Improvement of Cleaning Effectiveness through Statistical Process Control in Active Pharmaceutical Ingredient (API) Manufacturing

by

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Submitted to the MIT Sloan School of Management and Department of Mechanical Engineering in partial fulfillment of the requirements of the degrees of

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Abstract

This thesis presents work that was done to improve the effectiveness of cleaning processes at an active pharmaceutical ingredient (API) manufacturing site that was in the phase of engineering trials and cleaning cycle development. Cleaning cycles executed on the site prior to the project were found to be inconsistent in cleaning the equipment to the desired specifications. Lack of repeatability of cleaning processes was hypothesized to be a resultant of inadequate process control and monitoring.

Statistical Process Control (SPC) implemented using process automation was found to improve the success rate of cleaning processes significantly. SPC introduction required breaking down the cleaning operation into component steps, identifying critical process parameters (CPPs) and calculation of control limits using Shewhart Control Charts for these CPPs. Significant modifications were done to the automation controls for the recipe to ensure deviations from recipe are captured and appropriate actions are taken by the system or the operator to bring the process back in control. The success rate of cleaning processes improved from 38% to 72% post the implementation of Phase I of SPC with the newer non-conformances being associated to special external causes outside the control of the process.

Real-time Multivariate Statistical Process Monitoring (RT-MSPM) was also introduced and piloted as a future opportunity for enhanced control and continuous quality improvement. Multivariate statistical process control eliminates the need to monitor multiple control charts (one for each variable) at the same time accounting for the correlations among process variables.

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API	Active Pharmaceutical Ingredient
USFDA	United States Food and Drug Administration
CGMP	Current Good Manufacturing Practices
PPQ	Process Performance Qualification
SPC	Statistical Process Control
RT-MSPM	Real-time Multivariate Statistical Process Monitoring
LGO	Leaders for Global Operations (MIT Program)
QbD	Quality by Design
CQA	Critical Quality Attributes
DOE	Design of Experiments
CPP	Critical Process Parameters
CTQ	Critical To Quality
CL	Center Line (in a Control Chart)
UCL	Upper Control Limit (in a Control Chart)
LCL	Lower Control Limit (in a Control Chart)
PDF	Probability Distribution Function
PCA	Principal Component Analysis
PLS	Partial Least Squares
DModX	Distance from Mod X
CIP	Clean In Place
rpm	rotation per minute
OSR^2	Out of Sample R^2

1. Background and Motivation

This thesis describes research that was performed during a six-month on-site internship at an Active Pharmaceutical Ingredient (API) manufacturing facility for a large biopharmaceutical company. The site in question is a single product manufacturing facility which was undergoing engineering trials for commercial scale manufacturing of an active ingredient. The thesis represents work that was done to improve the effectiveness of cleaning operations for this manufacturing site. The following sections in this chapter describe the background of the industry and some specifics on process validation in the pharmaceutical industry followed by a brief summary of validation of cleaning processes and the key industry terminologies associated with these.

In Chapter 2, a description of the current state of the cleaning operations has been provided. This description gives the necessary information needed to understand the manufacturing and cleaning operations for the site. It also defines the problem of cleaning effectiveness through the measure of success rate and consistency in execution. Chapter 3 dives into the literature review of how quality issues in manufacturing have been addressed in the past using statistical process control (SPC). This chapter explains the history of SPC and delves into the mathematics of control charts. It also delves into a review of recent implementation of SPC and particularly multivariate SPC to solve quality problems and achieve consistency in execution of manufacturing operations

Following this Chapter 4 dives into developing a hypothesis for improving the performance of cleaning operations at the Amgen site in question. It also lays the foundation of explaining the technical details of the cleaning recipe and identifying critical process parameters for the processes. Chapter 5 will go into the details of implementation of Phase I SPC on the site. It will explain while focusing on a representative equipment, how control limits were derived and how these were implemented on the equipment for use on the live system. Chapters 6 and 7 summarize the results of the implementation of Phase I SPC and give guidance on future work for Amgen to further improve the effectiveness of cleaning processes.

1.1 Biopharmaceutical Industry

The overarching Biopharmaceutical industry produces three major classes of products that differ in the core technology – Pharmaceutical, Biotechnology and Biopharmaceutical products. Pharmaceutical products are drugs synthesized using chemical synthesis processes [1]. On the

other hand, biotechnology drugs use live organisms or their products, such as bacteria, to manufacture drugs [2]. Some drug products are also manufactured in, extracted from or semi synthesized using biological sources. These are known as Biopharmaceutical products [3]. The extent of usage of biological sources and chemical synthesis varies from one biopharmaceutical product to another.

Independent of product type, each of these is subject to strict laws and regulations that govern the patenting, safety, testing, efficacy and marketing of drugs. Early enforcement of some serious laws surrounding patient safety and product efficacy were established in the beginning of the 20th century in the United States and were a result of incidents of tetanus outbreaks and deaths caused by distribution of contaminated smallpox vaccine [4]. The Regulatory environment of the biopharmaceutical industry evolved overtime to give rise to several regulatory agencies across countries enforcing quality standards on the pharmaceutical drug products. With the United States being the largest pharmaceutical market in the world [5], the United States Food and Drug Administration (USFDA) is a critical regulatory organization for the global pharmaceutical market. Over the years, the USFDA has defined and revised the standards and guidance for pharmaceutical manufacturing and product lifecycle management. Some of these standards are critical to this thesis are explained in the following sections.

1.2 Current Good Manufacturing Practices (CGMP) in Pharmaceutical Industry

CGMPs are regulations enforced by the USFDA and other regulatory authorities for food and drug administration in different countries that provide systems for proper design, monitoring and control of manufacturing processes and facilities in the pharmaceutical industry [6]. These represent the minimum requirement a pharmaceutical company must meet to assure that the products are of high quality and do not pose any harm to consumers. The CGMP regulations span the entire supply chain of pharmaceutical products starting from raw material procurement, to manufacturing operations within the facility as well as storage and logistics operations for distribution including product recalls. Compliance to CGMP is a legally enforced requirement for pharmaceutical companies and any product produced under situations that violate CGMP is considered as "adulterated" under the law. The USFDA conducts frequent and rigorous audits for all pharmaceutical facilities worldwide that are responsible for manufacturing products that are sold in the US to ensure the CGMP standards are met. Some of the key guiding principles behind CGMP regulations for pharmaceutical manufacturing are as below [7]:

1. Clean and hygienic manufacturing facilities
2. Control environment for avoiding cross contamination of products
3. Clear definition and control of manufacturing processes
4. Validation of processes to ensure consistency and compliance with specifications
5. Evaluation of changes in the process
6. Good Documentation Practices for clarity of instructions
7. Trained manufacturing personnel for designated operations
8. Traceability of products to records, personnel and operating conditions
9. System for managing quality defects and ensuring prevention of recurrence

These guiding principles are intended to ensure that quality is built into the product during manufacturing as against one final quality check before commercial use. Additionally, CGMP guidelines focus on continuous improvement by identifying deviations in the process, going to the root causes of those deviations and eliminating these across possible platforms where it could reoccur. Starting 2004, the USFDA adopted a "**risk based approach**" as a key element of the CGMPs for the 21st century pharmaceutical manufacturing [6]. Under this approach, USFDA has created a framework which encourages early adoption of new technologies, new quality management approaches, continuous benchmarking against state-of-the-art pharmaceutical science and focus on identification of risk profiles that help organizations prioritize critical areas.

