi (2) which dilutes the powder and cools it. The venturi effect occurs when gas is discharged through a nozzle, creating a pressure drop that pulls the sample from the main process stream into the bypass loop. The powder exits the venturi as a fast moving turbulent air jet which breaks up any loosely bound aggregates. The conditioned powder is then transported to the measurement zone (3) where the laser beam is located before being returned to the process line (4).

As can be seen in the figure above, the particles are not measured inline, but rather online through a separate sample stream. Therefore, careful consideration must be applied in order to ensure that the sample stream particle size distribution is representative of the overall process stream. The air pressure differential will affect the representativeness of the bypass stream.

The RTSizer® software acquires data from the probe at 10 second intervals. The data are converted to particle size information, allowing the viewing, manipulation, and reporting of results

4.2.2. Benefits

As mentioned above, the quality testing is performed after the material has been unloaded into containers. Therefore, there is an inherent risk involved in unloading the material before knowing if the process specifications have been met. If the particle size is not adequate, the material will need to be re-micronized and blended which takes a substantial amount of time. The time required to transfer and analyze the sample in a separate facility is also time consuming. Additionally, there are issues with knowing whether the blending was in fact successful in homogenizing. The current testing procedure is to take a sample from each of the containers and rely on statistics to prove that the entire batch is in fact homogenous. There is much value, in terms of time and process knowledge, to be added by installing online PAT to measure the particle size in real-time during the entire milling operation.

4.3. Validation

4.3.1. Scope

The scope of the method validation is limited only to the online particle sizer for use during the micronization step in production. As the ultimate goal of the QbD initiative is to have a broad "design space" in which the process can operate, the online method needed to be evaluated over this entire design space region. More specifically, the online method had to be validated for multiple process conditions within the proposed design space (i.e. different pressures and classifier speeds). There are several limitations to validating the online analyzer for multiple process conditions. The particle size distribution in the sample stream, and hence level of representativeness to the bulk material, is dependent on the airflow rate. Experiments in the production scale had shown that the optimal sample air flow rate at normal operating conditions is 11 m^3/hr. This experiment was completed by testing various airflow rates between 10.0 and 14.0 m^3/hr and determining at which airflow rate the online and offline X_{90} values were most comparable (airflow rates disguised by using correction factor to protect confidentiality). Since

the particle size distribution within the mill affects the distribution of the sample stream, there is an optimal sample flow rate for each process condition in the mill. However, due to time and capacity constraints, it is not feasible to change the airflow rate to the optimal setting for each point within the design space. Therefore, only the airflow rate that was deemed optimal for normal operating conditions is used for every process condition. As this effects the accuracy of the online measurement, the scope of the validation is limited only to the region within the design space where the predefined acceptance criteria are valid.

4.3.2. Method

Sample collection:

The newly installed sampling port on the mill allows for samples to be collected during the mill operation and later tested offline. For each process condition, samples were collected every 20 minutes and analyzed offline. The X_{90} and X_{50} average and standard deviation of the steady state samples (those taken once fluidized bed level has stabilized) were calculated and used in the statistical test for the acceptance criteria. The RTSizer® software was used to calculate the average and standard deviation of the online X_{50} and X_{90} measurements for each time period that corresponds to when the offline measurement was taken.

Tested parameters:

- Accuracy of online X_{50} value when compared to offline X_{50}
- Accuracy of online X_{90} value when compared to offline X_{90}

Test statistic:

For the validation to be deemed successful, the 95% CI for the ratio of the corrected online value to the offline value for each condition must be entirely contained within the interval of 0.8 to 1.2. The justification for establishing this test statistic was that the process scientists determined that the online value could be used as an acceptable replacement to the offline value as long as the online value was within 20% of the offline value with a 95% confidence level. Therefore, the 95% confidence interval of the ratio of online to offline PSD was constructed for each process condition using the formula below:

Equation 1 Statistical Test for Cross Validation of PSD methods

95% Confidence Interval: $\bar{x} \pm 2.201 * s/\sqrt{n}$

Where, $r_i = \frac{online_i + 0.5}{offline_i}$, $\bar{x} = \frac{\sum_{i=1}^{n} r_i}{n}$ = sample mean

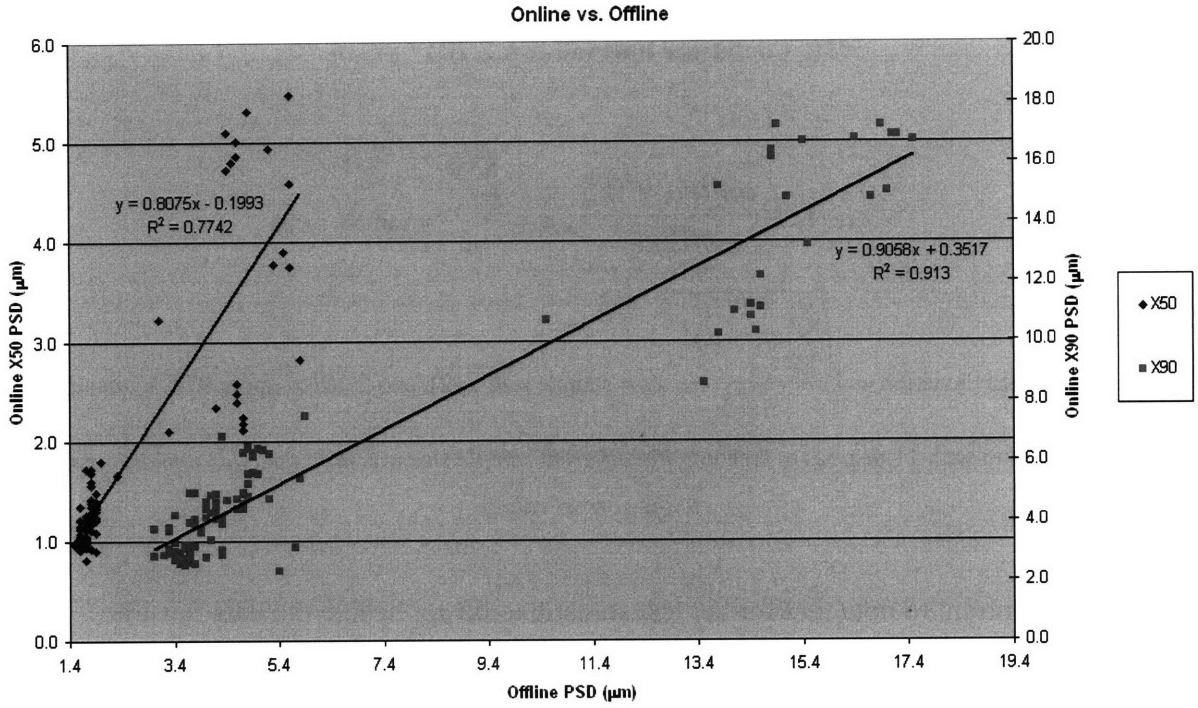
s= sample standard deviation = $\sqrt{\frac{\sum_{i=1}^{n}(r_i - \bar{x})^2}{n-1}}$, n= sample size (12), and ***2.201*** = upper 97.5% quantile of the student t distribution with 11 degrees of freedom *if a different sample size was used then this number was changed to the correct value).*

It is important to note that for the test statistic to be applicable the data must be approximately normally distributed. A correction factor of 0.5 μm was applied to the X_{50} values, based on the correlation that was calculated from previously collected data during a trial run. It is to be expected that the online results would be slightly lower than the offline results since the offline method utilizes a wet preparation that results in slightly larger particle sizes. Therefore, a correction factor will most likely be applied when using an online particle analyzer, especially for extremely small particle sizes where the impact of the wet preparation will be more prominent.

4.3.3. Results

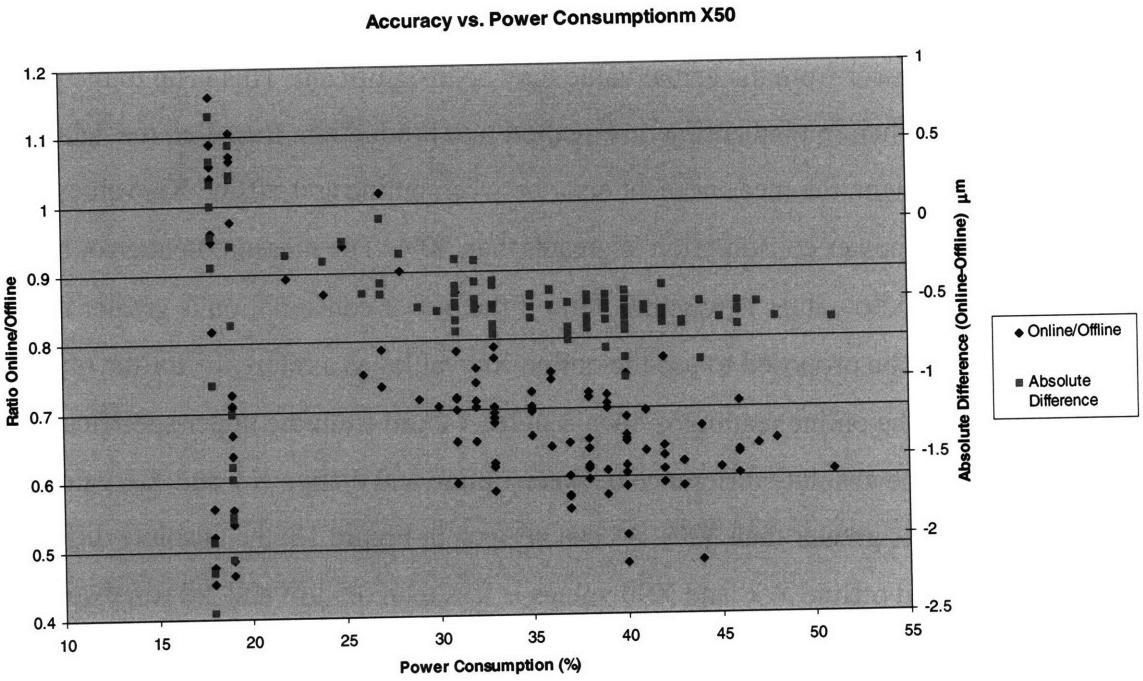
The conditions within the mill were not constant during the duration of each batch. Therefore, validating the online method individually for each batch, or process condition, proved difficult since the 10-12 samples taken during each batch were not homogenous. Instead, the data for all samples (10-12 samples/batch x 9 batches) were grouped together and analyzed. When the online values are plotted against the offline values for each measurement, a clear linear relationship can be observed. Figure 11 shows the values with the corresponding regression line equations.

Figure 11 Comparison of Offline to Online PSD Results



There are clearly two distinct populations in the data. The reason for these outliers is attributed to the effect of power consumption. The power consumption within the mill is a function of the solid load (dosing speed) within the mill, the nozzle pressure, and the classifier speed. The power consumption level varied for each condition tested. It was determined that the accuracy of the online particle sizer is dependent on the solid load, as measured by the power consumption, within the mill. When the mill was not filled to an adequate level, indicated by the power consumption being below approximately 30%, the online and offline values were significantly different. Figure 12 shows the results of the online and offline values compared to the power consumption within the mill.

Figure 12 Accuracy of Online Analyzer vs. Power Consumption X50



As can be seen in the data, at low power consumptions there is significantly more variability in the measurement accuracy. Based on this information, it was decided to analyze the data based on power consumption instead of individual ratio for each process condition. The test statistic holds true when all samples taken when the power consumption was greater than 30% are analyzed together. Table 2 shows the resulting test statistic results.

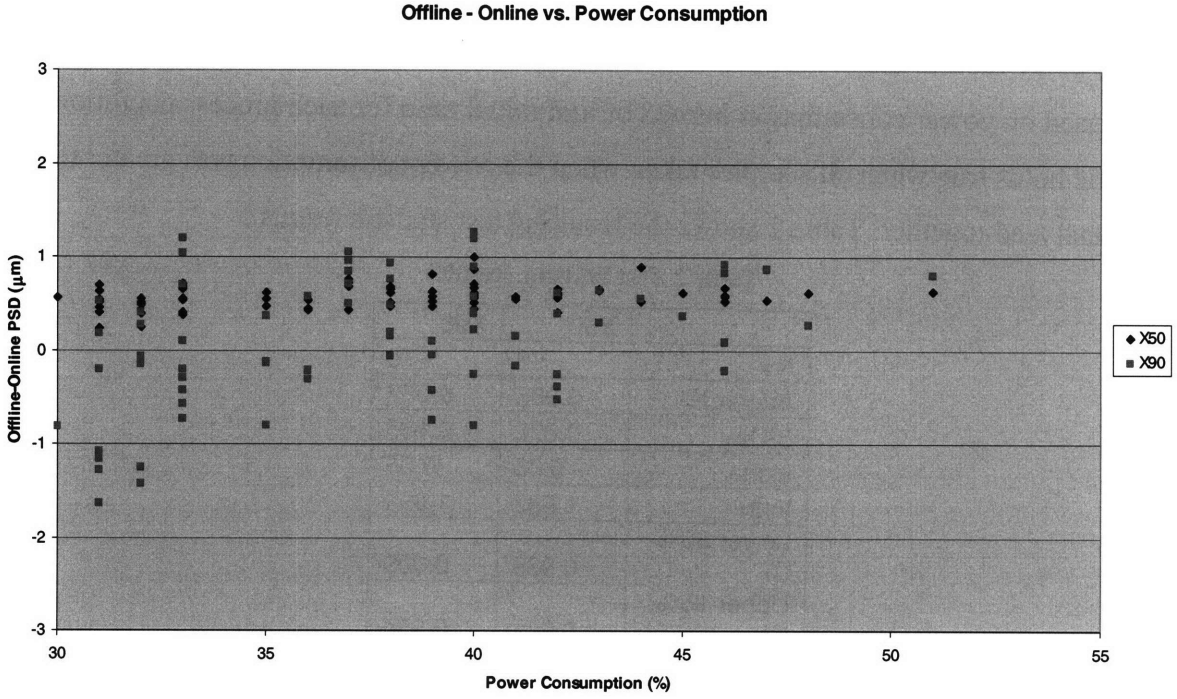
Table 2 Test Statistic Results

	X50	X90
N=	76	76
Average=	0.955	0.952
StDev	0.072	0.185
alpha	0.05	0.05
tcrit=	1.992	1.992
Lower 95% CI	0.938	0.909
Upper 95% CI	0.971	0.994

Instead of using the ratio of online to offline another way to interpret the data would be to analyze the absolute difference between the online and offline values. Given that this method will be used in production, it is important to think of the most practical applications of the technology. The ratios of online to offline were quite variable because of the low values being

measured. When the particle size is only 3 μm, a differential of only 1 μm results in a 33% measurement error. However, from a practical standpoint, having an online measurement that is 1-2 μm higher or lower from the actual value may be insignificant. This is up to the process experts to decide when implementing this method into production. Based on the data collected during this experiment, the measurement error between online and offline X_{90} values are always within 2 μm if the power consumption is greater than 30%. The measurement error between online and offline X50 values is within 0.5 μm if the power consumption is greater than 30%. Therefore, it could be proposed to use the online X_{90} values as a reference for the offline values, but to ensure that the online reading is always at least 2 μm from the upper specification limit. Figure 13 shows the absolute difference between online and offline X_{50} and X_{90} values for power consumption values greater than 30%. As can be seen in Figure 13, the absolute difference between online and offline X50 and X90 values is less than 0.5 μm and 2.0 μm respectively

Figure 13 Offline-Online vs. Power Consumption (>30%)

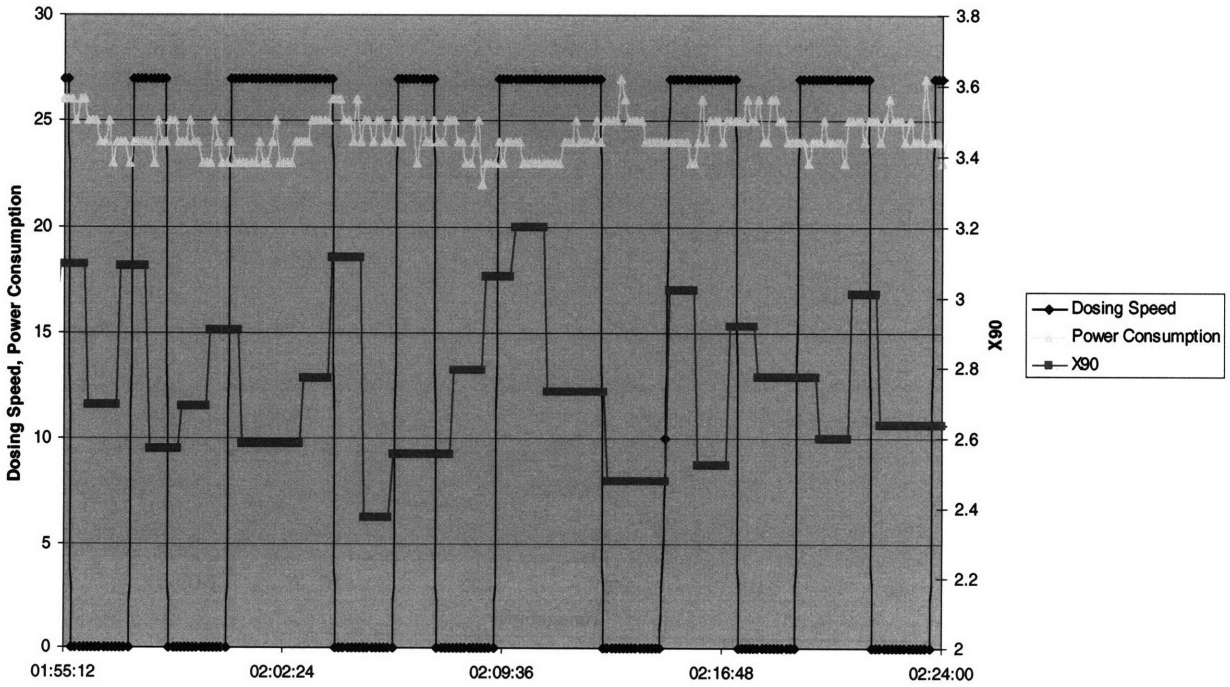


4.4. Increased Process Knowledge

The online particle size analyzer can also be used to monitor the particle size as a function of process conditions. The increased process knowledge allows for the optimization of the process. In this case, we were able to determine that the variability seen in the X90 values was caused by the variability in the power consumption values. The cycle time of the process could be reduced by increasing the feed rate at the beginning of the process.

The previous feed strategy was to start and stop the feeding based on the power consumption of the mill. As the feed is loaded at a constant rate, the power consumption increases. Once the power consumption reaches a maximum limit of 26%, the feeding stops. As the level in the fluidized bed decreases, the resulting power consumption also decreases. Once the power consumption reaches a minimum limit of 23%, the feeding is initiated again. This process continues for the entire operation of the mill, and results in frequent starting and stopping of the feed. The average time the feed is on and off is approximately 2.5 minutes. Figure 14 shows the relationship between power consumption, feed rate, and particle size for a typical run.

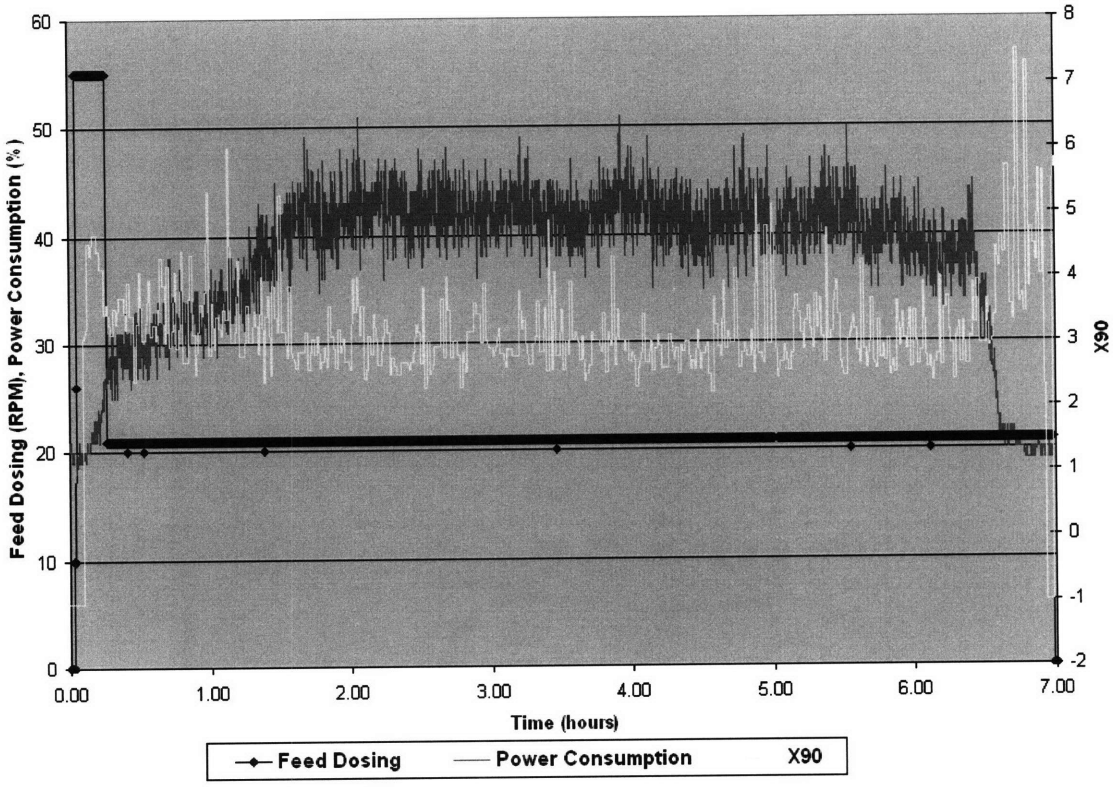
Figure 14 Process Trends during Milling



The range of 23-26% was implemented because historically this is what other processes at Novartis have used. Power consumptions greater than 26% have not been tested at the commercial scale at Novartis. However, other pharmaceutical manufacturers frequently achieve power consumptions of greater than 50% during milling. We tested reducing the frequency of the interruptions by increasing the operating range for the power consumption. The motivation was to determine the feed dosing speed that would result in steady-state feed dosing and power consumption during the milling operation.

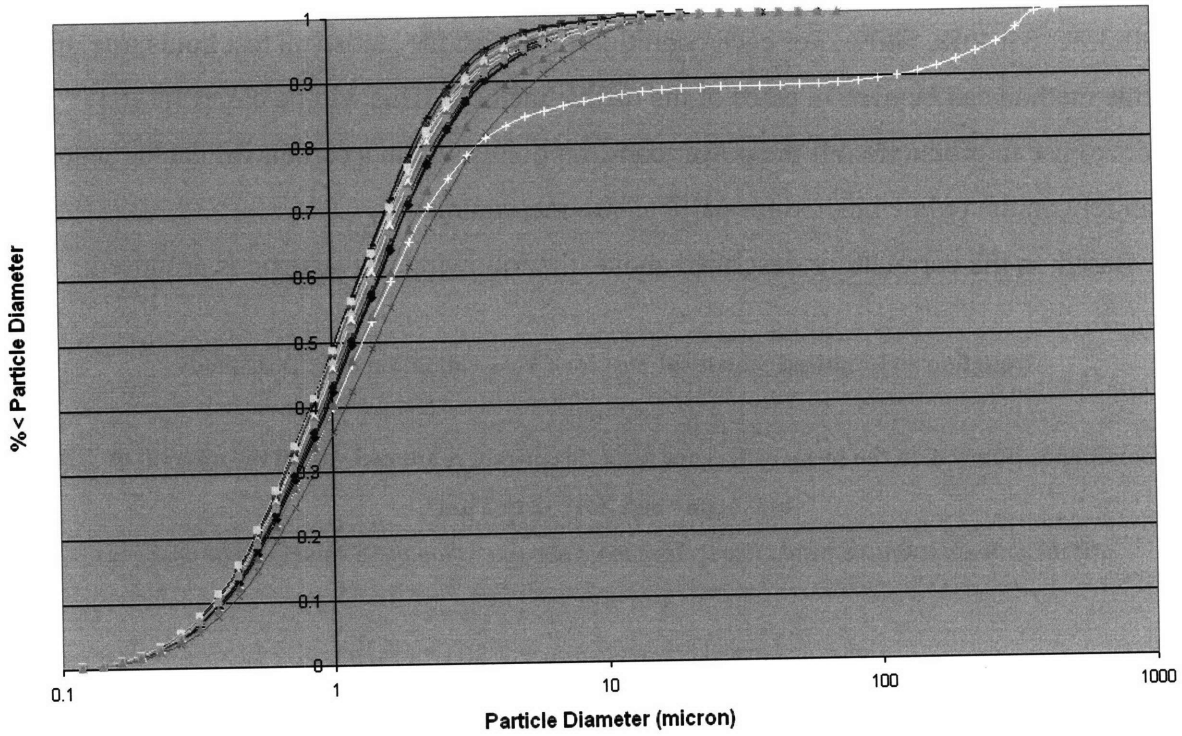
We were able to notice that as the power consumption increased, the particle size decreased. Given that the feed rate could be increased to fill the mill faster at the beginning of the run, the cycle time could be reduced significantly. At a high speed rate of 55 rpm for the first 15 minutes, the power consumption quickly surpasses the critical value of 30%. By maintaining a constant feed rate of 21 rpm, the power consumption, feed dosing, and particle size remain relatively constant. Figure 15 shows the optimized process.

Figure 15 Optimized Milling Process



Additionally, the particle size analyzer allowed for knowledge regarding the average particle size throughout the entire milling process. Instead of only taking a few samples for offline analysis once the process was completed, the online method collected between 2000-3000 samples during the duration of the process. The RTSizer® program then calculated the average particle size distribution and displays the data in a way that is easy to interpret. Figures 16 shows the cumulative particle size distribution for 25 batches. It is easy to see that there is one outlier batch, however the remaining batches are relatively consistent. By analyzing orders of magnitude more samples during the milling process, the online particle sizer allows for easier detection of abnormal batches.

Figure 16 Cumulative Particle Size Distribution Summary



4.5. Feasibility of Use in Production

The following action items are recommended for the future validation and implementation of the online particle sizer into production:

1) Validation

For future validation of the online method, the magnitude of the difference between offline and online values should be used instead of using the ratio of offline to online in the test statistic. Instead of validating the use of the online method for each batch condition, the author would instead propose to validate the online method for certain power consumption ranges. For example, perform the statistical test for different power consumption ranges such as 20-25%, 25-30%, 30-35%, 35-40%, >40%. For each condition for which the statistical test holds true, then the online method can be used in place of the offline method. This will be easier for the operators to use in production. If the power consumption is within a certain validated range, then they can rely on the online method for particle size measurements.

Based on the correlations described above, the following test statistic is proposed:

Equation 2 Optimized Statistical Test for Cross-validation of PSD methods

95% Confidence Interval on the mean difference must be entirely contained within the interval of X50: -0.5 to 0.5 μm* and X90: -2 to 2 μm*.

*(*If the process scientists would like to have more accuracy than these values can be changed).*

95% Confidence Interval: $\bar{x} \pm 2.201 * s/\sqrt{n}$

Where, $r_i = online_i - offline_i + CF$, $\bar{x} = \frac{\sum_{i=1}^{n} r_i}{n}$ = sample mean

s= sample standard deviation = $\sqrt{\frac{\sum_{i=1}^{n}(r_i - \bar{x})^2}{n-1}}$, n= sample size (12), and ***2.201*** = upper 97.5% quantile of the student t distribution with 11 degrees of freedom *if a different sample size was used then this number will be changed to the correct value),* ***CF***= correction factor=0.5 μm for X50 and 0 for X90

The author proposes the following steps be taken in order to validate this method:

1. Perform second DoE experiment and collect offline samples at 30 minute intervals during the batch processing
2. For each offline sample collected, calculate the corresponding online value by taking the average online reading for $\pm$ 3 minutes from time of offline sample. This time interval was chosen because it takes approximately 3 minutes to take an offline sample.
3. Compute the difference between online and offline measurements for each sample.
4. Determine if the data range is normally distributed (prerequisite for computing confidence interval)
5. Divide the samples into data groups based on power consumption within the mill at the time sample was taken.
6. Run statistical test for each power consumption range using all measurements that were taken when the power consumption was within given range.
7. If the test statistic is true, then the online method can be validated for that power consumption range.

If it is desired to have 99% confidence instead of 95 % confidence, then the multiplier of 2.201 will need to be changed. Instead of using the 97.5% quantile of the student t distribution with 11 degrees of freedom, the 99.5 % quantile should be used. This value can be calculated in Excel using the following formula: = tcrit (α, $\nu-1$), where $\alpha = 0.01$ and n= sample size.

Alternatively, if one would like to validate the online method for a given range of particle sizes, the test same test statistic could be applied. However, instead of comparing values for various power consumption ranges, the test would be performed for all values that fall within certain online particle size ranges, i.e. X_{90}= 2-3 μm, 3-4 μm, 4-5 μm, etc. Once the ranges for which the online method give accurate readings has been determined, the operator would know that whenever the online particle size is between a certain validated range, the method is deemed accurate.

2) **Use the online PSD as a replacement for the offline method only for consistent process conditions when there is little variability in the actual particle size in the batch**

It is clear that the sampling airflow rate for the bypass stream affects the accuracy of the online PSD analyzer and must be taken into consideration when using the instrument in production. The sampling flowrate can be optimized for a given particle size distribution to provide accurate online and offline measurements. However, if the particle size varies greatly between batches, the online measurement may not be accurate. For X_{90} particle sizes between 3-5 μm, a sampling flowrate of 5.5 m^3/hr was previously found to be the most optimal. However, at this flowrate, the online values are higher than offline values at low particle size distributions ($X_{90} < 3$ μm), and the online method is usually lower than offline at high particle size distributions ($X_{90} > 5$ μm). Based on this observation, validating the online method vs. particle size is a reasonable choice.

3) **The online method can be used to monitor particle size trends during the processing of the batch.**

There is a linear relationship between the online and offline methods. This will be useful to measure the homogeneity of the batch and potentially eliminate the blending step currently performed at the end of the batch. This step typically requires 1-2 hours of processing time and therefore elimination would translate into both cost and time savings. A statistical method will need to be developed to test for homogeneity based on the online data. It could also be concluded that as long as all online values recorded during the batch are below the critical value, then there is no need to blend the batch after processing. The online method is also useful to monitor the effect of certain process conditions on the particle size.

5. Level 3 Implementation - Design of Experiments

In order to understand the sources of product quality variability, the impact of each process input must be evaluated. Those that are considered quality critical parameters can then be further evaluated in order to identify interactions between variables and to establish acceptable operating ranges. A systematic approach to identifying these quality critical parameters and establishing operating ranges is to perform DoE. Through DoE, multiple parameters can be tested simultaneously, and statistical methods can be used to identify the parameter main effects and interactions. The goal is to achieve a mechanistic understanding of the process, i.e. the effects of each input variable on product quality are well characterized and understood.

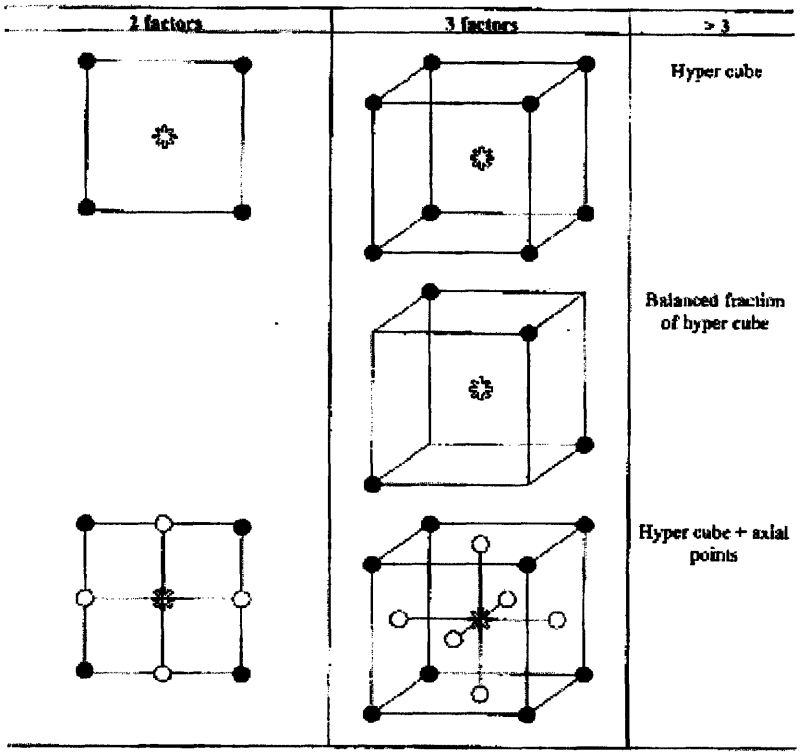
5.1. Design space development

There are two main experimental objectives for which DoE can be used- screening and optimization. Screening is used to identify main effects of key variables and to determine the ranges that the parameters should be tested. Typically, screening designs to not require many experiments to complete and therefore a low resolution design can be used, i.e. fewer experiments required per variable tested. Optimization is a follow up study in which the interaction between key variables is tested in order to identify the optimal operating conditions. Optimization is more complex than screening, and therefore requires a higher resolution design.

There are many different experimental designs that are utilized to meet these objectives. The three most commonly used are fractional factorial, factorial, and composite designs. Table 3 shows examples of the three designs used in DoE. The top row is an example of a full factorial design with three factors, in which all combinations of the factors are tested. This design can test for main effects and interactions and is therefore used in both screening and optimization. In a fractional factorial, only a fraction of the total combinations are used. As this design has low resolution, it is primarily utilized in screening experiments where there are a large number of factors to screen and only main effects need to be determined. The composite design consists of the corner factorial experiments, center point experiments, and axial (or star) experiments. These designs are used extensively in optimization studies as quadratic terms can be estimated. Typically, two ranges are tested for each variable, plus 1 centerpoint condition. It is desirable to

perform at least 2-3 replicates for each condition in order to estimate the measurement variability.

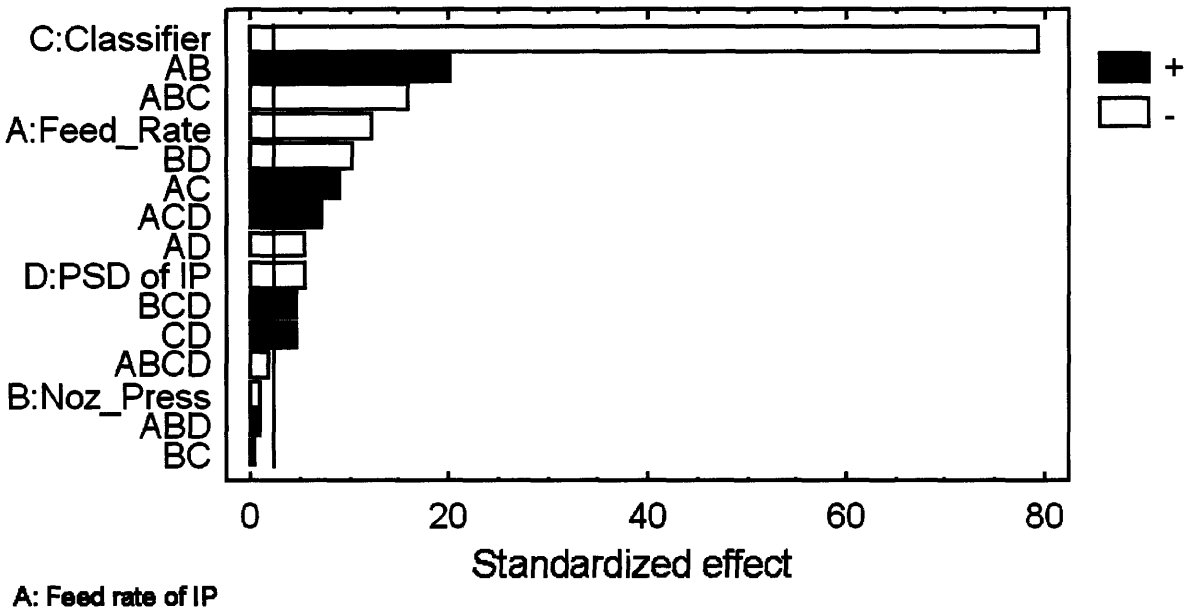
Table 3 Example of Experimental Designs used in DoE



Source: Erikkson, Umetrics Textbook.