It is important to note that CGMP regulations apply to pharmaceutical facilities that are manufacturing products for commercial purposes. Manufacturing of investigational drugs for use in clinical trials have different standards to comply given the lack of understanding of the manufacturing process and the experimental nature of the product itself. Also, manufacturing sites in early stages of commissioning and trials where the product manufactured is not for human use are exempt from this requirement. The work presented in this thesis forms a part of the activities required to be done to ensure successful compliance to CGMP regulations as a new facility transitions from commissioning and trial runs to commercial production. The author conducted this research at a pharmaceutical manufacturing site that was undergoing this transition. The next sections describe some key elements of these CGMP guidelines relevant to this thesis. Specifically, it focuses on

1. Qualification of Pharmaceutical Manufacturing
2. CGMP Practices for equipment cleaning

1.3 Qualification Process for Pharmaceutical Manufacturing

According to the USFDA, any facility manufacturing pharmaceutical product for commercial use is required to comply with the policies and practices prescribed under the CGMP guidelines as a bare minimum operating standard. Under the CGMP regulations, Process Validation is a legally enforceable requirement that governs the licensure of a facility to produce a pharmaceutical product. Process Validation is defined as the "as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product" [8]

Process Validation ensures that before any batch from the process is made commercially available to consumers, "the manufacturer has gained high degree of assurance in the performance of the manufacturing process such that it will reliably produce products meeting specifications of identity, strength, quality, purity and potency" [8]. Process Validation thus ensures that quality, safety and efficacy are designed or built into the product through appropriate controls at each stage of the manufacturing process. It is based on the premise that quality cannot be adequately assured by in-process and finished product inspection and testing. Process Validation involves a series of activities over the lifecycle of the product which can be divided into three distinct phases shown in **Figure 1** [8]

Figure 1: Phases of the lifecycle approach to process validation

Phase 1: Process Design – a commercial manufacturing process is designed at this stage using the knowledge gained through development and scale up activities. This phase typically occurs on lab scale and is aided by simulations of commercial scale process.

Phase 2: Process Qualification – the process design is evaluated by running and fine tuning it on commercial scale equipment in a manufacturing facility to determine if the process is capable of reproducible commercial manufacturing.

Phase 3: Continued Process Verification – ongoing assurance is gained through routine production that the process remains in a state of control.

During the time of the internship, the manufacturing site was about to enter Process Qualification (Phase 2). The work presented in this thesis supported the efforts of ensuring readiness for Process Qualification for the site. Process Qualification phase has two key elements as shown in **Figure 2** [8]–

1. Design of facility and qualification of equipment and utilities
2. Process Performance Qualification (PPQ)

Figure 2: Stages of the Process Qualification phase in Process Validation

The site had completed the qualification of equipment and utilities before the start of the internship and was preparing for PPQ phase. The PPQ phase combines the actual facility, utilities, equipment and trained personnel along with process knowledge gained during process development and any trial runs to manufacture the product using commercial manufacturing process, control procedures and components. The product manufactured during PPQ can be used as commercial product and hence all operating procedures and facility operations must comply with CGMP guidelines during the PPQ run [9]. Success at the PPQ stage is a critical milestone in the lifecycle of the product since the PPQ must be completed before a manufacturer can distribute the drug product. The qualification phase can be further divided into two key sub phases which are characterized by a key shift in the operating environment

1. PPQ Protocol Definition – This is a documentation phase where the facility defines manufacturing conditions, controls, testing and expected outcomes. This includes a

comprehensive understanding of critical and non-critical process parameters, processing limits and raw material inputs as well as tests to be performed and sampling plans for those tests. The Protocol should also define methods for collecting and analyzing data, provision for addressing deviations, validated measurement methods and analytical studies. It should be approved by all units of the facility including the quality unit.

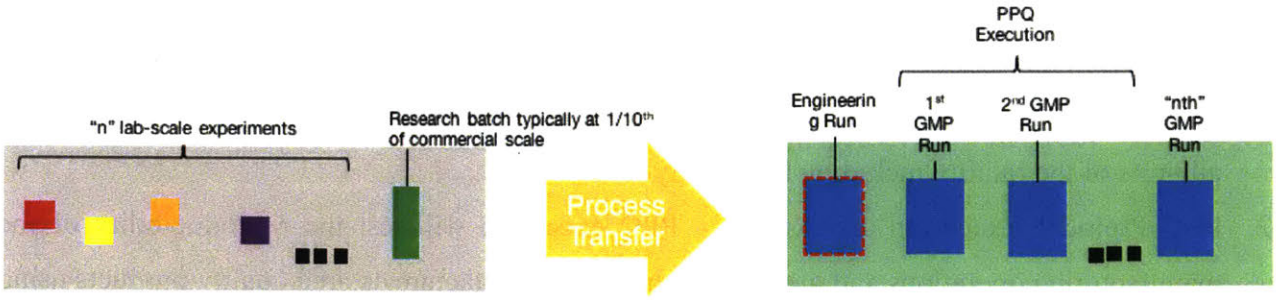
2. PPQ Protocol Execution and Report – PPQ execution will test the reproducibility of the manufacturing operations and their repeatability to manufacture desired quality products using these systems and procedures. Data is captured and documented during "normal operating conditions" of PPQ along with any unexpected observations and how these were handled. The PPQ report will conclude if the data indicates that the process met the conditions established in the protocol and whether the process is considered to be in a state of control while being able to produce the desired product reliably.

Now, the Process Design phase described earlier ends at lab scale trials and some simulations at commercial scale to understand and characterize effects of scale on the process – all of which provide theoretical and practical experience. However, these might not be sufficient for the manufacturer to gain the "high degree of assurance" in the performance of the manufacturing process to produce product reliably. Moreover, the process design phase does not provide ground for testing the supporting CGMP Quality processes and systems. This is more critical for a new facility than for an existing facility receiving a new molecule. As a result, a last stage of development trials is generally performed on the commercial scale equipment on-site. These runs are commonly termed as full-scale preliminary runs or **engineering runs** [10]. An engineering run is thus defined as an initial run that mimics the formal CGMP performed at the same scale. The purpose of this run is two-fold

1. **Technical Readiness:** Implement and fine-tune manufacturing and cleaning processes designed at lab scale during process development on commercial scale manufacturing equipment
2. **Systems Readiness:** Implement and test robustness of the several quality systems in alignment with internal company standards and CGMP standards

Figure 3 shows the positioning of the engineering runs in Process Validation in a visual manner

Figure 3: Illustration of Process Transfer Highlighting Engineering Run [11]



The data collected during this engineering run along with all the data collected during the lab scale experiments leading up to the process transfer is used as a key input to the definition of the PPQ protocol. At the end of an engineering run, a commercial readiness assessment is done to ensure complete compliance to CGMP standards and internal Amgen standards before the actual PPQ run.

1.4 Cleaning in the Pharmaceutical Industry

Equipment cleaning is a critical part of manufacturing operations in the pharmaceutical industry. With patient safety, quality and efficacy being fundamental expectations from pharmaceutical products and legally enforced requirements by the FDA, equipment cleaning processes are responsible for minimizing the probability of contamination and/or cross contamination that can lead to catastrophic patient outcomes if undetected. With patient lives at stake, contamination, if any, identified at a pharmaceutical manufacturing site is extremely expensive for pharmaceutical companies to manage. Over and above the cost of eliminating the contamination from the site through special cleaning actions, the company needs to dispose all products that might be affected by the contamination, issue a product recall if they suspect contamination in the products under distribution as well as shut down the site for future manufacturing leading to idle capacity with high fixed costs. However, the most important loss which cannot be quantified easily is the loss of brand image and loss of trust among healthcare practitioners and patients alike. A company might take years to recover from a tarnished brand image leading to perpetual losses in business.