In this pilot case, extensive studies were performed at the pilot scale by the development group (primarily Michael Juhnke) in order to gain process understanding and propose a design space for the commercial scale based on the scale-up of the pilot scale design space established. First, a Failure Mode and Effects Analysis (FMEA) of the milling process was conducted in order to identify the key variables that needed to be investigated. A main effects screening fractional factorial DoE was performed covering the 5 key variables that were identified. The response variables for these experiments were the resulting particle size distribution, i.e. X_{50} and X_{90}. The results show that classifier acceleration had the strongest effect on particle size, and feed rate of IP and nozzle pressure had statistically significant effects, but smaller compared to classifier acceleration. Figure 17 shows the results of the main effects screening.

Figure 17 Milling Screening DoE Results



A: Feed rate of IP
B: Nozzle pressure
C: Classifier rotation speed
D: PSD of IP
E: Sampling flow rate

Credit: Michael Juhnke

A follow up optimization DoE to test for statistically significant interactions between the three main effects identified classifier acceleration as clearly the strongest effect for controlling particle size. Nozzle pressure also was identified as having a strong effect on particle size, whereas feed rate was identified as having a negligible effect.

5.2. Full Scale Design Space

5.2.1. Proposal

Based on the results of the pilot scale optimized DoE, a full scale DoE was proposed based on scaling parameters and model prediction equations. When proposing the full scale design space, a 25% safety factor was used in order to account for uncertainty with the accuracy of the scaling equations. The technical boundary for the proposed design space is as follows (Numbers disguised by applying correction factor to protect confidentiality):

- **Nozzle pressure** between 5.3 and 8.3 bar
- **Classifier rotation speed** between 1500 and 3000 rpm
- All other quality critical parameters at setpoint

Within these process conditions, the particle size was predicted to be within the acceptance criteria based on the results of the pilot scale data. In order to confirm the commercial scale design space, the team statistician decided to use a central composite design with star points, which allows the linear by linear interaction between nozzle pressure and acceleration to be estimated. The star points for acceleration also allow for the quadratic term to be estimated, therefore requiring five different levels (---,--,0-,0,0+,++,+++) of classifier speed to be included in the design. Seven additional runs (those labeled information) were tested in order to supplement the fitted equation and to help test for the edge of failure. Table 4 shows the experimental design and purpose of each condition. The nozzle pressure and classifier acceleration setpoints are coded to protect confidentiality.

Table 4 Description of Full-scale Experimental Design

Run Number	Type	Nozzle pressure (bar)	Classifier acceleration (m2/s2)	Purpose	Material Source
1	Center	0	0	DOE	Commercial
2	Factorial	+	+	DOE	Commercial
3	Extra B star	0	++	Information	Commercial
4	Extra A star	0	0+	Information	Commercial
5	Factorial	-	+	DOE	Commercial
6	Center Replicate	0	0	Error estimate	Commercial
7	Star A	0	+	Quadratic	Commercial
8	Extra 2	-	0	Information	Commercial
9	Extra 1	+	0	Information	Commercial
10	Factorial	+	-	DOE	Pilot Plant
11	Factorial	-	-	DOE	Pilot Plant
12	Extreme B star	0	---	Information	Pilot Plant
13	Star A	0	-	Quadratic	Pilot Plant
14	Factorial Rep	-	-	Error estimate	Pilot Plant
15	Factorial Rep	+	-	Error estimate	Pilot Plant
16	Extra B star	0	--	Information	Pilot Plant
17	Extra A star	0	0-	Information	Pilot Plant

In order for the design space confirmation to be deemed successful, all batches within the proposed design space had to produce material within the acceptable ranges. The quality test was performed using the normal testing procedure where one sample is collected after the milling and blending is completed and analyzed offline.

5.2.2. Implementation in production

The ranges that needed to be tested for the full scale design space confirmation were outside of the previously validated ranges. Therefore, it was desirable not to use commercial material for all batches. Instead, regular commercial batches were used to test some of the conditions, and pilot plant material was used to test the extreme conditions. Given that each process condition did not need to be tested for the entire time required to mill one batch, each batch was divided into smaller batches that were each used to test one process condition. This method can be used for milling operations where the quality parameter, particle size, can be monitored in real-time and therefore it is not necessary to complete the entire batch at each process condition. This minimizes risk and saves time and material. For each condition tested, the online trends for all process parameters were monitored in order to ensure that the classifier speed, feed dosing, and nozzle pressure were all maintained at the pre-defined setpoints. Although the online particle size was monitored during each run, the final product quality testing was done offline as the online method had not yet been validated at the time of the study.

5.2.3. Results

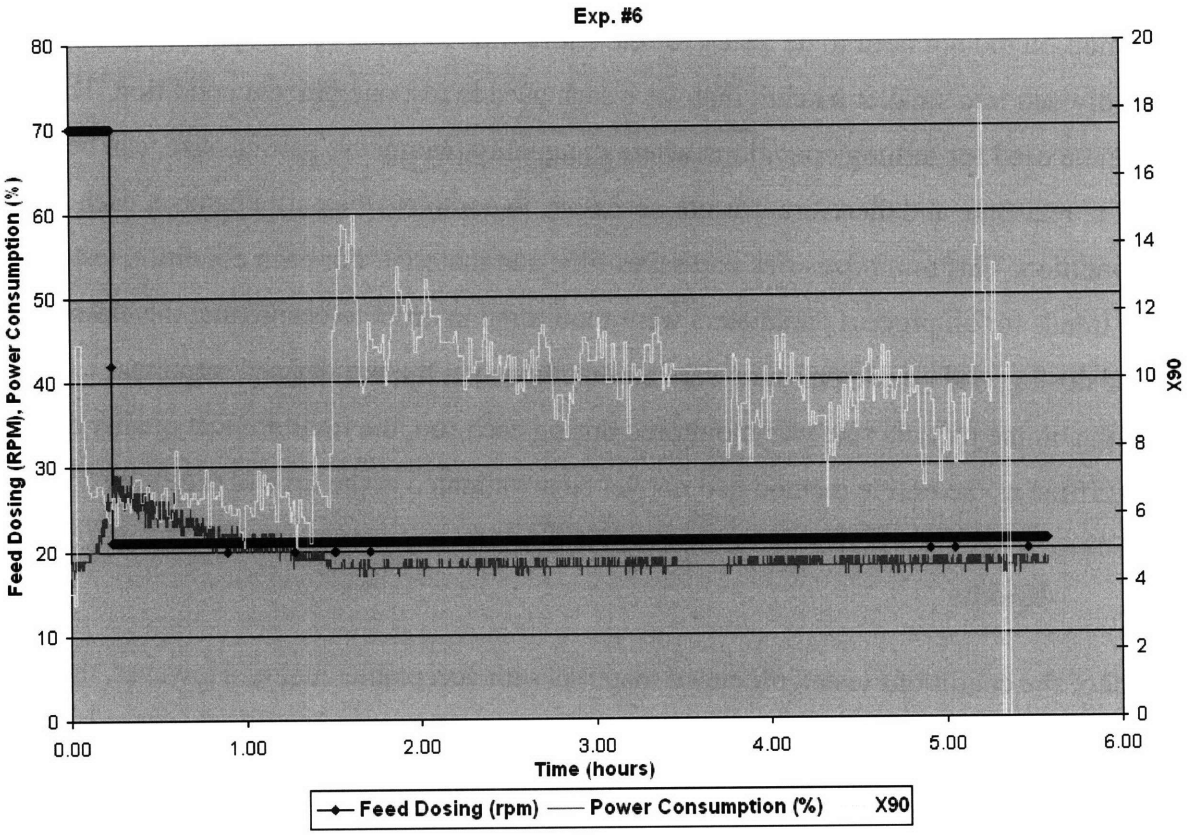
All of the conditions tested produced material with acceptable quality. However, the confirmation was not successful as defined in the protocol as parameters that were considered to be non-critical at the pilot scale were in fact critical at the commercial scale. Based on the data acquired during this full-scale confirmation study, several conclusions can be drawn regarding the operation of the milling process.

- ***The mill must be filled to a certain level in order for the particle size to be of acceptable quality***

  It was observed that if the mill was not filled, the resulting particle size and variability is exceptionally high. Although product level within the mill cannot be directly monitored, both power consumption and mill pressure are direct indicators of the solid load within the mill. The baseline power consumption when the mill is empty is approximately 20%. In order for the mill to be efficient, the power consumption must be higher than this baseline value. When the mill is filled up to a certain level, frequent particle-particle

interaction results in reduction of the particle size. As can be seen in Figure 18, the online particle size increased significantly when the power consumption fell to the baseline value.

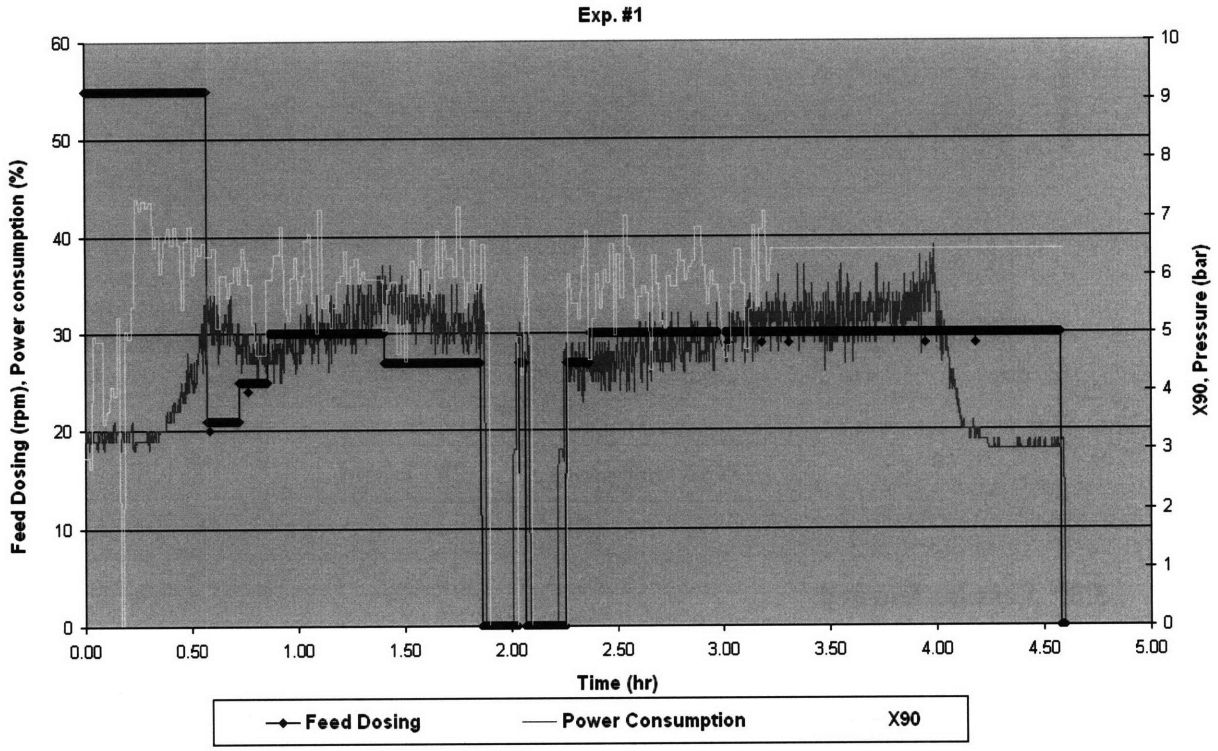
Figure 18 Power Consumption Effect on Milling Performance – 1



- ***The screw feed rate and resulting power consumption have a significant effect on particle size.*** The particle size is not consistent when the classifier speed and nozzle pressure are the same between two batches, if the feed rate and resulting power consumption are different. This is shown in experiments #1 and #6. For both batches, the classifier speed was and nozzle pressure were held constant at the center points. However the feed rate and power consumption were different for the two batches. In experiment #1, the feed rate was increased to 30 rpm and the power consumption was maintained at approximately 30%. For experiment #6 the feed was held constant at 21 rpm. At this feed rate, the mill was not filled and the power consumption remained at the baseline level of 19%. The process trends

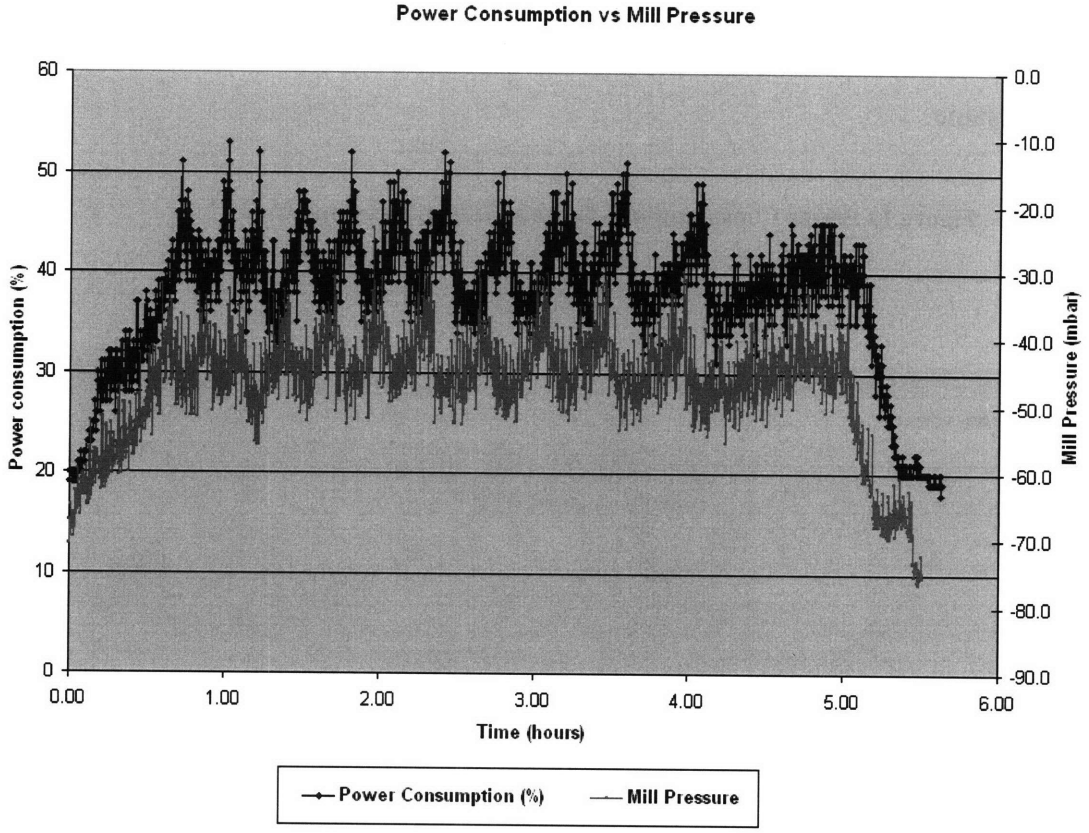
for batch experiment #1 are shown in Figure 19. When compared to experiment #6 (Figure 18) it is evident that the particle size varies significantly depending on the power consumption even when the classifier speed and mill pressure are the same.

Figure 19 Power Consumption Effect on Milling Performance -2



- ***Mill pressure and power consumption are directly correlated.*** In order to monitor the solid load within the mill, either mill pressure or power consumption can be monitored. The two are directly correlated, as shown in Figure 20. In the future, the milling process could be controlled by ensuring that the power consumption and/or mill pressure are within acceptable limits.

Figure 20 Power Consumption vs. Mill Pressure



5.3. Lessons learned

- ***Parameters that are deemed insignificant at the lab or pilot scale may prove to be significant at the commercial scale.*** When scaling up a process in which mechanical forces are important, such as in milling, the results at pilot scale may not be predictive of the commercial scale results.
- ***The operational limitations of the full-scale equipment must be considered when proposing the design space.*** It may not be possible to operate the full-scale mill at the conditions proposed by the development group and scaled from the pilot scale equipment. When the mill was operated at low pressure and high classifier speed during experiment #5, the mill nozzles clogged and the milling operation had to be stopped. The mill had to be taken apart in order to remove the power from the piping. In order to continue operating the mill, the pressure had to be raised to by 0.5 bar or the classifier speed reduced to the center point value.

5.4. Future recommendations

For this particular case, it is recommended that the design space definition should be revised to include the process parameter solid load within the mill. As solid load cannot be directly monitored, either the power consumption or mill pressure should be considered as these are both direct indicators of the solid load within the mill. These two parameters, power consumption and mill pressure, cannot be directly controlled but are directly correlated to the screw feed rate at each process condition. Therefore, the design space should include not only classifier speed and nozzle pressure, but feed rate as well. The power consumption or mill pressure should be monitored for each process condition in order to define the limits in which acceptable quality product is produced. When defining the conditions to test at large scale, the operational limitations of the full-scale equipment must be carefully considered.

For future DoE experiments, it is advisable to only run the commercial scale DoE for scale-dependent operations such as milling as it is difficult to predict commercial scale results based on the pilot scale data. In order to minimize the risk of producing out-of-specification material, it is recommended to use material that is not intended for commercial use for the DoE study. If this is not feasible, then the commercial batches should be split into smaller sub-batches. However, if a qualified/representative scale-down model does exist for a particular unit operation, then the screening and follow-up DoE should be conducted at the laboratory and/or pilot scales.

This page has been intentionally left blank

6. Level 4 Implementation- Multi-Variate Data Analysis

6.1. Description

Historically, each process parameter has been monitored individually using statistical process control (SPC). Control charts are generated for each critical process parameter to ensure that the process is in control. However, with multiple variables to monitor, this process can be cumbersome. Additionally, finding the root cause when there is an abnormal event may prove difficult since many of the parameters are correlated. This makes it difficult to isolate and correct the source of the problem. Combining these multiple control charts into a single chart can be achieved by using multi-variate methods. Multi-variate analysis reduces the dimensionality of a system by using principle component analysis. Principle component variables are calculated using the weighted averages of each process variable. The first principal component accounts for the largest source of variability, the second to the next largest source of variability and so on. Typically, only 3-4 principal components are required to describe the variability in a system. Each principle component is then plotted against each other to visualize the process performance and detect outliers.

The second main multivariate tool most commonly used is partial least squares (PLS). It is a regression extension of PCA, which models the association between input variables (X) and the output variables (Y). Although PCA is sufficient for process monitoring, PLS is necessary when building a model to predict quality based on process data. A more in-depth description of PCA and other multi-variate methods can be found in the article by Balboni (2003) and in the Umetrics text book (Ericsson, 2006).

Multivariate analysis can be used for three purposes: monitoring, prediction, and control:

Monitoring- Batch progress monitored in real-time allows for early fault detection.

Prediction- Build a correlative model from previous data that can predict quality of current batch.

Control- Adjust process conditions to control the batch quality in real time.

Although prediction based on a model and control through feedback loop implementation are required for real-time release, batch monitoring is exceptionally useful as it allows for early

fault detection and reduces the number of control charts needed to only 1. When MVDA is used only to monitor the batch, quality testing is still required. However, once the model has been built and qualified, offline quality testing can be removed because the model will predict and ensure final product quality. It is important to note that an MVDA model is purely a correlative model that utilizes previous data to predict the final product purity of the current batch. In order to develop a mechanistic model that predicts product purity based on the process variables, predictive equations need to be established through intensive DoE studies.

The following section explains the implementation of MVDA in order to monitor the crystallization process and provides recommendations on how this tool can be used. There are several different software programs that will perform this analysis. One that is widely utilized and is relatively easy to use is Simca P+ by Umetrics. In this pilot project the Simca P+ Batch program was used.

6.2. Implementation

6.2.1. Data filtering

The most difficult aspect of the MVDA analysis was deciding what unit operations should be incorporated into the model. In the batch recipe, each step has an operation number that is used for communication between the vessel and the SCADA. All unit operations can be incorporated into the model, but non-critical parameters can complicate the model and lead to inaccurate modeling of the process. Therefore, only parameters that are known to impact quality should be included. A comprehensive analysis was completed for each process step in order to determine what unit operations should and should not be included into the model. In general, steps that involved pre-heating of the empty vessel, or chilled holds that were known not to impact product quality were excluded. The reason for this is that often non-critical steps are performed at different times based on equipment and operator availability. However, this does not impact product quality and therefore does not need to be included into the model. An example of a batch recipe for the crystallization step is shown in Table 5. It was decided that although data for all 9 steps would be recorded, only steps 5 through 7, heating, Anti-solvent addition, and crystallization, were selected as quality relevant operations and therefore the MVDA analysis only included these four operations.

Table 5. Crystallization Batch Recipe Steps

Operation Name	Operation Number
Pressure Test	1
Inertization	2
Pre-heat vessel	3
Product Addition	4
Heat	5
Antisolvent Addition	6
Hold	7
Discharge to Centrifuge	8

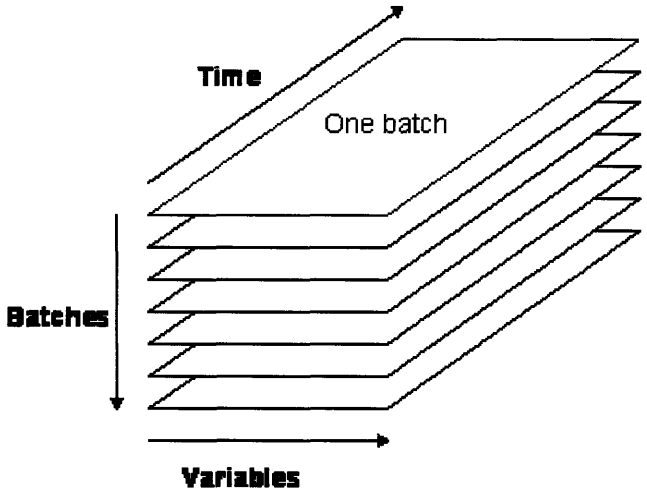
6.2.2. Data formatting issues

Once it was decided what unit operations, or recipe numbers, should be included into the model, the data had to be formatted in such a way that the software would be able to analyze it. The data query and formatting was initially done manually for this proof of concept phase, but ultimately an automatic query and formatting process will be implemented.

For batch processes, the data need to have time columns for every continuous process variable, including controlled and uncontrolled variables. Additionally, columns need to be created for discrete variables such as raw material product quality and/or initial conditions from the previous step if these are to be included in the model. Each row represents a different time point, and each batch should be listed sequentially. Figure 21 shows a picture description of the batch data, and an example of how the data need to be formatted for each batch in order to be imported into Simca P+ can be found in Appendix A. Additionally, in formatting the data for Simca P+, the following points need to be considered:

- Data can be in Excel or .cvs formats
- Small amounts of missing data can be tolerated
- For each batch, data should be collected at the same timepoints.

Figure 21. Picture of MVDA data Format



6.3. Proof of Concept

In order to prove the concept of MVDA, all parameters for each unit operation were analyzed using Excel and Simca P+. Then, the two results were compared to ensure that any abnormalities identified using Excel were also captured with Simca P+. Although there are a multitude of ways in which to interpret the MVDA data, it was decided to use the scores contribution plots. This plots the principle components as a function of time. Each new batch can be compared to the performance of previous batches in order to easily detect when a batch is abnormal. The analysis discussed here was done retrospectively, after all batches had been completed. However, in future production use, the data from each batch will be monitored in real-time during the evolution of the process.

For each unit step, the data were formatted and imported into Simca P+. Figure 22 is an example of the principle component chart for step 5 of the crystallization process- heating. As can be seen there are two abnormal batches, A and B, as represented by the black and the blue lines. The score contribution plot can be opened by clicking on the time point where the abnormality occurred. By viewing the score contribution plot for A at time = 23 minutes, shown in Figure 21, one can quickly notice that the source of the abnormality is a drop in the jacket temperature (T61).

Figure 22 Principle Component Chart

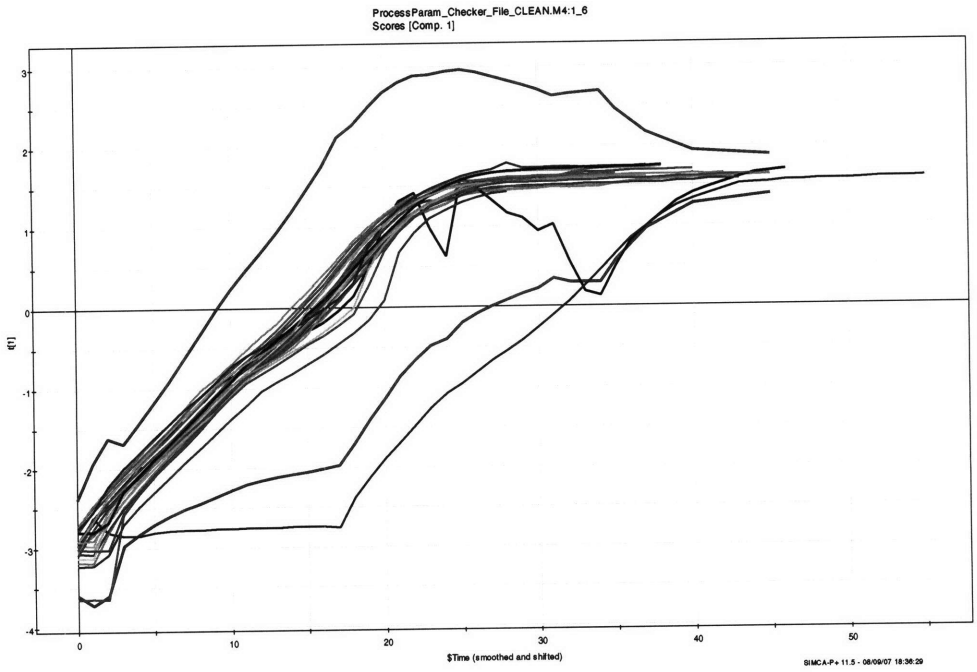
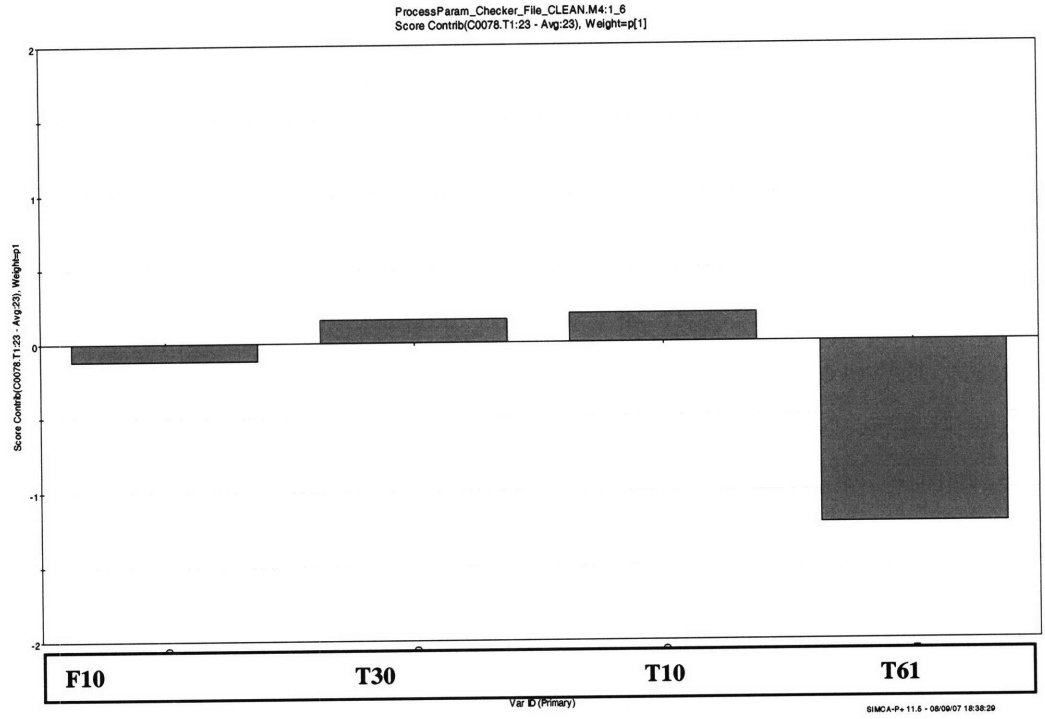
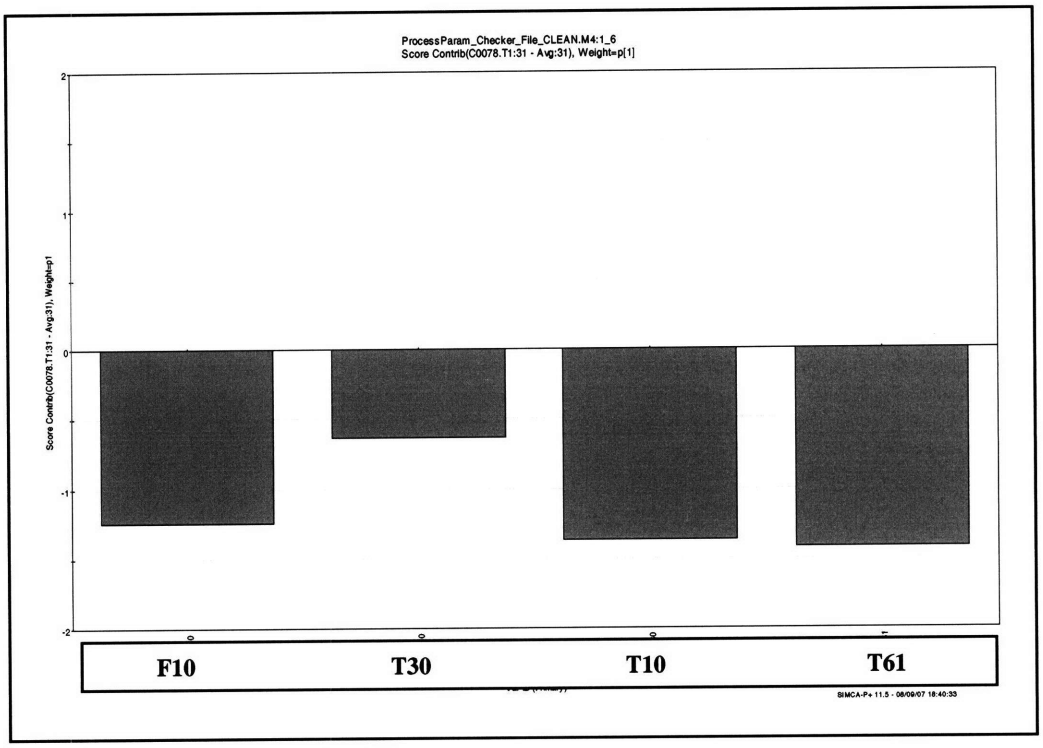


Figure 23 Score Contribution Chart T= 23 Minutes



By viewing the score contribution plot for batch A at time = 46 minutes, it is clear that the drop in jacket temperature later resulted in a drop of pressure (P10), and the two other measured variables (T30 = vapor temperature and T10= temperature in the vessel).

Figure 24 Score Contribution Chart T=46 Minutes



The excel charts for all four variables are shown in Appendix A.

From the individual Excel trend charts, it is difficult to determine which parameter caused the abnormality. However, using MVDA one can easily determine that it was a drop in the jacket temperature that caused the other variables to be abnormal. This is a very simplified example, but it does demonstrate how MVDA can be used to simplify batch monitoring and enable for easy, real-time root cause identification of process abnormalities. In this case, the raw material attributes were not monitored, nor were the unit operations linked together. The ultimate goal is to build a model that would incorporate all critical process variables and raw material attributes, and link all unit operations to achieve a holistic view of the entire process.

6.4. Future implementation issues

MVDA is a critical enabler of achieving Quality by Design. However, it requires substantial collaboration from scientists, process engineers, IT experts, and statisticians. To fully achieve the benefit previous unit operations must be linked to subsequent unit operation in order to achieve "holistic" fingerprint for entire process. Ideally, the process should be in control from the first raw material testing to the final tabletting. In order to implement MVDA into production, the following steps need to be achieved:

1. Development of standard, simple data query method to pull relevant data from historian and input into Simca P+.
2. Development of standard procedures for how to validate the data queries from the PI historian, the model, and the feedback control
3. Linking process steps by importing the "scores" from each unit operation as input variables for the following unit operation
4. Development of procedure for handling large amounts of data like raw NIR data for the drying step. This data need to be formatted in such a way, using a program such as Matlab or Simca P+, to convert raw data into feasible form for MVDA that won't overwhelm the model.
5. Method for how to synchronize batches of different durations.

Novartis' experience accomplishing these tasks has demonstrated that linking these layers is complicated. However, other industries have been successful in implementing MVDA to achieve real-time release, and therefore the rest of the pharmaceutical industry should be able to overcome these implementation challenges as well.