1.4.1 History of Contamination in Pharmaceutical Industry

The foundation of the current regulations surrounding contamination and patient safety such as those under the USFDA are a result of evolution driven by incidents of contamination

across the world. The Vaccine Act of 1813, which is considered to be the first federal law concerning consumer protection and pharmaceuticals enacted to encourage vaccination against small pox, was repealed as a result of an 1821 outbreak of smallpox in North Carolina, which was traced to contamination of the vaccines [12]. Post this incident, a series of events relating to contamination of pharmaceutical products have played an important role in shaping the regulatory framework for the industry. Below is a list of some key contamination incidents and their impact on regulations:

1. **1902:** Two incidents leading to the death of 22 children who contracted tetanus from contaminated vaccines resulted in the Biologics Control Act also known as the Virus-Toxin Law [13][14]. This was the first law that implemented federal regulations on biologics products
2. **1938:** Improperly prepared sulfanilamide medicine using diethylene glycol caused mass poisoning killing more than a 100 people. This and similar other incidents led to the enactment of Federal Food, Drug and Cosmetic Act of 1938[15][16]
3. **1982:** Tylenol brand of drug commonly used for reducing pain, fever, allergies, cold etc. [17] was found to be laced with potassium cyanide leading to death of seven people. The contamination in this case was identified to have been done by a culprit after the bottles had been made available to consumers. However, the parent company, Johnson and Johnson issued a nationwide callback of as many as 31 million bottles with a retail value of $100M. This incident led to reforms in packaging of over-the-counter medicines and federal anti-tampering laws [18]. The market share of Tylenol in over-the-counter medicine market dropped from 35% to merely 8% within weeks of the incident [19].
4. **2007:** A Panamanian Pharmaceutical company manufactured cough syrup diethylene glycol which they believed to be glycerin. As many as 367 deaths were reported in Panama due to this incident. The incident was found to be a result of failure in the quality processes for inbound material at the pharmaceutical company [20]. Several incidents involving diethylene glycol instead of glycerin have been reported in countries such as China, Nigeria, Haiti, Bangladesh etc.
5. **2009:** Genzyme detected a viral contamination at its Allston Massachusetts manufacturing site which was followed by bits of steel, rubber and fiber found in drugs made by the company and shipped from the site [21]. The five drugs that were affected by this

contamination represented roughly half of Genzyme's $4.6B in annual sales with Cerezyme (for Gaucher disease) and Fabrazyme (for Fabry disease) being the top sellers. The company's earnings fell by 26% for the quarter compared to the year before. This contamination resulted in shutdown of the facility for more than two years as Genzyme failed to supply the product to patients suffering from life threatening rare diseases. Genzyme was required to write-off products worth ~$30M. The company later informed consumers that it would take three to four years for the facility to be free of contamination [22]. The news also led to a 9% drop in the share price of the company [23]. The USFDA also contacted several competing pharmaceutical companies with drugs for similar indications under trial to expedite their approval as an alternative to the Genzyme product [24] while asking Genzyme to outsource production to contract manufacturing sites. Over and above this was the loss of trust among consumers. This was particularly important in this case since the diseases treated by Genzyme through the products are rare and inherited diseases with a market size of merely 1000 – 2000 patients across the country with each patient spending $200,000 per year for the treatment [25]. Given such a small base of high paying customers, Genzyme took a big hit on their brand image with this news and their subsequent inability to restore supplies for years after the incident. The root cause was identified to be a tainted nutrient medium.

1.4.2 Lifecycle Approach to Cleaning Validation

With such high stakes, pharmaceutical companies of today are willing to do more than what is just about necessary to ensure no contamination of manufactured product. Equipment cleaning is one of the most critical activities for avoiding contamination of products. This is especially true for sites which are multi-product in nature. CGMP regulations provide guidance for managing the cleaning activities with the intent of avoiding any possible contamination or cross-contamination. They also provide specific guidance on how to manage multiproduct sites or equipment. In order to have effective cleaning, it is essential to have defined cleaning processes for each equipment that the manufacturer can prove effectiveness of using scientific data. This is achieved through Cleaning Validation

The USFDA guidelines for Process Validation extend to cleaning processes as well. This means that Cleaning also follows a lifecycle approach to validation as described in Section 1.3 of this document. Hence, cleaning validation is also a three-stage process

1. **Cleaning Process Design:** Cleaning Processes are designed at this stage to develop the best-case hypothesis of an effective cleaning process. This stage takes into account the complexity of manufacturing operations (single product / multi product), quality specifications of the cleaning process (maximum allowed residual product, visual cleanliness requirements) etc. to develop the initial cleaning processes. A popular philosophy for design of cleaning processes is Quality by Design (QbD) approach which attempts at minimizing the cleaning validation process through a scientific approach to cleaning. Cleaning processes designed at lab scale undergo multiple iterations when implemented on actual equipment under manufacturing conditions (essentially revision of the best-case hypothesis developed on lab scale). This iterative process is known as Cleaning Cycle Development.
2. **Cleaning Process Qualification / Cleaning Validation:** Once the manufacturer has gained enough confidence on the cleaning processes developed, the site can start the process of qualification of the cleaning processes. This main aim of this phase is to collect required data to scientifically prove the effectiveness and consistency of the designed cleaning processes in meeting the cleaning standards defined. It involves a clearly defined plan which details the cleaning cycle that will be executed, key parameters and their control limits, sampling plans, quality outcomes expected from the cleaning process (acceptance criteria), analytical methods. These are defined in the Cleaning Validation Protocol. This phase is characterized by a higher set of controls and checks during and post execution of the cleaning process to ensure each cycle is executed as planned.
3. **Continued Cleaning Verification:** As with the life-cycle approach to Process Validation, cleaning processes are required to undergo verification tests at regular intervals to prove the process is still effective for the purpose. These cleaning events are classified as continuous verification run or re-validation runs or confirmatory runs.

1.4.3 Cleaning Validation v/s Cleaning Verification

Cleaning Validation is defined as the methodology used to assure that a cleaning process removes residues of the Active Pharmaceutical Ingredient (API) or Intermediates of the product manufactured in a piece of equipment. The core principles surrounding cleaning validation are a direct derivation of the USFDA guidelines on process validation. The validation of cleaning processes requires the manufacturer to scientifically prove through carefully designed experiments

the efficacy and consistency of the designed cleaning process. A validated cleaning process, just like a validated manufacturing process, is assumed to deliver the desired output (clean equipment to below the acceptable level of residual drug). Hence, manufacturers need not test the cleanliness of their equipment if they cleaned it using a validated process given no change in the context or conditions under which the cleaning occurred and if the cleaning process was performed as defined under the validated procedure.

Generating data for the validation exercise requires several iterations of producing the actual product in the actual equipment under real manufacturing conditions. This activity is commonly referred to as Cleaning Validation Plan or Cleaning Validation Protocol execution and each iteration of cleaning activity during a cleaning validation protocol execution is called a validation run [26]. Data from cleaning processes executed as validation run is used for validating the process. However, cleaning processes are commonly designed on lab scale with knowledge of process and residues and are best case hypothesis of what might work. As a result, when executed on reach equipment under actual conditions, these cleaning processes might require some changes due to new knowledge gained about difficult to clean areas etc. The activity of developing the cycle and fine tuning it before the execution of the Cleaning Validation Plan is commonly known as Cleaning Cycle Development. Execution of these cleaning cycles requires verification as proof of cleanliness for each iteration before the equipment is used for the next process. This one-time process for determining the effectiveness of a cleaning process for a specific cleaning event is called "cleaning verification" and each such iteration is called a "cleaning verification run". Hence, cleaning verification is a one-time activity in the sense that data generated during a cleaning verification run is applicable to that cleaning event only.