This page has been intentionally left blank

7. PAT and Lean Process Optimization

7.1. Overview

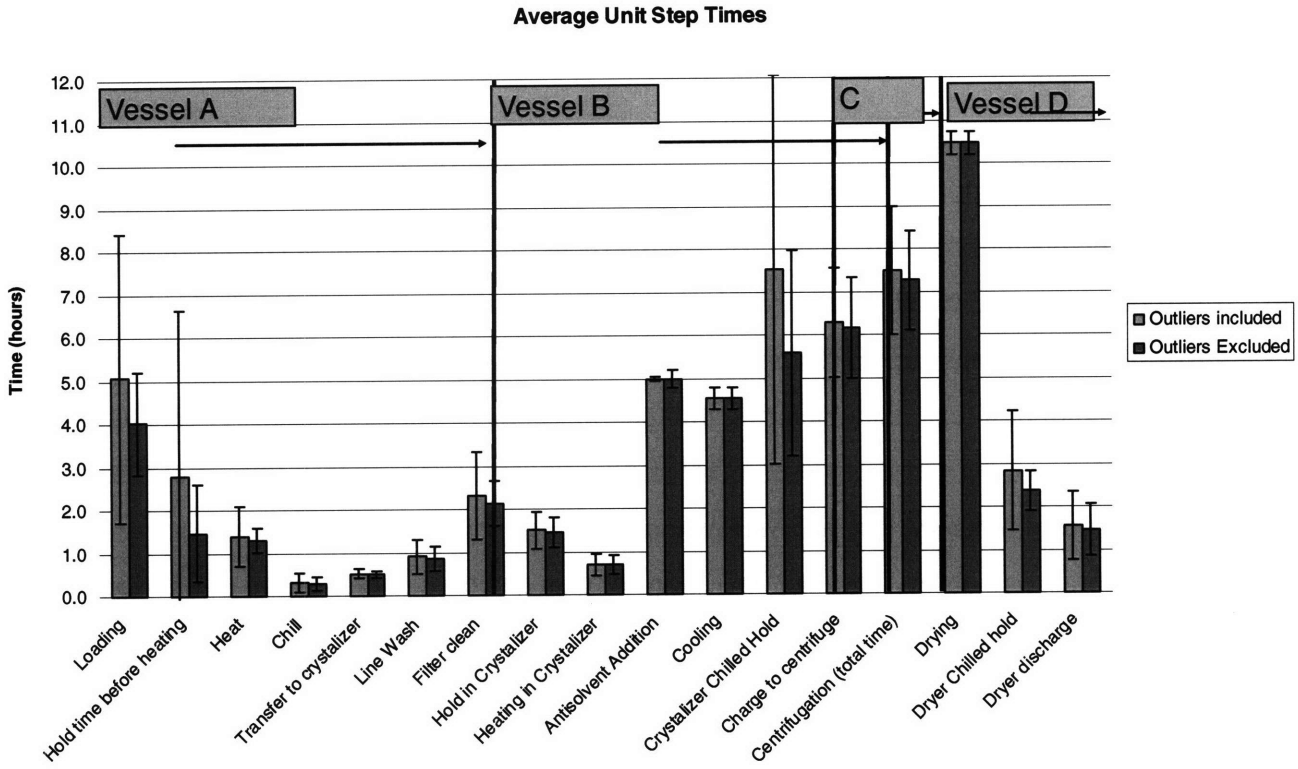
There is a link between PAT and lean optimization. With PAT, a more thorough process understanding is achieved through the analysis of the online data. By analyzing the data collected during a campaign, one can clearly see where process variability occurs and attempt to eliminate the root cause. A throughput time analysis of two campaigns was completed in order to find process inefficiencies and use lean manufacturing principles to propose an optimized process. Implementation of lean manufacturing into pharmaceutical processes is slowly catching on, and Lewis (14) provides a extensive summary and recommendations of lean implementation in the pharmaceutical industry. The analysis included recording unit step times based on the existing batch records, and observing plant operations to gain a better understanding of the work required to complete each unit step. The following sections summarize the analysis, and offers recommendations in order to ensure successful and sustainable implementation of the new "leaned" process.

7.2. Analysis

Step and Batch Times

The first step in applying lean principles is to perform an internal benchmarking analysis to identify the minimum cycle time and maximum throughput for a process. The data for this analysis were acquired from the batch records for 25 previous batches. The start and stop times for each unit step were recorded and subsequently the average, standard deviation, and minimum step times were calculated. The average and standard deviation were calculated with and without extreme outliers (more than 3σ away from average) included. Figure 25 displays the data in graphical form.

Figure 25 Average Unit Step Times

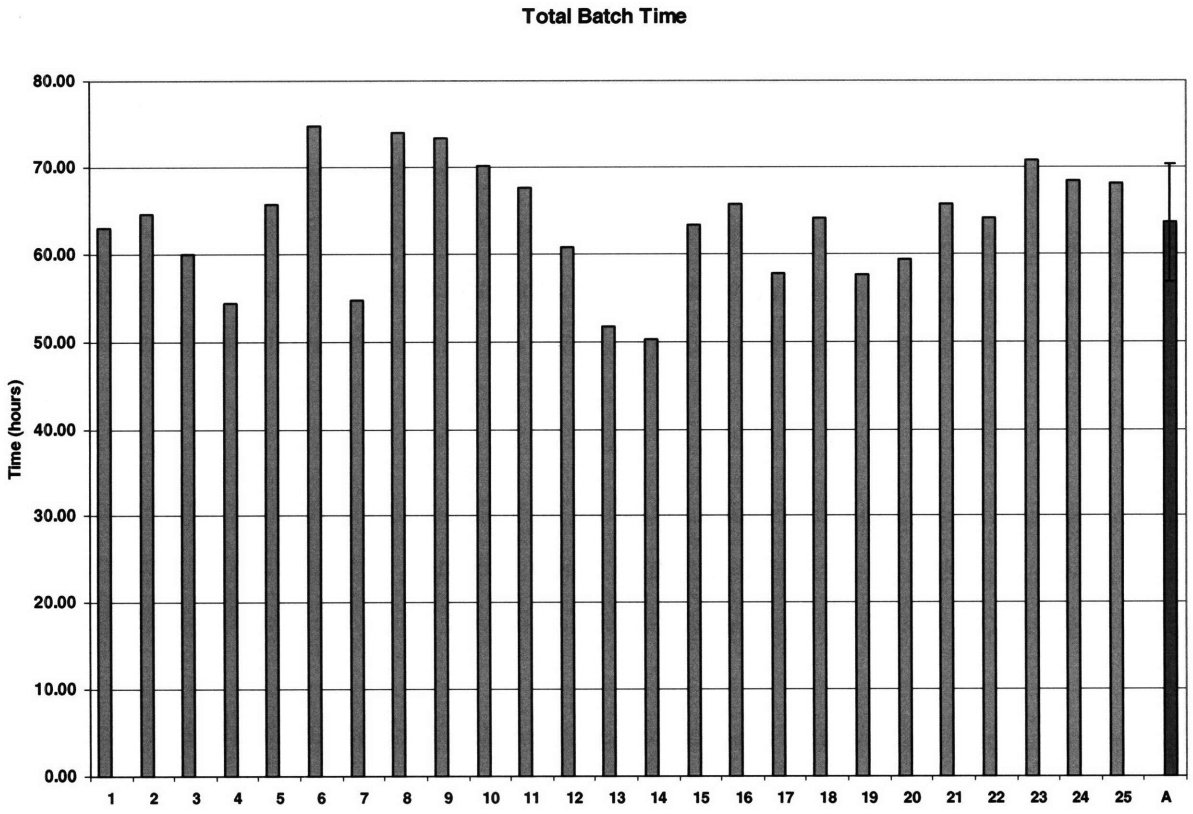


Note: Antisolvent addition time changed to protect confidentiality.

As can be seen in Figure 25, the process variability is primarily attributed to variability in the holding times between unit operations. The actual unit operations, such as heating or water addition, show little to no variability between batches. This is to be expected since unit operation times are carefully monitored and controlled by the operators. The exception to this is the centrifugation time which is dependent on operator skill level and therefore the total centrifugation time varies. These data demonstrate that the process is well controlled, and batch time variability is attributed to differences in the holding times.

The average individual batch time was calculated as the elapsed time from start of liquid loading in the first half of the batch until the discharge of the dryer is completed. The batch times are shown in Figure 26. The batch time rages from 50 to 74 hours, with the average being 64 hours.

Figure 26. Average Total Batch Time



Observations:

The following observations were made while watching the operations on the plant floor and discussing improvement options with operators and various technical experts.

1. While the production schedule is clearly defined, the detail timing of each unit operation is not. The operators are required to complete a predetermined number of batches per week (typically between 5-7); however, on any given day there is no visualization standard by which to track whether or not the operations are ahead or behind schedule. With a schedule clearly listing the responsibilities of each shift and each person, focus can be improved to ensure the 'waste time' can be removed from the process. A schedule will also provide a benefit to the operators by helping them to keep track of the start and end times of each unit operation, and

therefore make shift changeovers easier. It will also provide a metric by which to measure the performance in more detail.

2. The heater required to heat the filter prior to filtration is shared by three different processes. Since these three processes require a different temperature setpoint for the heater (ranging from 50-65 C), the heater can only be used for one process at a time. The operators are trained not to begin heating in vessel A until the filter has been preheated. The heater is often not available, thereby causing a process delay while waiting for another filter to finish heating. This process delay averages 3 hours, although holds as long as 15 hours were recorded during the 2007 campaigns.

3. The procedure for sampling the dryer and testing the loss on drying requires approximately 30 minutes, of which during this time the operator is fully occupied. For all batches produced, the LOD result after 10 hours of drying was $\leq$0.04, which is well below the limit of $\leq$ 0.2%.

4. The steps for which the operator must be present the entire time are the loading of vessel A, the centrifugation (B) and the unloading of dryer (D). Therefore, with only one operator these steps cannot be completed concurrently and must be considered when developing a detailed operator schedule. The remaining steps require the operator to be present only for short intervals to record data into the batch record or to progress the recipe forward.

7.3. Lean Proposal

Based on the above mentioned analysis and observations, I recommend the following proposal be implemented:

1. ***Eliminate the filter pre-heating.*** This will eliminate the holding time between loading and heating, as the operators will no longer have to wait for another process to be finished using the heater before they can proceed with the heating. The average current wait time between these two steps is currently 3 hours, so this will reduce the overall cycle time. The current starting concentration of product in the process is approximately 17.1 % and the temperature setpoint for filtration is 65 °C. Table 6 shows the solubility profile for the active product between 20 and 70 °C (data generated by E. Ndzie at Novartis). The

solubility profile clearly shows that the solution is undersaturated and can be filtered at temperatures well below 65 °C without precipitation occurring. Based on these data, the pre-heating of the filter is not required and the filtration can proceed at room temperature. At a minimum, the acceptable filtration range can be broadened to include the temperature used in other processes therefore eliminating the holding time.

Table 6. Solubility vs. temperature of product in a mixture of THF/Ethanol

Temperature (°C)	*Solubility (mass percentage)*
70	*23.8*
60	*21.4*
50	*20.2*
40	*18.8*
30	*19.1*
20	*19.6*

2. ***Eliminate the end of process testing for the drying step and shorten the drying time from 10 hours to 2 hours.*** Data collected from the July campaign demonstrate clearly that the LOD of the sample after 2 hours is less than <0.05 %. Table 7 shows the measured LOD after 2 hours of drying for 8 batches. The current IPC requires that the LOD be less than 0.2%. Based on the data presented below in Table 7, I propose that the drying time can be reduced to 2 hours. The newly installed NIR probe that measures residual solvent concentration during the drying cycle will provide further assurance that the drying is completed after 2 hours.

Table 7. Loss on Drying after 2 hours drying time

Batch	2 hr LOD (-%)
A	0.04
B	0.04
C	0.03
D	0.04
E	0.04
F	0.04
G	0.04
H	0.03
Average	0.038
Std Dev	0.005

4. ***Implement the following drumbeat proposal.*** Based on the January and July campaign data, the current average step times (with outliers eliminated) were calculated and shown in Table 3. T1 and T2 refer to the first and second halves of each complete batch. The second step, crystallization, is performed in two separate vessels and therefore the batches are split into halves and combined later during the drying step. Additionally, the average downtime between equipment uses was calculated and the results are shown in Table 8. With these step times, it takes on average 67 hours to complete one full batch and the overall cycle time is 40 hours. Overall refers to the average time to complete a batch when calculated as total batches per campaign/# of total hours. This number is lower than average batch time due to the staggered scheduling. This equates to a throughput of approximately 4.2 batches/week. A representative time schedule for a full batch utilizing the optimized schedule can be found in Appendix B.

Table 8. Average Process Unit Step Times

Time analysis		
	T1	T2
Time between Vessel A cycles	10	5
Inert and prepare	0.17	0.17
Wait before loading	1.5	1.5
Loading Vessel A	4.0	4.0
Hold time before disolution start	1.5	1.5
Heating	1.5	1.5
Chill	0.25	0.25
Hold before transfer	0.3	0.3
Transfer to crystalizer	0.5	0.5
Ethanol line wash	1.0	1.0
Filter cleaning	2.0	2.0
Wait time in crystalizer before crystalization	1.5	1.5
Heating	0.75	0.75
Anti-solvent addition	5.0	5.0
Cooling	4.5	4.5
Hold before centrifuge	9.0	5.0
Charge to centrifuge	6.0	6.0
Centrifugation	7	7
Mother liquid and condensate discharge	0.1	0.1
First discharge to start of drying	16.5	6.5
Drying	10.5	10.5
Dryer chill and hold	2.5	2.5
Dryer discharge and condensate empty	1.5	1.5

Note: Antisolvent addition time disguised to protect confidentiality.

Table 9. Average Equipment Downtime

Vessel	T1-T2	T2-T1
A	7	12
B	N/A	15
C	6	19
D	N/A	5

In order to optimize the cycle time, the wait times between unit operations can be minimized. The proposed unit step times are shown in Table 10 and consequential equipment downtimes in Table 11. The values in grey are the same as the current process, and those in white have been changed. The justification for each change is based on the

current process data and is described below. The times that have been changed are based on either the minimum recorded time for that unit operation during the January and July campaigns, or slightly greater than the minimum time recorded to allow for some flexibility. Additionally, the equipment usage is scheduled so that downtime between equipment uses is minimized. With this optimized schedule, one full batch can be completed in 40 hours and the overall cycle time is 21.5 hours. This equates to a throughput of 7.8 batches/week. This presents a 46 % overall cycle time reduction and 86% throughput increase from the current process. A representative time schedule for a complete batch utilizing the optimized schedule is located in Appendix B.

Table 10. Proposed process step times and justification

	T1	T2	Justification
Time between Vessel A Cycles	6	3	Calculated from trial and error until optimal cycle and schedule time determined
Inert and prepare	0.17	0.17	
Wait before loading	0	0	No hold time required in recipe
Loading Vessel A	2.0	2.0	Minimum achieved djuring 2007 campaigns
Hold time before disolution start	0.30	0.30	Filter pre-heating eliminated, no need to hold
Heating	1.0	1.0	Minimum achieved during 2007 campaigns was 0.3 hr
Chill	0.1	0.1	Minimum achieved during 2007 campaigns was 0.05 hr
Hold before transfer	0.3	0.3	Minimum achieved during 2007campaigns was 0.05 hr
Transfer to crystalizer	0.5	0.5	
Ethanol line wash	1.0	1.0	
Filter cleaning	1.0	1.0	Minimum achieved during 2007campaigns
Wait time in crystalizer before crystalization	0.5	0.5	No hold time required in recipe
Heating	0.5	0.5	
Anti-solvent addition	5.0	5.0	
Cooling	4.5	4.5	
Hold before centrifuge	2.0	2.0	Time required to ensure equipmet is ready and leaves >1 hr between use
Charge to centrifuge	5.0	5.0	Minimum achieved during 2007 campaigns was 4.15 hr
Centrifugation	6.0	6.0	Minimum achieved during 2007 campaigns was 4.75 hr
Mother liquid and condensate discharge	0.1	0.1	
First discharge to start of drying	12	6	12 hours based on optimal schedule time, 4.5 hours is minumum achieved during 2007 campaign
Drying	2	2	Justified from LOD data
Dryer chill and hold	2	2	
Dryer discharge and condensate empty	1	1	Minimum time achieved during 2007campaigns was 0.8

Note: Antisolvent addition time disguised to protect confidentiality.

Table 11. Proposed equipment downtime

Vessel	T1-T2	T2-T1
A	3.2	6.2
B	N/A	5.5
C	3.2	6.2
D	N/A	1.3

Gantt Charts for both the current and proposed processes are shown in Appendix C. A more detailed view of the Gantt chart for the proposed process is also located in Appendix C. The Gantt chart demonstrates that the schedule is organized in such a way that the loading of vessel A, centrifugation, and the unloading of dryer D are never scheduled concurrently (highlighted with diagonal pattern). Therefore, the proposed schedule should only require one operator at all times to be dedicated to the production. The spreadsheet used to create these Gantt Charts can easily be updated for the current production schedule by imputing the start time of the first batch into cell B2. This tool will be made available for the technical assistants, shift supervisors, and process managers to use.

7.4. Action Items for Implementation:

1. ***Batch record revision***. In order to implement the broadened filtration temperature range and shortened drying time, the batch record must be revised and approved.

2. ***Training***- Training should be provided for all operators who will be working on this process. They need to know why the schedule was implemented, why it is important and how they are now expected to work differently. Additionally, they should be educated on why it is no longer important to heat the filter to 65 °C or to dry the product for 10 hours.

3. ***Incentive based system***- To support the implementation of the drumbeat an incentive based system for the operators could add value, since the operators will be required to work more efficiently and have more responsibility with the new schedule. This incentive could be something as simple as recognition at the end of the week or, could be a small monetary award to thank them for their hard work if they are able to maintain the drumbeat during their shift work.

4. **Clear communication channels**- The schedule needs to be updated frequently and posted where the operators can clearly see it at the operating stations for the vessel A, centrifuge C, and dryer D. There also needs to be a logbook that the operator can write in if any un-anticipated disturbances occur that cause the operations to fall behind schedule. This will serve two purposes- it will ensure that the operators record all issues so that they are not held accountable for occurrences that were unavoidable. Secondly, it will help the process managers to determine the feasibility of the proposed drumbeat and to identify any additional areas for future process improvements.

7.5. Impact Analysis

Implementing this optimized schedule will obviously impact the plant floor operations in the production facility. Although the implementation will have a positive impact overall, the operators may not be satisfied with the proposal as it will require them to be busier and have more responsibilities. Therefore it is very important that the benefits of the implementation, both operational and financial, be communicated clearly to the operators and shift supervisors.

7.5.1. Operations Impact:

1. Production schedule will be clearly defined for each day, enabling easier resource allocation. It will be the responsibility of the Technical Supervisor or Process Manager to ensure that the schedule is updated daily and posted where operators easily have access to it. If production falls behind schedule, it will be the responsibility of the operators to clearly document the reasons for the production delay.

2. Operators will be held accountable for the work that is required to be completed during their respective shifts.

3. Technical experts and process managers will know the status of each batch at any given point in time. If someone needs to be present during a specific step, the process manager will be able to tell them exactly when the drying is expected to start.

4. The future implementation of Multi Variate Data Analysis (MVDA) analysis will be easier with reduced process time variability. Additionally, for products for which extended hold times can impact product quality, the product quality will be improved.

5. Operators will be able to complete the batches in 50% of the current time, therefore enabling further capacity for other products by reducing throughput time

7.5.2. Capacity Increase

The average batch size for this product is 368 kg. For each batch produced, approximately 7.5 m^3 of reactor capacity is required (3 x 2.5 m^3). Table 12 displays the most recent production forecast and the corresponding capacity increase that results from reducing the overall batch time from 40 hours/batch to 21.5 hours/batch.

Table 12. Production Forecast and Corresponding Capacity Requirement

Year	2008	2009
Current production forecasts (tons)	22.5	25
Batches /IP	45	50
Current Campaign time Requirement (weeks)	10.71	11.90
Optimized Campaign time Requirement (weeks)	5.76	6.40
Time Reduction (weeks)	4.96	5.51
Capacity Increase (m3)	0.71	0.79

Note: Production forecast data and number of batches disguised to protect confidentiality

The increased capacity impacts the total utilization. For 2009, the total production time is estimated to be 27 weeks, of which production for this product consumes 12 weeks. With the optimized process, the total production time for 50 batches will be reduced to 6.4 weeks. As can be seen in Table 13 and 14, the 2009 utilization will decrease from 85% to 74% if the total production time is reduced by 5.5 weeks.

Table 13 Current Capacity Utilization for Line 4

2009		
Action	**Weeks**	**Percentage**
Production	27	52%
Setup/ Cleaning	15	29%
Maintainance	2	4%
Idle time	8	15%
Total Utilization	**52**	**85%**

Table 14. Proposed Capacity Utilization for Line 4

2009		
Action	**Weeks**	**Percentage**
Production	21.5	41%
Setup/ Cleaning	15	29%
Maintainance	2	4%
Idle time	13.5	26%
Total Utilization	**52**	**74%**

7.5.3. Financial Impact

There are no additional costs to implementing this proposal as there is no need for additional personnel or equipment. When doing the financial analysis, there are two different costs savings to consider. The first are the direct product costs savings, such as labor, energy, and equipment depreciation, resulting from a reduced cycle time. The second, and more indirect, are the avoided investment costs and inventory costs. By increasing the capacity of the plant, future investments to accommodate increased demand are delayed. In-process inventory is reduced because high-value drug intermediates are converted into final product faster. These savings can be quite substantial; in one estimate (Lewis, 2006) decreasing the cycle time of a process from 35 days to 24 days saved 11 days of inventory which translates to cost savings of over $3 million.

Direct Cost Savings:

Direct cost savings only account for the savings in labor, energy use, and equipment depreciation. The NPV can be calculated based on the future demand forecast, the cost per hour

of plant operation (labor, energy use, equipment depreciation), and the total time savings per batch. Labor is considered to be a variable cost in this analysis because it is assumed that the operators can work on a different product when not working on this product. The time savings is shown in Table 15 and an example of an NPV calculation of these savings is shown in Table 16.

Table 15 Time Savings

Equipment Use	Old (hr/batch)	New (hr/batch)	Hours Saved (hr/batch)
Reactor	22	12	10
Crystallizer	54	30	24
Centrifuge	16	12	4
Dryer	34	20	14
Labor	64	36	28
Energy	126	74	52

Table 16. NPV Analysis

	2008	2009	2010	2011	2012
Total Batches	45	50	55	60	65
Cost Savings/batch					
Vessel A					
Vessel B					
Vessel C					
Vessel D					
Labor					
Energy					
Total Savings/batch	SFr. 3,570	SFr. 3,570	SFr. 3,570	SFr. 3,570	SFr. 3,570
Total Savings/year	SFr. 120,299	SFr. 166,867	SFr. 194,031	SFr. 209,554	SFr. 213,434
NPV Total Savings	SFr. 143,484	SFr. 148,304	SFr. 151,753	SFr. 153,999	SFr. 155,192
Total NPV savings	SFr. 752,732				

Note: Cost savings data removed to protect confidentiality. Disguised NPV is approximate to actual NPV.

Note: NPV calculation uses a discount rate of 7.5%

7.6. Future Recommendations

An IT infrastructure was installed that collect the data from each piece of equipment in real time and store them on a PI historian. This enables one to measure the progress of a batch during each unit operation, and therefore to have a better understanding of process variability. With this information, the process managers can determine if and how the process variability can be eliminated. There may be processes in which the hold time does affect the product quality. By ensuring that each batch has the same intermediate hold times, product quality would be

improved. Therefore, it could be beneficial to incorporate the optimized schedule into the control recipe. The time evolution for a "golden batch" would be stored in the recipe and if the current batch significantly deviates from the standard then an alarm will sound. For example, if the batch is held longer than expected between recrystallization and centrifugation, an alarm would sound that would notify the operator. If there is an unavoidable reason why the operator cannot proceed with the centrifugation, the recipe would require that he enter the reason (i.e. centrifugation of previous cycle ongoing) into the SCADA. This will make it easier for operators to follow the schedule and also allow the process managers to understand bottlenecks in their process. These findings provide significant opportunities for optimization that do not require many resources and offer notable time and cost savings.

8. Barriers to PAT Implementation

The challenges facing PAT implementation within the pharmaceutical industry have been discussed frequently. In fact, Ajaz Hussein says that it won't be until the year 2020 that all pharmaceutical companies, including the small players, are implementing PAT technologies (McCormick, 2007). The major challenges appear to be the lack of infrastructure within the current manufacturing facilities, perceived regulatory barriers, cost of implementation, and industry mindset and concerns. Most of these challenges can be classified as either a strategic, cultural, or political challenge.

8.1. Strategic Challenges

The biggest barriers to PAT implementation are reluctance to invest in manufacturing and risk aversion. The return on investment is not immediate and often PAT implementation will be NPV negative initially (Neway, 2003). This is because the costs of the equipment, IT hardware and software, and personnel time required to implement PAT are substantial, and it is often hard to quantify the benefits of PAT in financial terms.

Defining business drivers and potential benefits from a PAT initiative is essential for a successful project. However, it is easy to make the scientific case, but much harder to make the business case. The high cost of investment and low initial return results in a lack of senior management support. One must stress that PAT is not just about comparison of cost of the current laboratory method with the cost of a replacement analyzer. Much bigger gains can be achieved through PAT, and it is necessary to clearly put into numbers how reduced cycle times and costs add value.

Project managers and engineers are also concerned that the increased data generation and process knowledge resulting from implementation of PAT may expose deficiencies in manufacturing processes. Because the online data may expose flaws that were previously unidentified, companies fear that they might face penalties from the FDA even though their process is operating correctly and producing product of acceptable quality (Neway, 2003).

8.2. Cultural Challenges

The plant that produces the active pharmaceutical ingredient for the pilot project is over 60 years old, and many of the processes and equipment were old as well. With PAT, new computers, probes, and IT infrastructure were installed. In this pilot case, some operators were very excited about the new technology, but I don't think it was communicated clearly to them what the purpose of it was. Many operators, especially the older ones, would prefer to have manual operations over the new automated operations. One operator told me "if something goes wrong I know how to fix it if all I have to do is turn a valve, but I don't know how to troubleshoot a computer recipe". In general, pharmaceutical manufacturing is very resistant to change given that it is such a highly regulated environment. Many people in manufacturing are asking why it is necessary to update the process. It is very hard to convince someone of the benefits of spending all of this time and money when the process is already producing acceptable quality product. Many people have the mentality of "if it's not broke, why fix it?" It has been built into the culture, not only at Novartis but of the pharmaceutical industry, that the current manufacturing processes are sufficient and that all products must be extensively tested. It is difficult to convince them otherwise. Therefore, culture change within an organization is necessary. In order to fully realize the benefits of QbD, a focused team with representatives from all functions impacted by PAT must be formed and dedicated to the project. Early feedback is important, especially between development, manufacturing, and QA.

8.3. Political Challenges

A company trying to implement PAT into the organization is likely to face some opposition, especially from the operators and from the QA functions. The plant operators might fear that with more technology, they will be required to do more work or that their job won't be needed. In this pilot case, the implementation of the new project required the operators to do a lot more work- more frequent sampling to calibrate the NIR probe, entering raw material numbers into the computer, and ensuring every 5 minutes that the N_2 flush on the dryer was operating. However, I don't believe they fully understood why they needed to be doing this extra work and what the clear benefits were.

There is also likely to be a political issue between the quality assurance (QA) group and the project management. The QA group will likely be reluctant to eliminate end-of-product testing. I noticed that scientists from the QA group were hesitant to believe that the online data are sufficient to prove product quality even though the process experts and project managers thought otherwise. They constantly questioned the risk of not catching a product quality deviation by using the online method only. There may be an issue with concern for their job security, which consists of running the labs that analyze all of the product samples.

This page has been intentionally left blank

9. Conclusions

9.1. Current state of Pharmaceutical Industry

Most companies in the pharmaceutical industry are currently at phase 1 or 2 of implementation. Once you have achieved level 4, the requirement to measure quality attributes online is not needed. If you can prove that your process is in control, as defined by the design space, measuring quality online becomes an added security measure but is not necessary. Ali Afnan from the FDA commented that quality analysis alone is monitoring only, not control, and thus should be considered an alternate method (Afnan, 2004). For example, with the milling operation it is known based on lab-scale and full-scale data that only classifier speed and nozzle pressure affect particle size. If it can be proven through online monitoring that the nozzle pressure and classifier speed are both within the pre-defined acceptable ranges (determined through DoE) throughout the entire process, then measuring particle size online is not necessary. Industry and FDA must work together to progress from phase 1 to phase 3 – 5. This is being achieved through increased partnership and more flexible validation requirements.

Replacement of offline with online product quality measurements is most beneficial when the process is being run at the same conditions. That is, before the design space has been developed and the process is running at the fixed process conditions. Often, online measurements are sensitive to the process conditions. Therefore, an online probe may be accurate at normal operating conditions, but once the process is run at a different point within the design space, the online measurement may not be accurate. We noticed this with the online laser diffraction probe. The settings of the probe were optimized at normal milling conditions; however when the milling conditions changed the accuracy of the probe decreased significantly. This supports the recommendation that online quality measurements are not necessary, and potentially not possible, when the process is being run within a flexible design space.

Online product quality measurements do however provide engineers with the ability to see in real-time the effect of variable process input on product quality. Therefore, online product quality measurements are extremely beneficial during the process optimization phase in the lab or pilot scale.

9.2. Validation of New Technologies

Standard procedures are needed. Even though many companies have achieved Phase 2 of implementation, there is no standard procedure on how best to cross-validate the methods. Companies are relying on internal statisticians and process experts, but the process could be streamlined if standard procedure established. I made recommendations in sections 3 and 4 above on how these technologies could potentially be validated, but I believe that by combining the collective knowledge of industry and the FDA a standard set of guidelines could be issued that would make the process more efficient. In general, the questions that should be answered in the standard procedure are:

1. How many samples need to be taken for the cross-validation?
2. What statistical test should be used?
3. Does the test need to be performed over the entire proposed design space?

There also exists much uncertainty on how to perform and confirm/validate full-scale design space. Recommendations need to be made on what ranges should be tested at the full scale. More specifically, the following questions need to be answered:

1. Should the ranges be based on the lab and pilot plant data, or on the actual sensitivity of the full-scale equipment (i.e. propose 3x operating range for equipment).

2. How many points within design space need to be covered in order to validate the entire design space?

3. How is successful validation measured? Does the exact product quality result need to be predicted before-hand based on lab and pilot data? This is often challenging due to scale effects. If the expected product quality for each condition can not be specified before the validation occurs, then is a confirmation sufficient?

9.3. Challenges in Full-scale Design Space Confirmation

There exists much uncertainty on how to perform and confirm or validate the full-scale design space. **Full scale design space confirmation is necessary, but difficult.** Even in cases where scale-down model is representative, scale-factors may come into play that were not anticipated. For steps that are equipment dependent and have many mechanical factors at play (i.e. milling, blending), full-scale confirmation plays an even more important role. If applying

QbD to established, approved process that must be operated within the pre-validated range, this can become difficult to do. Multiple options exist:

- Confirm design space only within narrow operating range that has already been approved.

- Cover the full range of design space (need to plan deviations), and set material aside until quality is proven significant. Trade-off between cost of raw materials, and predicted accuracy of design space based on lab-scale data (probability of OOS quality).

Development of good **scale-down model is critical** otherwise lab-scale DoE data are not useful. Plus, representative scale-down modeling will pave the future path towards continuous manufacturing. If representative scale-down model does not exist, then DoE experiments should be done only at full scale. This will obviously come at significant cost because material will not be able to be used if quality is not met. Additionally, it will be challenging to perform a high-powered DoE since the number of runs will be limited by material availability and other resource costs. However, if a representative scale-down model does not exist then performing lab scale DoE is not a value added activity.

9.4. QbD Implementation Considerations

Allocating between products in development and products in manufacturing offers the opportunity to balance short-term and long-term value contribution in company's product portfolio.

In Development- As stated in the FDA PAT guideline, applying QbD is easiest and most valuable when applied to a process that is in development. DoE studies can be performed early on and full-scale design space confirmation can be completed during pre-validation batches without the constraint of already approved operating ranges. However, the FDA will need to change their stance on how validation is done. Instead of doing 3 batches at the same conditions, multiple batches within proposed design space will need to be used to validate the design space. QbD will also offer the ability to quickly develop the

manufacturing process, scale-up to a robust process, and perform validation. Each successive product development effort will be more efficient as the knowledge set is built upon past experience. Therefore, the earlier companies start implementing QbD principles into their process development, the quicker they will see the advantages and decrease the product development timeframe.

Approved processes: With an approved process, the 1st and 2nd layers of PAT implementation are the easiest, i.e. replacing offline method with online method and monitoring online data. It is more difficult to perform DoE experiments and get full power of QbD because of the requirement to operate within previously approved process ranges. I also believe that it is too tedious to retrospectively perform design of experiments at the lab-scale in order to optimize the process. However, money can be saved by replacing offline with online product quality measurements. Priority should be placed on high-volume products or highly variable products to achieve most benefit from PAT implementation. Gerd Fischer of Sanofi-Aventis has said that products for a PAT pilot project should amount to more than 100 tons per year for API and more than 1000 batches per year for drug products (Fischer, 2005).

9.5. Implementing Lean Principles

Many companies tend to fall victim to the "legacy process" mentality. That is, steps and tests are performed even when they may not be necessary. There is always an urgency to get the product to market, and often a similar process to one that has already been developed for an existing product is applied to new products. This "works-before, let's do it again" attitude can often result in sub-optimal processes. Time and cost savings can be achieved by simply revisiting processes, performing a throughput analysis, and questioning why certain steps and tests are performed. Cycle time variability and bottlenecks can be identified and achieved through an analysis of historical data for each unit operation. An optimized process schedule can be developed by determining the minimum time required for each process step. Running the process on a "drumbeat schedule" offers significant benefits in terms of operations and cost savings. Lewis (2006) documents the benefits of internal benchmarking and lean optimization. These benefits do not require substantial investments in technology to achieve. Instead, only value

stream mapping, variability root-cause analysis, and other basic lean principles need to be applied to the process.

9.6. Enabler of Continuous Manufacturing

PAT and QbD are necessary precursors and enablers of continuous manufacturing, in which materials are modified and tested continuously to minimize delays in movement from start to finish during the process. Continuous manufacturing offers a significant advantage as it requires less square footage and equipment, and will greatly reduce cycle time. **In order to move to the future vision of continuous manufacturing, the next major foreseeable technology disruption in pharmaceutical manufacturing, companies MUST implement PAT, QbD, and Lean Manufacturing.** Continuous manufacturing relies fully on online process control and full understanding of input and output parameters. Additionally, the process must be extremely lean and run on a drumbeat. Therefore, finding the sources of variability within the process, eliminating them, and establishing a process drumbeat are necessary precursors to continuous manufacturing. If this is seen as next technical disruption, companies will need to adopt continuous manufacturing to remain competitive. Continuous manufacturing is 10-15 years away, but the time to start incorporating PAT, QbD, and Lean into processes is now.

Glossary

API= Active Pharmaceutical Ingredient

DoE = Design of Experiments

CDER= Center for Drug Evaluation and Research

CRADA= Cooperative Research and Development Agreement

DS= Drug substance

DP= Drug product

FDA = Food and Drug Administration

FMEA = Failure Modes and Effects Analysis

GC= Gas Chromatography

HPLC= High Pressure Liquid Chromatography

IP= Intermediate Product

IPC= In-process control

LOD= Loss on Drying

MVDA = Multivariate Data Analysis

NDA= New Drug Application

NIR = Near Infra-Red

NPV= Net present value

PCA = Principal Component Analysis

PLS = Partial Least Squares

QA = Quality Assurance

QC= Quality Control

QbD = Quality by Design

PAT = Process Analytical Technology

PSD = Particle Size Distribution

SCADA = Supervisory Control and Data Acquisition

SPC= Statistical Process Control

Bibliography

Aboud, L. and Hensley, S. (2003, September 3). New Prescription for Drugmakers: Update the Plants. *The Wall Street Journal.*

Afnan, AM (2004). PAT. *Journal Process Analytical Technology, 1* (1): 8-9.

Balboni, M. (2003). Process Analytical Technology: Concepts and Principles. *Pharmaceutical Technology, 27*(10), 54-66.

Benson, R.S. and MacCabe, D.J. (2004). From good manufacturing practice to good manufacturing performance. *Pharmaceutical Engineering, 24*, 26-34.

Cohen, F. (2005). Macro Trends in pharmaceutical innovation. *Nature Reviews Drug Discovery,* 4 , 78-85.

Cook. J. "The 5 Steps of Starting PAT", *Pharmaceutical Technology: Monitoring, Automation, and Control,* 2007, 16-21. Retrieved March 3, 2008 from http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=407613&sk=&date=&pageID=2.