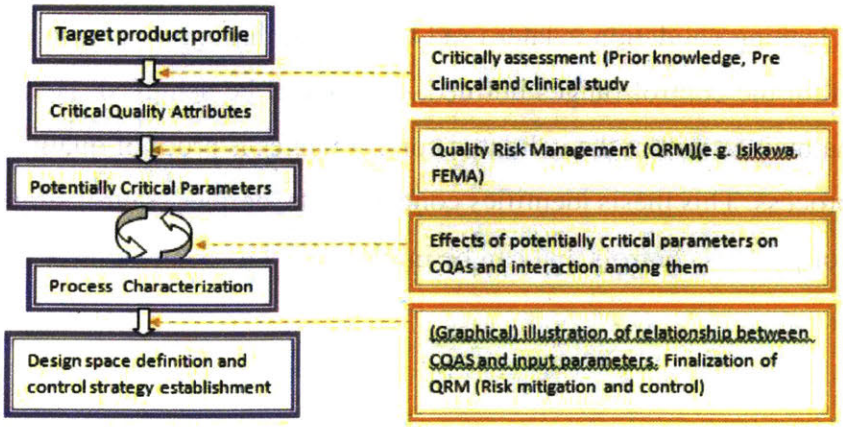
Cleaning verification events might have deviations from the expected outcome or from the planned execution cycle. However, these are not fatal to the cleaning verification since the only metric that counts for a verification exercise is if the equipment is cleaned to the acceptable limits. In case the verification reveals that the cleaning is not adequate, manufacturers can repeat the cleaning exercise or a modified cleaning cycle to achieve the desired outcome. In short, in a cleaning verification run, manufacturers can "clean until its clean". Cleaning verification is undesirable for a manufacturer because it is inefficient. A cleaning process that is not validated and is being run under "cleaning verification mode" has a lot of variability in effectiveness and might require multiple runs to achieve the desired outcome. Moreover, it generally requires

additional time due to the sampling and testing of a sample in every iteration. It is desirable for the manufacturer and expected by the regulators that cleaning validation be performed for a cleaning activity that will be repeated multiple times.

1.4.4 Quality by Design (QbD) in Cleaning Processes

Quality by Design (QbD) is a methodology for developing cleaning processes from a product-lifecycle perspective. This approach takes a holistic view of cleaning cycle development and provides a framework for implementing a systematic approach to process design, development and monitoring. This approach was first highlighted in *Juran on Quality by Design* and is based on the belief that "quality can be planned and that most quality crises and problems relate to the way in which quality was planned in the first place" [27]. While the approach has been adopted widely in the automotive industry, USFDA adopted it as a recommended practice for the discovery, development and manufacturing of drugs as a part of the adoption of a Risk Based Approach to Pharmaceutical Quality [28] [29] [6]. QbD approach involves identification of the product attributes that are of significant importance to product safety and/or efficacy, such as a quality target product profile and critical quality attributes (CQAs) design of the process to deliver these attributes; a robust control strategy to ensure consistent process performance; validation and filing of the process, demonstrating the effectiveness of the control strategy; and finally, ongoing monitoring to ensure robust process performance over the life cycle of the product [29]. Design of Experiments (DOE) is often used as a tool in the implementation of QbD approach to come up with control strategies for the process [30]. **Figure 4** briefly describes the Quality by Design approach

Figure 4: Simplified Flow for QbD Approach



Cleaning processes have often been developed following a trial-and-error mindset or a "Quality by Chance" approach. This approach can lead to adverse consequences specially during product launches since companies often resolve to reactive approaches such as using extreme cleaning processes to avoid failures in cleaning [31]. However, application of QbD to cleaning can help eliminate these wastes in the development and manufacturing environment through a better understanding of the process.

1.5 Motivation for the research

The pharmaceutical industry has evolved over time and has sharpened its focus on patient safety as it continues to learn from newer developments in technology as well as from failures and success within the industry. This evolution has, in due time, led to an increased focus on cleaning processes to an extent that it wouldn't be completely wrong to say that manufacturing processes and cleaning processes are of equal importance. Pharmaceutical manufacturers are increasingly trying to ensure product quality through a lifecycle approach to cleaning validation. This approach follows a systematic method of developing cleaning methods with a deeper understanding of cleaning processes that help develop confidence in the process performance.

At the same time, manufacturers understand that cleaning is an activity that consumes a good portion of the available time of the manufacturing equipment and hence provides a lot of scope of improvement in productivity if optimized to the need of the site. Quality by Design principles are increasingly being applied to cleaning processes in order to gain deeper understanding of cleaning requirements and optimize the cleaning processes while ensuring required performance. A key part of the QbD process is identification of the Critical Process Parameters (CPP) and their control ranges that help achieve the desired Critical Quality Attributes. The process for cleaning validation is later used to confirm through scientific evidence that given the CPPs are within the control ranges defined, CQAs will be achieved. Hence, for a validated process, CPPs maintained within the validated control ranges is proof of quality and effectiveness of the cleaning process. This thesis identifies control limits, defines control strategy and evaluates several options for process controls that can be implemented to ensure adherence to limits.

2. Current State Analysis

2.1 Amgen Inc.

Amgen Inc., formerly **A**pplied **M**olecular **Gen**etics, is the world's largest independent biotechnology firm [32]. It is an innovator company that develops and supplies therapeutics targeting grievous human illnesses. In 2016, Amgen generated $23B in revenues with an operating profit of 33.5% [33]. With a "biology first" approach to research and development [34], >80% of Amgen's business is in the biologics space which represents any pharmaceutical product manufactured in or extracted from biological sources [3]. However, the company also markets a few small molecule products which represents traditional pharmaceutical products where the active ingredient is manufactured through chemical synthesis.

Pharmaceutical manufacturing consists of two separate stages – drug substance (active ingredient) manufacturing and drug product (finished dosage form of an active ingredient) manufacturing. In biologics, Amgen considers its drug substance manufacturing capabilities a competitive advantage. However, in the small molecule space, Amgen has historically outsourced the manufacturing of drug substance investing only in the product development cycle until the product is ready for commercial scale manufacturing. Over the last few years, Amgen has been working to commission its first facility for commercial scale small molecule API manufacturing. The research presented in this thesis was done as a part of a six-month internship at this Amgen site at an international location from February 2017 to August 2017 under the Leaders for Global Operations Program. The author joined the facility during the pre-commercial trial engineering runs of the site and supported the stabilization of key operational challenges as a part of the start-up phase of the facility.

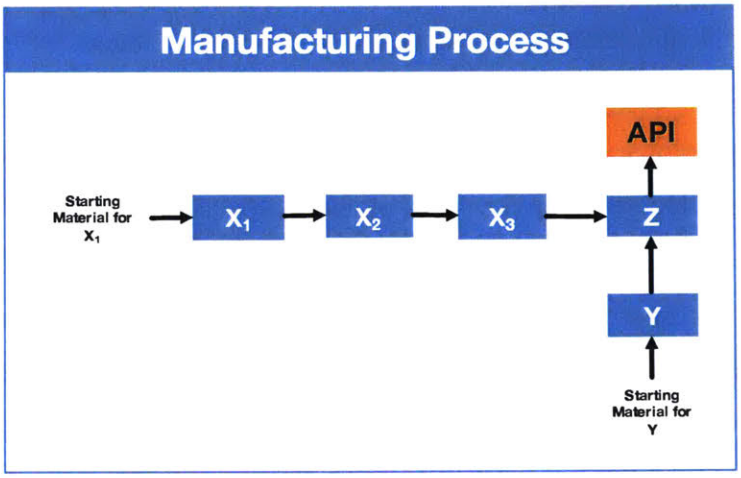
2.2 Site Manufacturing Operations Design

The site was designed as a single product facility for the manufacturing of a small molecule. Within the value chain of the product for commercial purposes, the site was responsible for executing a portion of the manufacturing process for the API. The drug substance would then be supplied to an appropriate part of the Amgen network for conversion to drug product for commercial sales.

The portion of the value chain at the site consisted of five manufacturing steps – say steps 1 through 5. Steps 1, 2 and 3 were sequential in nature meaning the output of step 1 is a key starting

ingredient for step 2 and similarly for step 2 and 3. Material used in step 4 are independent of outputs from step 1, 2 and 3. Finally, output of step 3 and step 4 are combined in step 5 to manufacture the API. For ease of use, the sequential steps were named by the same alphabet (say X) with incremental number subscript and the independent steps were named with a separate alphabet series. With this nomenclature, the manufacturing process can be described using the nomenclatures X_1, X_2, X_3, Y and Z where X_1, X_2, X_3 are the sequential steps, Y is the independent step and Z is the final manufacturing step combining output from Steps X_3 and Y. **Figure 4** shows a schematic of this manufacturing process.

Figure 5: Simplified Manufacturing Process at Amgen site



The choice of commissioning a single product facility meant that equipment design and capacity planning were also done keeping only the expected demand of that product in mind. Under these considerations, the site was designed to have a single chemical train that will be utilized in different ways for each step of the process in scope to provide the final product. This chemical train consisted of four key pieces of equipment – labelled A, B, C and D. Each of the manufacturing process steps described earlier would require a subset of this chemical train for execution.

This operations design meant that only one step of the process can be executed at one time and the chemical train will be required to undergo a changeover procedure to be ready for the next step. For example, Equipment A is used in Steps X_2, X_3, Y and Z. **Table 1** shows which equipment is used in which steps of manufacturing. Hence, while the facility was a single product facility, at

an equipment level, each equipment was a multiproduct equipment. This information is critical to the design of cleaning process.

Table 1: List of key pieces of equipment and usage by manufacturing step

STEP --- >	X_1	X_2	X_3	Y	Z
Equipment A		√	√	√	√
Equipment B	√		√		√
Equipment C			√		
Equipment D	√	√	√	√	√

In order to avoid multiple changeovers from one manufacturing step to the next, the site is expected to run campaigns of fixed number of batches for each step to meet the eventual needs of the downstream manufacturing network for the product.

2.3 Operating Standard for Equipment Cleaning at Amgen Inc.

Amgen follows the lifecycle approach to cleaning validation and verification which is derived from the lifecycle approach to process validation for pharmaceutical manufacturing [35] prescribed by USFDA. As a part of this approach, in early clinical development, products can be introduced into manufacturing areas using a cleaning verification process. As the product lifecycle develops further, a complete product cleaning validation study is performed prior to filing the marketing application. Cleaning Validation utilizes a risk based approach [6] for design / development of the cleaning process, process qualification, and validation maintenance.

For development of cleaning cycles for an equipment or process, Amgen follows a Quality by Design (QbD) approach [36] [37]. Within this approach, cleaning cycles are designed to ensure pre-defined quality at the end of the process. As a part of QbD, process characterization is done at small scale, a design space and control space for the Critical Process Parameters (CPP) is defined through experiments on worst case scenarios and then the process is transferred to full scale for fine tuning for differences in scale.

According to Amgen standards, the transition from engineering to PPQ run is characterized by a transition from a non-commercial environment to a commercial manufacturing environment. Hence, CGMP applies to all batches manufactured in the PPQ run. Cleaning standards for commercial manufacturing at Amgen require validated cleaning procedures for all product contact equipment. The cleaning recipes for the site were under cycle development phase during

engineering run and would require to be validated before the marketing application for the product is filed from that site and the product manufactured at the site is sold commercially.

2.4 Cleaning Operations at the site

For the site, cleaning studies were performed at lab scale to identify a broader recipe to be followed for ensuring sufficient removal of residues post each manufacturing step. This is in line with the Quality by Design (QbD) approach followed by Amgen. These broad recipes were developed further on site to accommodate the equipment level differences in cleaning boundary and difficult to clean areas. During cycle development phase for cleaning, cleaning is operated in the verification mode since the recipes available for execution have not been validated for the commercial scale equipment. In verification mode, success of each cleaning cycle needs to be assessed against the quality parameters defined for that recipe and equipment. These parameters are derived from the next intended use of the equipment. In this case, visual cleanliness and / or residual limits for end of step residues had been defined for each equipment – step combination.

The manufacturing operation design of the facility discussed in **2.2 Site Manufacturing Operations Design** governs the cleaning requirements for the site. With a single chemical train for the five-step manufacturing process, the equipment utilized in one step is required to be cleaned to a desired specification before its next intended use. Given five manufacturing steps and usage of equipment across multiple steps for equipment A, B and D, these equipment fall under the category of multiproduct equipment. Equipment C, on the other hand, is a single product equipment dedicated to processing only a portion of Step X_3. For the multiproduct equipment, lab tests done for the QbD approach helped indicate possible worst case / toughest to clean soil. The site decided to follow the worst-case soil approach and designed one recipe for each equipment. As a result, the site started its engineering run with the best-case hypothesis of a cleaning recipe in place for each equipment.

2.5 Cleaning Cycle Development Status

At the beginning of the internship, an overall status update was compiled to understand the current progress of the cleaning cycle development. Approximately 10 weeks into the engineering run, the site had gone through engineering run trials for Steps X_1, X_2 and X_3. This means that all four of the key pieces of equipment (A, B, C and D) had undergone at least one cleaning cycle development run and hence the best-case hypothesis of the cleaning recipe had been tested for

each equipment for some residual materials. The overall cycle development success rate was found to be 38% (6/16) for the trials conducted. **Table 2** summarizes equipment level trials and success rate.

Table 2: Cleaning Cycle Development Status

	# Cleaning Cycle development runs	# Successful runs	Success Rate (%)
Equipment A	5	2	40%
Equipment B	3	2	67%
Equipment C	1	0	0%
Equipment D	7	2	28%

2.6 Problem Statement

With a 38% success rate in cleaning cycle development runs, it is clear that the site needed to improve the effectiveness of their cleaning processes. The site will be able to open a cleaning validation protocol only after gaining sufficient confidence in their cleaning cycle design. With the manufacturing process approaching Process Performance Qualification (PPQ), if the site is unable to improve cleaning effectiveness using existing recipes, it will have to undergo PPQ run with equipment cleaning in the "cleaning verification" mode meaning that each cleaning iteration will have to be tested and proven for efficacy independent of any previous historical run. As described previously, verification mode is often more inefficient since there is a lot of process variability and the equipment state needs to be verified through tests after every cleaning iteration. Additionally, volume projections for the site are based on approval of the site from several regulatory bodies across the world where the product is being sold. Health authorities of several of these countries insist on cleaning validation data of the site for approval of the dossier. As a result, improving the effectiveness of cleaning processes is a key business requirement for the site.

3. Literature Review

The research for this thesis includes application of Statistical Process Control (SPC) and specifically Control Charts to cleaning processes for API manufacturing. The research goes through understanding and identification of Critical Process Parameters (CPP) and the calculation of control limits for these parameters. This thesis also explores the application of multivariate statistics to monitor and control cleaning operations for the site. The following sections explain the relevant theoretical concepts associated with this thesis and highlights some historical applications of these.

3.1 Statistical Process Control (SPC)

Statistical Process Control (SPC) is a set of tools that aid control of product quality. Montgomery defines quality as "fitness for use" [38]. This fitness for use is evaluated across eight dimensions of quality as defined by Garvin [39]. Montgomery defines two general aspects of fitness for use: Quality of Design and Quality of Conformance [38]. Quality of Design represents the intentional choices made in the design stage that define the grade or level of quality to be expected from the product. Quality of Conformance, on the other hand, represents the extent to which the product conforms to the specifications of the design. Another modern definition of quality given by Montgomery is that "quality is inversely proportional to variability" [38]. This definition shifts focus from several aspects and dimensions to critical quality attributes and variability in these attributes. This definition drives a newer understanding of Quality Improvement as the continuous reduction of variability in processes and products. Statistical methods are required to express variability hence the dependency of SPC on statistical analysis of process data.