Crosby, T. (2008) "Designing For the Future of Continuous Manufacturing" *Pharmaceutical Processing.* Retrieved March 10th, 2008 from http://www.pharmpro.com/ShowPR.aspx?PUBCODE=021&ACCT=0000100&ISSUE=0601&RELTYPE=PR&ORIGRELTYPE=ATO&PRODCODE=0000&PRODLETT=A&CommonCount=0.

Dean, D. and Bruttin, F. (2001). Productivity and the Economics of Regulatory Compliance in Pharmaceutical Production. Presented to FDA Science Board, Rockville, MD on Nov 16, 2001. Retrieved March 10th, 2008 from http://www.fda.gov/ohrms/dockets/ac/01/slides/3799s1_02_Dean.ppt.

Deming, W.E. (1986) *Quality, Productivity, and Competitive Position*. Cambridge: Massachusetts Institute of Technology Press.

Erikkson, L. (2006) *Multi-and Megavariate Data Analysis Part 1: Basic Prinicples and Applications*. Umetrics Academy.

Femia, Dave. "Process Analytical Technology: Real-Time Reliability", *Pharmaceutical Technology*, November, 2005. Retrieved March 12, 2008 from: http://pharmtech.findpharma.com/pharmtech/Article/Process-Analytical-Technology-Real-Time-Reliabilit/ArticleStandard/Article/detail/261888.

Fischer G. (2005). Experiences from a PAT pilot project, presentation at the 19th international forum process analytical technology. IFPAC 2005, January 10-13, Arlington, VA.

FDA. (2003). Final report on pharmaceutical cGMPs for the 21st century-Arisk-based approach. http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm.

FDA (2004). Guidance for Industry PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. Retrieved January 20th, 2008 from: http://www.fda.gov/cder/guidance/6419fnl.pdf.

FDA. (2005). Submission of Chemistry, Manufacturing, and Controls Information in a New Drug Application Under the New Pharmaceutical Quality Assessment System Notice of Pilot Program. *Federal Register 70* (134), 40719-40720.

FDA. New Drug Application Approvals and Receipts, Including New Molecular Entities, 1938 to Present. Retrieved April 15th, 2008 from http://www.fda.gov/oc/history/NDAapprovals.html.

Han SM, Faulkner PG. (1996). Determination of SB 216469-S during tablet production using near-infrared reflectance spectroscopy. *Journal of Pharmaceutical and Biomedical Analytics*, 4, 1681-9.

Hinz, D.C. (2006). Process analytical technologies in the pharmaceutical industry: the FDA's PAT initiative. *Analytical Bioanalytical Chemistry*, 384, 1036-1042.

Hussain, Ajaz (2005). Process Analytical Technology: A First Step in a Journey towards the desired state. *Journal of Process Analytical Technology,* 2(1) , 8-13.

Kourti, T. (2006). The Process Analytical Technology initiative and multivariate process analysis, monitoring, and control. *Analytical Bioanalytical Chemistry*, 384, 1043- 1048.

Lewis, N.A.(2006) "A Tracking Tool for Lean Solid-Dose Manufacturing" *Pharmaceutical Technology, 30* (10) 94-108.

Macher, J. and Nickerson, J (2006). Pharmaceutical Manufacturing Research Project Final Benchmarking Report. Georgetown University and St. Louis University. Retrieved on April 2nd, 2008, from http://www.olin.wustl.edu/faculty/nickerson/results/PMRPFinalReportSept2006.pdf.

Martinez, B. and Goldstein, J. (2007, December 6). Big Pharma faces grim prognosis. *The Wall Street Journal.*

Maes, Ingrid (2006).The need for a broader perspective if process analytical technology implementation is to be successful in the pharmaceutical sector. *Journal of Pharmaceutical Innovation*, 1, 19-21.

McCormick, D. (2005). PAT Survey Reflects Optimism, Uncertainty. *Pharmaceutical Technology, 29*(1), 24.

McCormick, D. (2006). Reinventing FDA: A Mid-Course Report. *Pharmaceutical Technology, 30*(8), 32-39.

Moffat AC, Trafford AD, et al. (2000). Meeting of the International Conference on Harmonisation's Guidelines on Validation of Analytical Procedures: Quantification as exemplified by a near-infrared reflectance assay of paracetamol in intact tablets. *Analyst,* 125, 1341-1351.

National Science Foundation (2003), Research and Development in Industry. Retrived on April 16th from http://www.nsf.gov/statistics/nsf07314/pdf/tab26.pdf.

Neway, J. (2003). Filling the Void: PAT in a Connected Manufacturing Environment. *Pharmaceutical Technology*, *27* (10), 46-52.

Nocera, J. (2006, July 1st). Generic Drugs: The Window Has Loopholes. *The New York Times.*

Parris, J., Airiau, C. et al (2005).Monitoring of API Drying Operations with NIR. *Spectroscopy,* 20 (2), 34-42 .

Raju, G.K. (2001). Continuous Quality Verification. Advisory Committee for Pharmaceutical Science, Rockville, MD. Retrieved April 10th from http://www.fda.gov/ohrms/dockets/ac/01/slides/3763s1_15_raju/sld018.htm

Schenider, R. (2006) Achieving Process Understanding: The Foundation of a Strategic PAT Program. Retrieved on April 10th from http://pharmamanufacturing.com/articles/2006/109.html

Scott, B. and Wilcock, A. (2008). Process Analytical Technology and Validation. *Validation of Pharmaceutical Processes, 3rd Addition,* Informa Healthcare USA.

Sellars, L.J., Feighan, C. and Kelley,G, (2002). Top 50 Pharmaceutical Companies of 2001. *Pharmaceutical Executive.* Retrieved on April 20th from http://pharmexec.findpharma.com/pharmexec/data/articlelong//pharmexec/182002/17966/article.pdf

PhRMA (2008). R&D Spending by U.S. Biopharmaceutical Companies Reaches Record $58.8 Billion in 2007. Press Release, March 24, 2008. Retrieved on April 10th, 2007 from http://www.phrma.org/news_room/press_releases/us_biopharmaceutical_companies_r&d_spending_reaches_record_$58.8_billion_in_2007/

PhRMA (2008). Industry Profile. Retrieved April 5th, 2008 from http://www.phrma.org/files/2008%20Profile.pdf.

Reich, G. (2005). Near infrared spectroscopy and imaging: Basic Principles and pharmaceutical applications. *Advanced Drug Delivery Reviews*, 57, 1109-1143.

Thomas, B.A.M. (1961). Some industrial applications of multivariate analysis. *Applied Statistics*, 10(1), 1-8.

United States Congress (2003, June 10). S.1225 Greater Access to Affordable Pharmaceuticals Act.

Weschler, J. (2002). Modernizing Pharmaceutical Manufacturing. *Pharmaceutical Technology, 14* (2), 16-24.

Winkle, Helen (2007, September 24). Implementing Quality by Design. Presented at PDA/FDA Joint Regulatory Conference. Retrieved on April 20th from http://www.fda.gov/Cder/OPS/ImplementingQualitybyDesign.pdf

Woodcock, J. (2007). Critical Path: Focus on Your Customers. Keynote speech from IFPAC plenary session. Retrieved March 10th, 2008 from http://www.pharmamanufacturing.com/articles/2007/022.html?page=print

Yu, L. et al. (2004). Applications of process analytical technology to crystallization processes. *Advanced Drug Delivery Reviews, 56*, 349-369.

Yu, L. (2007). Pharmaceutical Quality by Design: Product and Process Development, Understanding, and Control. *Pharmaceutical Research, 25* (4), 781-791.

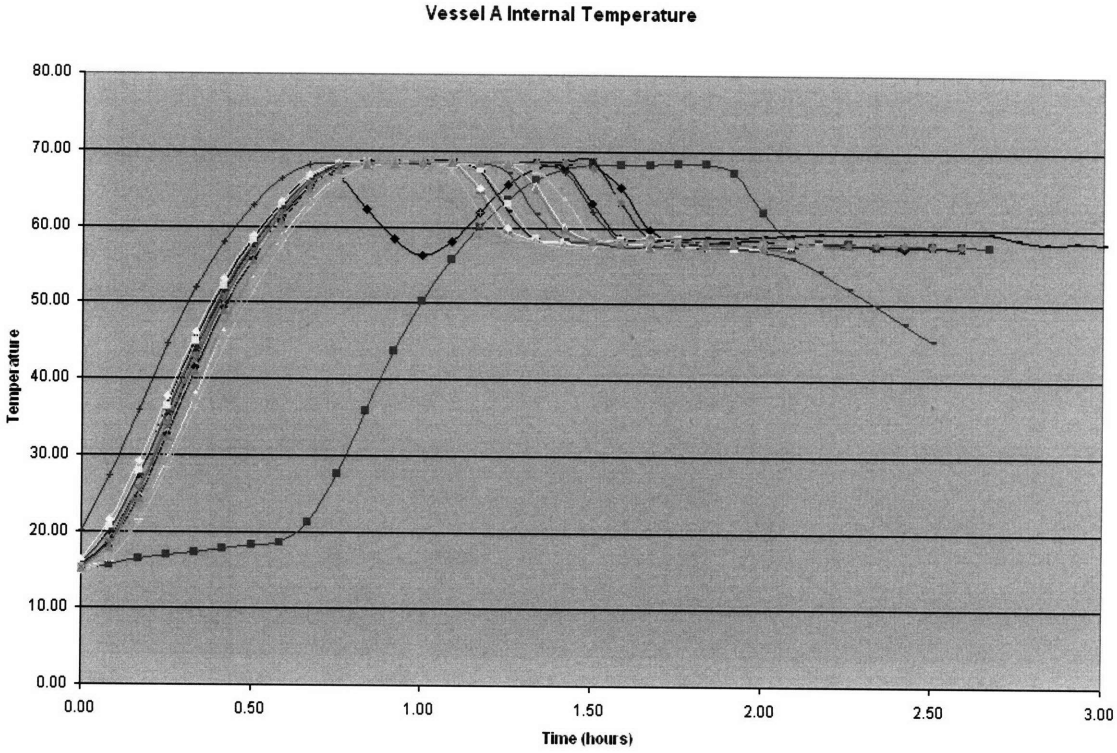
Appendix A. MVDA

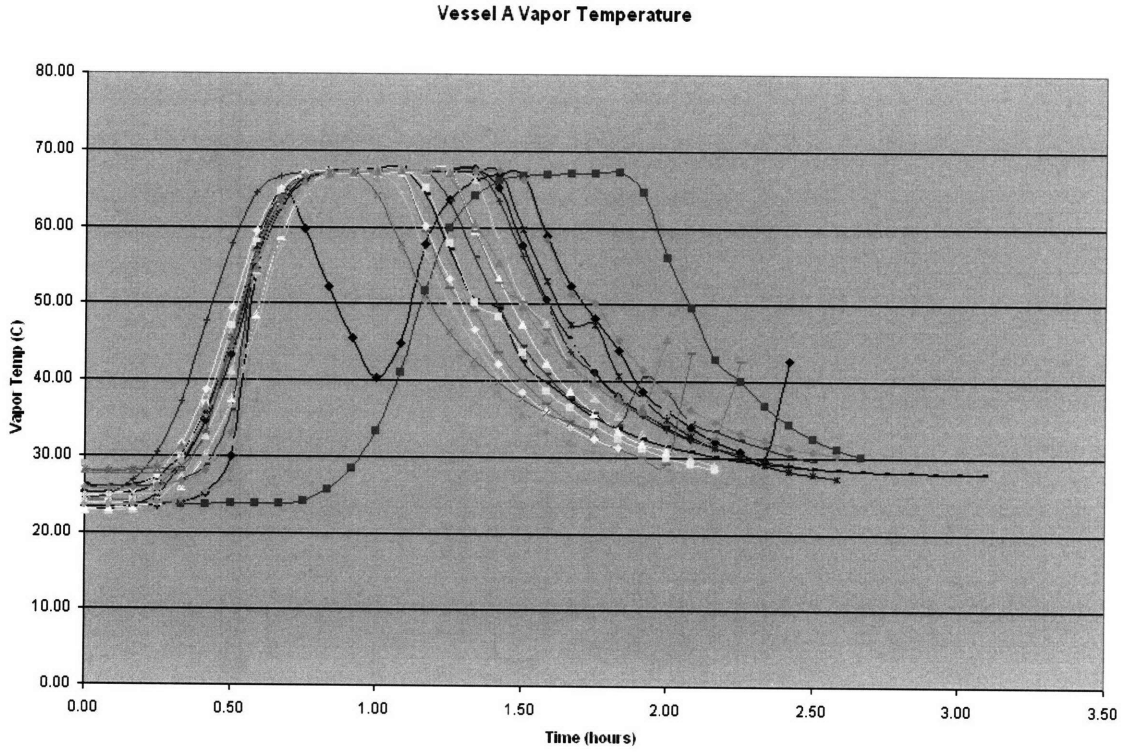
Example of data formatting for batch processes

		Controlled Process Variables			Uncontrolled Process Variables				Initial Conditions for Batch			Final Quality for Batch	
BatchNo	Time	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
B001	1	0.975235	0.2323	0.4239	0.456456	0.234324	0.346343	0.99788	12	16	19	89	91
B001	2	0.987235	0.239269	0.436617	0.47015	0.241354	0.356734	1.027816					
B001	3	0.974633	0.246447	0.449716	0.484254	0.248594	0.367436	1.058651					
B001	4	0.949909	0.25384	0.463207	0.498782	0.256052	0.378459	1.09041					
B001	5	0.985056	0.261456	0.477103	0.513745	0.263734	0.389813	1.123123					
B001	6	1.021503	0.269299	0.491416	0.529158	0.271646	0.401507	1.156816					
B001	7	1.059299	0.277378	0.506159	0.545032	0.279795	0.413552	1.191521					
B001	8	1.098493	0.2857	0.521344	0.561383	0.288189	0.425959	1.227267					
B001	9	1.085467	0.294271	0.536984	0.578225	0.296835	0.438737	1.264085					
B001	10	1.072596	0.303099	0.553093	0.595572	0.30574	0.4519	1.302007					
B001	11	1.059877	0.312192	0.569686	0.613439	0.314912	0.465457	1.341067					
B001	12	1.04731	0.321558	0.586777	0.631842	0.324359	0.47942	1.381299					
B001	13	1.034891	0.331204	0.60438	0.650797	0.33409	0.493803	1.422738					
B001	14	1.02262	0.34114	0.622511	0.670321	0.344113	0.508617	1.46542					
B001	15	1.010494	0.351375	0.641187	0.690431	0.354436	0.523875	1.509383					
B001	16	0.998512	0.361916	0.660422	0.711144	0.365069	0.539592	1.554665					
B001	17	0.986672	0.372773	0.680235	0.732478	0.376021	0.555779	1.601304					
B001	18	0.974972	0.383957	0.700642	0.754452	0.387302	0.572453	1.649344					
B002	1	0.95287	0.3434	0.23423	0.46565	0.309823	0.364543	0.899108	15	13	20	92	95
B002	2	0.985268	0.353702	0.241257	0.47962	0.319118	0.375479	0.926081					
B002	3	0.970752	0.364313	0.248495	0.494008	0.328691	0.386744	0.953864					
B002	4	0.94236	0.375242	0.255949	0.508828	0.338552	0.398346	0.98248					
B002	5	0.977227	0.3865	0.263628	0.524093	0.348709	0.410296	1.011954					
B002	6	1.013385	0.398095	0.271537	0.539816	0.35917	0.422605	1.042313					
B002	7	1.05088	0.410038	0.279683	0.55601	0.369945	0.435283	1.073582					
B002	8	1.089762	0.422339	0.288073	0.572691	0.381043	0.448342	1.105789					
B002	9	1.07684	0.435009	0.296716	0.589871	0.392475	0.461792	1.138963					
B002	10	1.064071	0.448059	0.305617	0.607568	0.404249	0.475646	1.173132					
B002	11	1.051454	0.461501	0.314786	0.625795	0.416376	0.489915	1.208326					
B002	12	1.038986	0.475346	0.324229	0.644569	0.428867	0.504613	1.244576					
B002	13	1.026666	0.489606	0.333956	0.663906	0.441734	0.519751	1.281913					
B002	14	1.014492	0.504294	0.343975	0.683823	0.454986	0.535344	1.32037					
B002	15	1.002463	0.519423	0.354294	0.704337	0.468635	0.551404	1.359982					
B002	16	0.990576	0.535006	0.364923	0.725468	0.482694	0.567946	1.400781					
B002	17	0.97883	0.551056	0.37587	0.747232	0.497175	0.584984	1.442804					
B002	18	0.967223	0.567588	0.387147	0.769648	0.51209	0.602534	1.486089					
B003	1	0.935521	0.35235	0.298734	0.78692	0.510053	0.423034	0.90872	17	11	23	95	92
B003	2	0.875199	0.362921	0.307696	0.810528	0.525355	0.435725	0.935982					
B003	3	0.907581	0.373808	0.316927	0.834843	0.541115	0.448797	0.964061					
B003	4	0.941162	0.385022	0.326435	0.859889	0.557349	0.462261	0.992983					
B003	5	0.975985	0.396573	0.336228	0.885685	0.574069	0.476128	1.022772					
B003	6	1.012096	0.40847	0.346315	0.912256	0.591291	0.490412	1.053456					
B003	7	1.000095	0.420724	0.356704	0.939624	0.60903	0.505125	1.085059					
B003	8	0.988236	0.433346	0.367405	0.967812	0.627301	0.520278	1.117611					
B003	9	0.976518	0.446346	0.378427	0.996847	0.64612	0.535887	1.151139					
B003	10	0.964939	0.459737	0.38978	1.026752	0.665503	0.551963	1.185673					
B003	11	0.953497	0.473529	0.401474	1.057555	0.685469	0.568522	1.221244					
B003	12	0.94219	0.487735	0.413518	1.089281	0.706033	0.585578	1.257881					
B003	13	0.931018	0.502367	0.425923	1.12196	0.727214	0.603145	1.295617					
B003	14	0.919978	0.517438	0.438701	1.155619	0.74903	0.62124	1.334486					
B003	15	0.90907	0.532961	0.451862	1.190287	0.771501	0.639877	1.374521					
B003	16	0.89829	0.54895	0.465418	1.225996	0.794646	0.659073	1.415756					
B003	17	0.887638	0.565418	0.47938	1.262776	0.818485	0.678845	1.458229					
B003	18	0.877113	0.582381	0.493762	1.300659	0.84304	0.699211	1.501976					