SPC was pioneered by Walter Shewhart at Bell Laboratories in 1920s with the introduction of control charts and has evolved over the last century to encompass a large number of tools [40]. World War II saw a widespread application of these methods in the American Industry followed by global spread of the methods through the works of Dr. Edwards Deming and Dr. Joseph Juran [41]. Montgomery defines SPC as "achieving process stability and improving capability through the reduction of variability" [38]. Starting off with quality control charts, SPC now encompasses several tools described below for quality control of any process [42]:

1. Histogram
2. Pareto Chart
3. Cause and Effect Diagram
4. Probability Plots or Scatter plots
5. Control Chart
6. Defect Concentration Diagram
7. Check Sheets

SPC must be implemented in two phases: the first phase is the initial establishment of the process and the second phase is the regular production use of the process. The second phase involves the decision on regular revision of critical attributes and their values depending on the changes in the process associated with man, machine, material, method, movement and environment. While SPC underscores the implementation of one or several of these tools for monitoring and controlling quality of products, one key aspect of SPC is the culture and attitude of all individuals in the organization for continuous improvement in quality through systematic reduction of variability. Shewhart's control charts are the most technically sophisticated of the SPC tools and have been applied in this thesis. The next section explains Shewhart's control charts in detail.

3.2 Control Charts

Before control charts are plotted and utilized, it is important to understand the attributes or parameters that need to be plotted and used for quality control. Every process has a number of elements that the consumer uses to jointly describe the quality of the output. These elements are known as Critical-to-Quality (CTQ) characteristics. These can be of several types [38]:

1. **Physical:** length, density, etc.
2. **Sensory:** taste, appearance etc.
3. **Time Orientation:** reliability, durability etc.

Any manufacturing process can be described by a system of inputs that undergo a transformation process to generate an output which is the desired product. **Figure 6** shows a schematic of a process with input and output variables. In the case of a manufacturing process or a process such as cleaning, controllable variables $(x_1, x_2, \ldots, x_p)$ are process variables such as temperature, pressure, volumetric flow rate, etc. Additionally, there are certain variables on which there is limited control such as external environment, quality of raw materials supplied by external

suppliers. The output is measured in terms of Critical to Quality (CTQ) characteristics that are defined by the customers directly or indirectly. Control Charts can be plotted and utilized for the CTQ characteristics as well as for input variables that affect the output. In order to identify input variables that affect the output quality and quantify their impact, several techniques such as design of experiments, regression analysis and time series analysis are utilized. A deeper understanding of the process can also help identify the critical parameters of the process. These input variables that affect the quality of the output are known as critical process parameters (CPPs). Once CPPs are known and their correlation is understood, online statistical process control techniques such as control charts can be applied for monitoring of the process and taking appropriate action if deviations are detected.

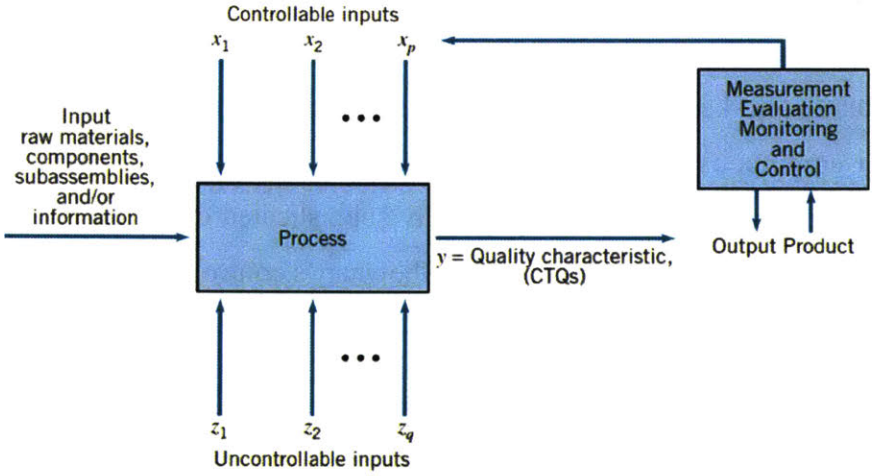


Figure 6: Schematic of a Process with inputs and outputs [38]

A control chart is one of the fundamental techniques in SPC. A typical control chart plots the averages of the measurements of a given quality attribute or process parameter in samples taken from the process against time. **Figure 7** shows a typical control chart. The center line (CL) represents the value of the process characteristic or parameter in an ideal state with no variation. UCL and LCL represent the Upper Control Limit and Lower Control Limit which are determined through statistical techniques that are discussed in the next sections. When influential variables are found to deviate from their scientifically determined control limits, the processes are adjusted to ensure the product characteristics are within defined specifications as a result of adjustments in the process parameters. The routine adjustments to the process can be done using **engineering control**, **automation control** or **feedback controls**.

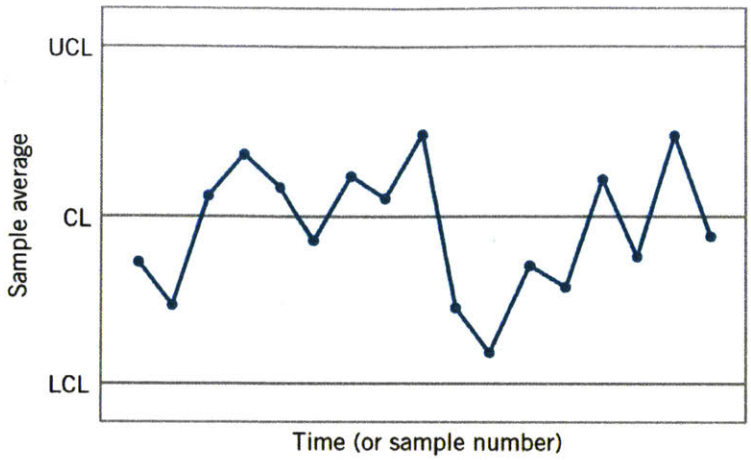


Figure 7: Typical Control Chart [38]

Any process has some amount of natural variation built into it which are called background noise and are due to common causes. Other kinds of variability that are due to causes such as improper adjustment of machines, operator errors or defective raw materials are known as assignable or special causes. Control charts help in differentiating special causes from common causes and help align focus on special causes that can be worked upon. **Figure 8** shows how control charts are used for quality improvement. Once deviation from common cause variation is detected in a process through control charts, a root cause analysis is done to identify the special cause leading to the deviation. Following this, corrective actions are implemented for elimination of the special cause and verification is done using control charts on future data.

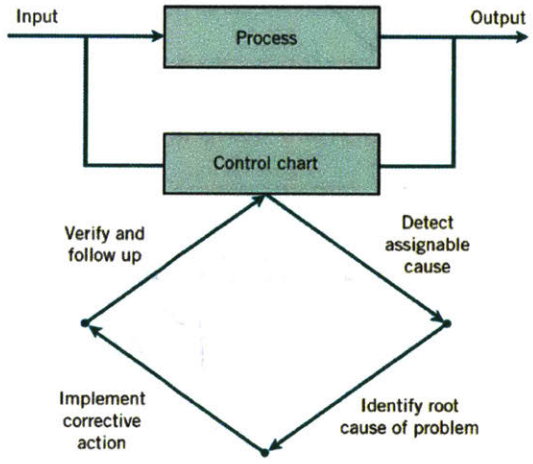


Figure 8: Quality improvement using Control Charts [41]

3.2.1 Statistical Tests in Univariate SPC

The use of Shewhart's Control Charts relies on analyzing individual key parameters of the process in order to analyze the quality of the output. SPC Control Charts continuously monitor and test the null hypothesis

$$H_0 = The\ Process\ is\ in - statistical - control$$

against the alternative hypothesis

$$H_1 = the\ process\ is\ out - of - statistical - control$$

Given a random process variable z which is normally distributed with a mean of $\bar{z}$ and variance of σ_z^2 and has a probability distribution function (PDF) $f_0(z)$. H_0 is accepted if for a random sample $z(k)$, the values fall within the control limits. Given the probabilistic nature of this exercise, this hypothesis testing is subject to two major types of errors commonly known as Type I and Type II errors [41] (see **Figure 9**).

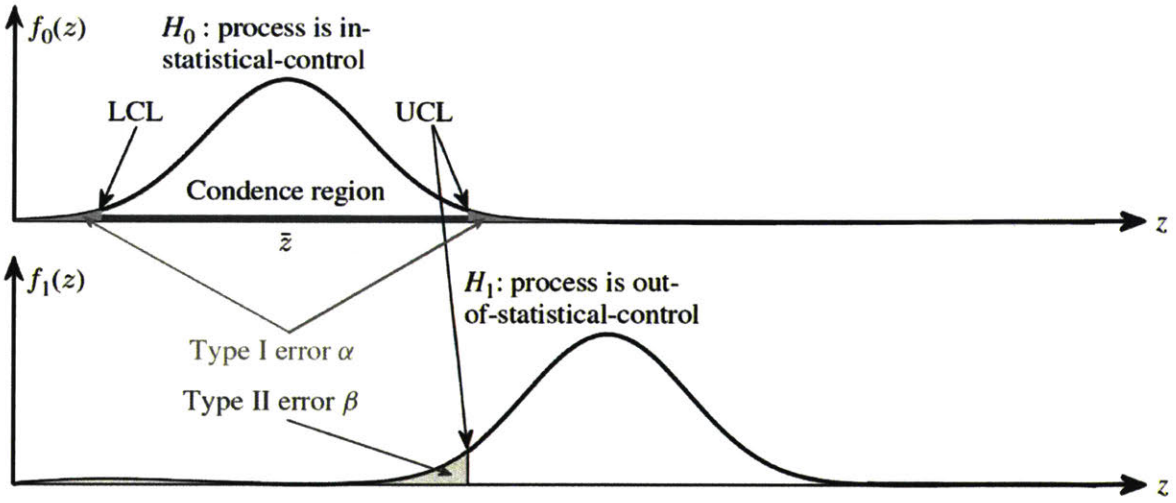


Figure 9: Type I and Type II error in the SPC context [43]

Type I error: Occurs when H_0 is rejected while, in fact, it must be accepted. The probability of Type I error is the significance level (α) defined for the hypothesis.

$$F_0(rejecting\ H_0/H_0\ is\ true) = \alpha = \int_{-\infty}^{LCL} f_0(z) \cdot dz + \int_{UCL}^{\infty} f_0(z) \cdot dz$$

Type II error: occurs when $H_0$is accepted while, in fact, it must be rejected. The probability of Type II error depends on the magnitude of the corresponding mean shift in the underlying variable.

Given a mean shift of Δz in the variable resulting in a PDF of $f_1(z)$ for the variable, the probability of Type II error is given by

$$F_1(Failing\ to\ reject\ H_0/H_1\ is\ true) = \beta = \int_{-\infty}^{UCL} f_1(z) \cdot dz$$

The focus of the SPC method is to reduce Type I error since that is an indication of false alarms which, if repeated multiple times, reduce the confidence of operators in the quality of the process.

3.2.1 Determining and Using Control Limits

For any sample statistic Q that measures a quality attribute or process parameter, suppose the mean is μ_Q and the standard deviation is σ_Q^2. Then the Center Line (CL), Upper Control Limit (UCL) and Lower Control Limit (LCL) are expressed as

$$UCL = \mu_Q + k \cdot \sigma_Q$$

$$CL = \mu_Q$$

$$LCL = \mu_Q - k \cdot \sigma_Q$$

where k is the distance of the control limits from the center line expressed in multiples of standard deviation. The most common value for k is 3 in which case these control limits are known as the 3σ control limits. The 3σ limits are known as control limits and 2σ limits are known as warning limits. In most cases for manufacturing related processs, the critical process parameters such as length, density etc. are continuous variables. For any such critical parameter (say x), samples are collected and measured at random intervals and mean ($\bar{x}$) is calculated for each sampling instance and plotted on a time series plot. Since this control chart utilizes sample mean to monitor process mean, it is called an $\bar{X}$ control chart. For a sample size n, the standard deviation of the sample average $\sigma_{\bar{X}}$is calculated as

$$\sigma_{\bar{X}} = \frac{\sigma_x}{\sqrt{n}}$$

This standard deviation value is then used to calculate control limits by the formulae described above.

While control charts indicate out of control behavior when data points outside the control limits are visible, patterns on the control chart also sometimes indicate nonrandom behavior pattern. Western Electric Handbook (1956) suggests a set of decision rules for identifying nonrandom patterns of data on control charts which may suggest an out of control pattern. These decision rules divide the control chart into regions A, B and C as shown in **Figure 10** on the

basis of the distance of the region from the center line in terms of number of standard deviations. Region between 2σ and 3σ from the center line on both sides is called region A. Region between σ and 2σ on either side of the center line is called region B and region within $\pm\sigma$ of the center line is called region C.

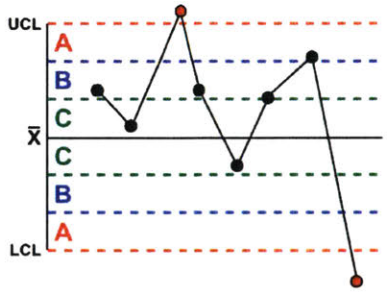


Figure 10: Regions A, B and C on a control chart [44]

These rules suggest that a process is out of statistical control if either [45]

1. One point plots outside region A
2. Two out of three consecutive points plot within region A
3. Four out of five consecutive points plots within region B or
4. Eight consecutive points plot on one side of the center line

Over the years, several new rules that help detect patterns in control charts were developed and used in industry.

3.2.2 Implementation of Control Charts

Implementation of control charts is done in two distinct phases [41]:

Phase I: in this phase, a set of historical data is gathered and analyzed retrospectively. Statistical analysis of this data is carried out to construct trial control limits for the critical parameters of the process. These trial control limits determine if the process has been within or out of control historically. Data used for calculation of trial control limits needs to be selected appropriately from all available historical data for determining trial control limits. Work presented in this thesis represents phase I of control charts implementation. Calculation of these control limits generally requires 20 – 25 subgroups of data. Initially all data points are utilized to plot control charts and points outside control limits are investigated and appropriate actions are taken to avoid repetition of these deviations. Post this, points outside the control limits are excluded and new control limits

are calculated. Control charts are implemented with these limits and new data are collected to compare and revise control limits. Shewhart's Control Charts with the several decision rules are a great resource for Phase I since they can detect major deviations fairly easily. Once the process achieves reasonable stability, Phase II of the control chart implementation begins.

Phase II: The process can be assumed to be fairly stable in phase 2. The emphasis during phase II is on process monitoring. It is safe to assume that most of the major assignable causes have been eliminated during phase I and that the current state will provide indications of causes that lead to smaller shifts. Shewhart's control charts are less effective in this phase since they are less sensitive to smaller shifts in the process. Cumulative Sum or Exponentially Weighted Moving Average (EWMA) control charts are utilized in this phase for better detection of deviations [41].