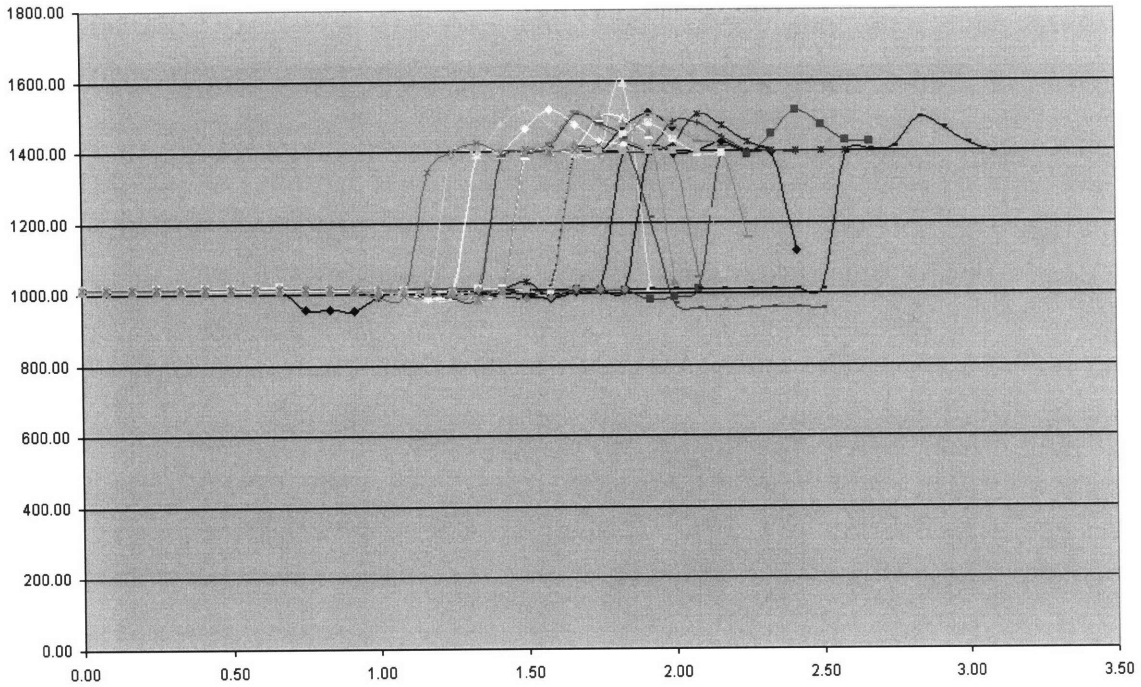
Source: Adapted from Umetrics website

Uni-variate Excel Charts

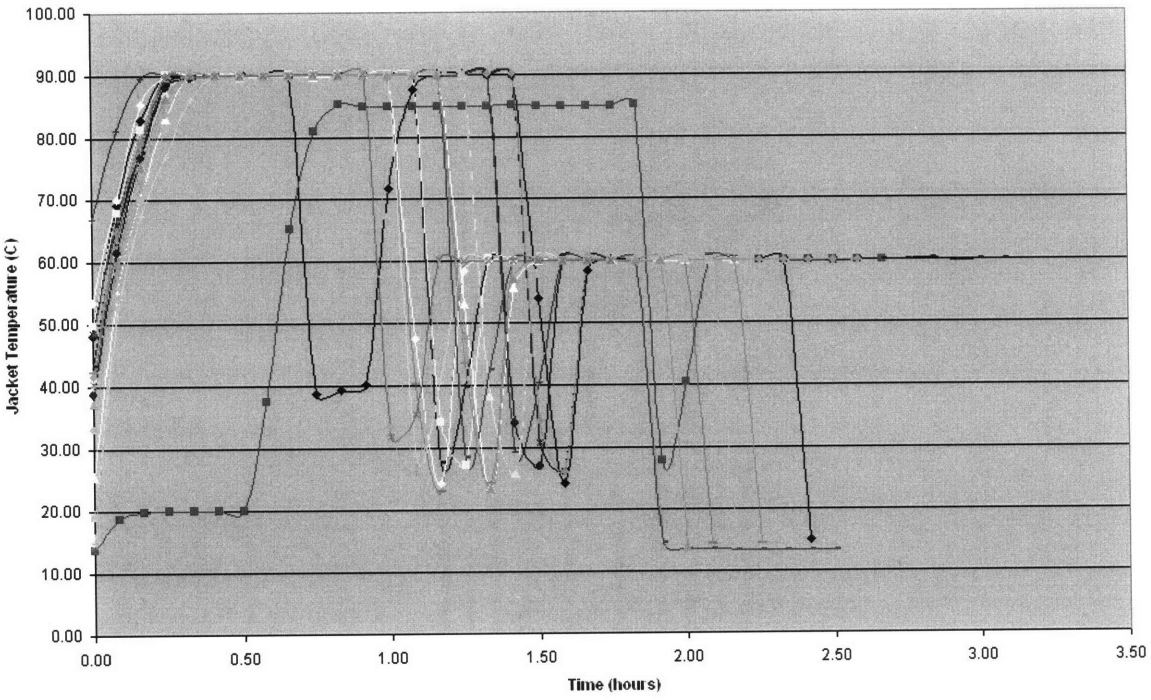




Vessel A Pressure



Vessel A Jacket Temperature



Appendix B

Drumbeat schedule Current

			Start	Finish	days	hours	Step Time (days)	Batch time (hours)
Batch 1 T1	A	Inert and prepare	7/12/07 10:00	7/12/07 10:10	0.01	0.17		
		Wait before loading	7/12/07 10:10	7/12/07 11:40	0.06	1.50		
		Loading Vessel A	7/12/07 11:40	7/12/07 15:40	0.17	4.00		
		Hold time before heating start	7/12/07 15:40	7/12/07 17:10	0.06	1.50		
		Heating	7/12/07 17:10	7/12/07 18:40	0.06	1.50		
		Chill	7/12/07 18:40	7/12/07 18:55	0.01	0.25		
		Hold bfore transfer	7/12/07 18:40	7/12/07 18:58	0.01	0.30		
		Transfer to crystalizer	7/12/07 18:58	7/12/07 19:28	0.02	0.50		
		Ethanol line wash	7/12/07 19:28	7/12/07 20:28	0.04	1.00		
		Filter cleaning	7/12/07 20:28	7/12/07 22:28	0.08	2.00	0.45	
	B	Wait time in crystalizer before crystalization	7/12/07 20:28	7/12/07 21:58	0.06	1.50		
		Heating	7/12/07 21:58	7/12/07 22:43	0.03	0.75		
		Anti-solvent addition	7/12/07 22:43	7/13/07 3:43	0.21	5.00		
		Cooling	7/13/07 3:43	7/13/07 8:13	0.19	4.50		
		Hold before centrifuge	7/13/07 8:13	7/13/07 17:13	0.38	9.00		
		Charge to centrifuge	7/13/07 17:13	7/13/07 23:13	0.25	6.00	1.11	
	C	Centrifugation	7/13/07 17:13	7/14/07 0:13	0.29	7.00		
		Mother liquid and condensate discharge	7/14/07 0:13	7/14/07 0:19	0.00	0.10	0.30	
	D	First discharge to start of drying	7/13/07 18:10	7/14/07 14:09	0.83	19.97		
		Drying	7/14/07 14:09	7/15/07 0:39	0.44	10.50		
		Dryer chill and hold	7/15/07 0:39	7/15/07 3:09	0.10	2.50		
		Dryer discharge and condensate empty	7/15/07 3:09	7/15/07 4:39	0.06	1.50	1.44	65.0
Batch 1 T2	A	Inert and prepare	7/13/07 3:28	7/13/07 3:38	0.01	0.17		
		Wait before loading	7/13/07 3:38	7/13/07 5:08	0.06	1.50		
		Loading Vessel A	7/13/07 5:08	7/13/07 9:08	0.17	4.00		
		Hold time before disolution start	7/13/07 9:08	7/13/07 10:38	0.06	1.50		
		Heating	7/13/07 10:38	7/13/07 12:08	0.06	1.50		
		Chill	7/13/07 12:08	7/13/07 12:23	0.01	0.25		
		Hold bfore transfer	7/13/07 12:08	7/13/07 12:26	0.01	0.30		
		Transfer to crystalizer	7/13/07 12:26	7/13/07 12:56	0.02	0.50		
		Ethanol line wash	7/13/07 12:56	7/13/07 13:56	0.04	1.00		
		Filter cleaning	7/13/07 13:56	7/13/07 15:56	0.08	2.00	0.52	
	B	Wait time in crystalizer before crystalization	7/13/07 13:56	7/13/07 15:26	0.06	1.50		
		Heating	7/13/07 15:26	7/13/07 16:11	0.03	0.75		
		Anti-solvent addition	7/13/07 16:11	7/13/07 21:11	0.21	5.00		
		Cooling	7/13/07 21:11	7/14/07 1:41	0.19	4.50		
		Hold before centrifuge	7/14/07 1:41	7/14/07 6:41	0.21	5.00		
		Charge to centrifuge	7/14/07 6:41	7/14/07 12:41	0.25	6.00	0.95	
	C	Centrifugation	7/14/07 6:41	7/14/07 13:41	0.29	7.00		
		Mother liquid and condensate discharge	7/14/07 13:41	7/14/07 13:47	0.00	0.10	0.30	
	D	First discharge to start of drying	7/14/07 7:39	7/14/07 14:09	0.27	6.50		
		Drying	7/14/07 14:09	7/15/07 0:39	0.44	10.50		
		Dryer chill and hold	7/15/07 0:39	7/15/07 3:09	0.10	2.50		
		Dryer discharge and condensate empty	7/15/07 3:09	7/15/07 4:39	0.06	1.50	0.88	47.5

Note: Anti-solvent addition time disguised to protect confidentiality

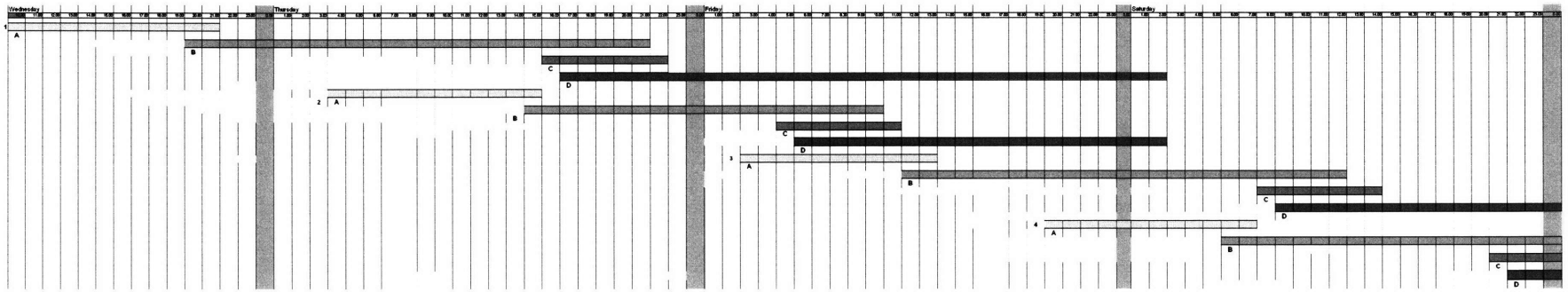
Drumbeat Schedule- Optimized

			Start	Finish	days	hours	Step Time (days)	Batch time (hours)
Batch 1 T1	A	Inert and prepare	7/12/07 10:00	7/12/07 10:10	0.01	0.17		
		Wait before loading	7/12/07 10:10	7/12/07 10:10	0.00	0.00		
		Loading Vessel A	7/12/07 10:10	7/12/07 12:10	0.08	2.00		
		Hold time before heating start	7/12/07 12:10	7/12/07 12:28	0.01	0.30		
		Heating	7/12/07 12:28	7/12/07 13:28	0.04	1.00		
		Chill	7/12/07 13:28	7/12/07 13:34	0.00	0.1		
		Hold bfore transfer	7/12/07 13:28	7/12/07 13:46	0.01	0.30		
		Transfer to crystalizer	7/12/07 13:46	7/12/07 14:16	0.02	0.50		
		Ethanol line wash	7/12/07 14:16	7/12/07 15:16	0.04	1.00		
		Filter cleaning	7/12/07 15:16	7/12/07 16:16	0.04	1.00	0.25	
	B	Wait time in crystalizer before crystalization	7/12/07 15:16	7/12/07 15:46	0.02	0.50		
		Heating	7/12/07 15:46	7/12/07 16:16	0.02	0.50		
		Antisolvent addition	7/12/07 16:16	7/12/07 21:16	0.21	5.00		
		Cooling	7/12/07 21:16	7/13/07 1:46	0.19	4.50		
		Hold before centrifuge	7/13/07 1:46	7/13/07 3:46	0.08	2.00		
		Charge to centrifuge	7/13/07 3:46	7/13/07 8:46	0.21	5.00	0.73	
	C	Centrifugation	7/13/07 3:46	7/13/07 9:46	0.25	6.00		
		Mother liquid and condensate discharge	7/13/07 9:46	7/13/07 9:52	0.00	0.10	0.25	
	D	First discharge to start of drying	7/13/07 4:43	7/13/07 20:00	0.64	15.27		
		Drying	7/13/07 20:00	7/13/07 22:00	0.08	2.00		
		Dryer chill and hold	7/13/07 22:00	7/14/07 0:00	0.08	2.00		
		Dryer discharge and condensate empty	7/14/07 0:00	7/14/07 1:00	0.04	1.00	0.84	38.8
Batch 1 T2	A	Inert and prepare	7/12/07 19:16	7/12/07 19:26	0.01	0.17		
		Wait before loading	7/12/07 19:26	7/12/07 19:26	0.00	0.00		
		Loading Vessel A	7/12/07 19:26	7/12/07 21:26	0.08	2.00		
		Hold time before disolution start	7/12/07 21:26	7/12/07 21:44	0.01	0.30		
		Heating	7/12/07 21:44	7/12/07 22:44	0.04	1.00		
		Chill	7/12/07 22:44	7/12/07 22:50	0.00	0.1		
		Hold bfore transfer	7/12/07 22:44	7/12/07 23:02	0.01	0.30		
		Transfer to crystalizer	7/12/07 23:02	7/12/07 23:32	0.02	0.50		
		Ethanol line wash	7/12/07 23:32	7/13/07 0:32	0.04	1.00		
		Filter cleaning	7/13/07 0:32	7/13/07 1:32	0.04	1.00	0.26	
	B	Wait time in crystalizer before crystalization	7/13/07 0:32	7/13/07 1:02	0.02	0.50		
		Heating	7/13/07 1:02	7/13/07 1:32	0.02	0.50		
		Anti-solvent addition	7/13/07 1:32	7/13/07 6:32	0.21	5.00		
		Cooling	7/13/07 6:32	7/13/07 11:02	0.19	4.50		
		Hold before centrifuge	7/13/07 11:02	7/13/07 13:02	0.08	2.00		
		Charge to centrifuge	7/13/07 13:02	7/13/07 18:02	0.21	5.00	0.73	
	C	Centrifugation	7/13/07 13:02	7/13/07 19:02	0.25	6.00		
		Mother liquid and condensate discharge	7/13/07 19:02	7/13/07 19:08	0.00	0.10	0.25	
	D	First discharge to start of drying	7/13/07 14:00	7/13/07 20:00	0.25	6.00		
		Drying	7/13/07 20:00	7/13/07 22:00	0.08	2.00		
		Dryer chill and hold	7/13/07 22:00	7/14/07 0:00	0.08	2.00		
		Dryer discharge and condensate empty	7/14/07 0:00	7/14/07 1:00	0.04	1.00	0.46	29.6

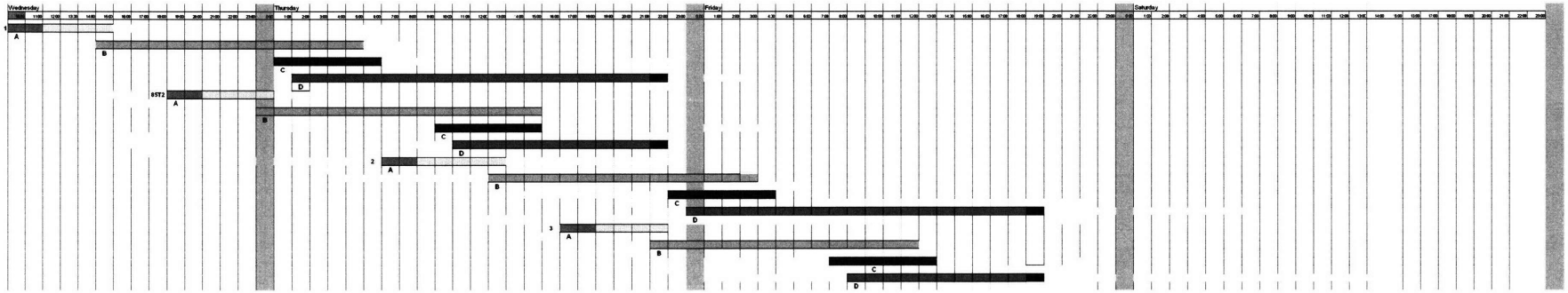
Note: Anti-solvent addition time disguised to protect confidentiality

Appendix C.

Gantt Chart for Current Schedule.



Gantt Chart for Optimized Schedule



Gantt Chart for Optimized Schedule Magnified