3.3 Multivariate Statistical Process Control

3.3.1 Motivation for Multivariate SPC

Despite its widespread applicability and success, it must be noted that univariate SPC method ignores the correlation between process variables. In a process with multiple critical process parameters, correlation among the variables plays an important role in determining whether the process is within or out of statistical control. The correlation between process variables can lead to a substantially higher probability of Type II error [43]. Which means that null hypothesis will be accepted, although it must be rejected, leading to an incorrect inference of in-control-process when the process is actually out-of-control. Hence, under conditions of correlated variables, higher Type II error may render abnormal behavior difficult to detect [43].

Following is a brief explanation of how ignoring correlation among process variables can lead to higher probability of Type II error. Let z_1 and z_2 be two random variables with a correlation coefficient r_{12} $(-1 \leq r_{12} \leq 1)$ expressed in terms of the variances of z_1 (σ_1^2) and z_2 (σ_2^2) as and their covariance σ_{12}^2 as follows

$$r_{12} = \frac{\sigma_{12}}{\sigma_1 \cdot \sigma_2}$$

If these random variables associated with a manufacturing process are highly correlated (say correlation coefficient of -0.95), the resultant process output combining the effects of both the variables can be seen in **Figure 11**.

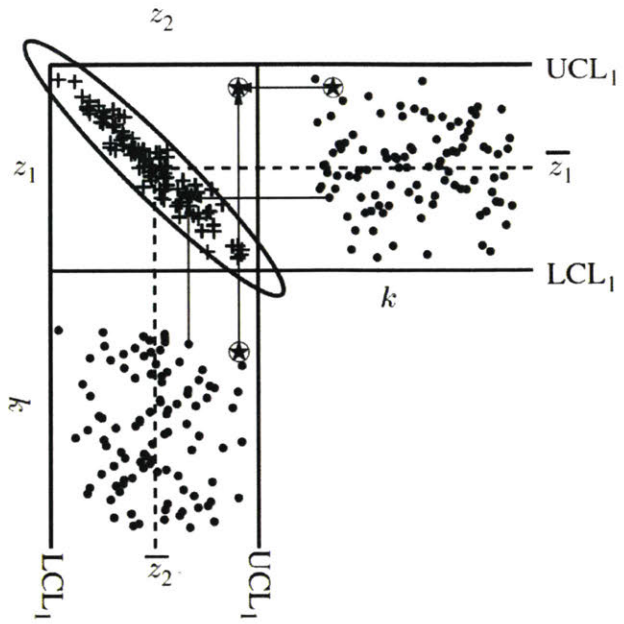


Figure 11: Schematic diagram showing two highly correlated variables [43]

Figure 11 shows a two-dimensional representation for a process with two critical process variables. SPC control charts for the two variables $z_1$and z_2 can be seen along the horizontal and vertical axis respectively. The central part of the graph represents a scatter plot of the projections from both variables on a common plane $z_1 - z_2$. The confidence region for the scatter plot can be obtained from the joint PDF $f(z_1, z_2)$ which is the control ellipse shown in **Figure 11**. The point marked by a star symbol on Figure 11 shows a typical point which falls within the control limits for individual variables but the resultant process is out of control due to the correlation between variables. Type I and Type II errors for the combined PDF $f(z_1, z_2)$ are shown in **Figure 12** showing a high probability of Type II errors in the case of correlated variables. The circular region represents the control region under the assumption of no correlation which standard SPC control charts make. Multivariate processes can hence benefit from a combined statistical analysis that accounts for the correlation between critical variables making it a powerful tool for process control.

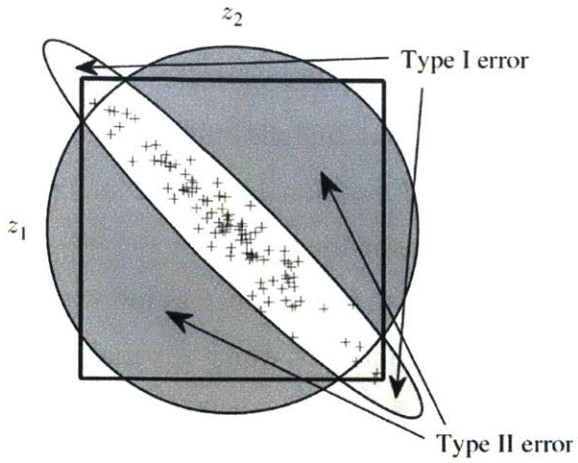


Figure 12: Type I and Type II error Regions for Correlated Variable Sets

3.3.2 Multivariate SPC Method

Multivariate Statistical Process Control involves defining a test statistic that incorporates all critical process variables that affect the output of the process as well as their correlation with each other and uses that test statistic to monitor the process. It uses a set of t-variables called "score variables" to test the standard SPC hypothesis [43]. These t-variables are generated by projecting recorded data of process variables in a way that extracts maximum possible information to capture the significant variations in the data. Multivariate SPC achieves this through several data reduction techniques two of which are introduced here and utilized in this thesis. These are also most commonly associated with process monitoring.

1. **Principal Component Analysis (PCA):** PCA was developed by Pearson (1901) and Hotelling (1933) [46]. It is a form of unsupervised learning as it depends solely on the input data itself without reference to a target data set. Such methods are known as single block techniques [43]. PCA method uses orthogonal transformation to convert the "data into a new set of variables, known as principal components, which are linear functions of the original variables, are uncorrelated and defined in a way that the greatest variance by any projection of the data lies on the first component, the second greatest variance on the second component and so on" [46]. Intuitively, PCA can be described as fitting an n dimensional ellipsoid to the data where each axis represents a principal component.
2. **Partial Least Squares (PLS):** "PLS regression is a technique that reduces the predictors to a smaller set of uncorrelated components and performs least squares regression on these

components, instead of on the original data" [47]. Since both predicted and observed variables are projected, PLS is a dual-block technique of data reduction. This method is different from PCA in that it tries to find the multidimensional direction in the X space that explains the maximum multidimensional variance in the Y plane as against finding individual components that explain the variance.

Mathematically, multivariate analysis can be described as follows [48]:

Let $\boldsymbol{X}[I \times N]$ represent a dataset of I samples for which N variables have been measured. Multivariate analysis methods such as PCA converts the matrix X into a combination of a matrix of loadings $\boldsymbol{P}[N \times A]$ and a matrix of scores $\boldsymbol{T}[I \times A]$, where A stands for the number of Principal Components selected to describe the systematic variability of the data:

$$X = TP^T + E$$

and $\boldsymbol{E}$ is the $[I \times N]$ matrix of errors which generate by the reconstruction of $\boldsymbol{X}$. A is usually determined through cross-validation or rules of thumb. In order to study how the variables in the input to a system are related to the output, a regression model relating the matrix of inputs $X[I \times N]$ to the matrix of outputs $Y[I \times M]$ is used. A multivariate regression model like Partial Least Squares reduces the matrices to a lesser dimensional model space in which the covariance between the projections (i.e. the scores) of the original smaples is maximized.

$$X = TP^T + E_X$$

$$Y = TQ^T + E_Y$$

$$T = XW^*$$

- $\boldsymbol{P}$ and $\boldsymbol{Q}$ represent respectively the $[N \times A]$ and $[M \times A]$ loading matrices relating the projections in the latent space $\boldsymbol{T}$ with the data matrices $\boldsymbol{X}$ and $\boldsymbol{Y}$,
- $\boldsymbol{W}*$ $[N \times A]$ is a weight matrix for projecting the data in $\boldsymbol{X}$ in the latent space to give $\boldsymbol{T}$, while
- $\boldsymbol{E_X}$ $[I \times N]$, and $\boldsymbol{E_Y}$ $[I \times M]$ are matrices of residuals between the actual data and data predicted using the multivariate regression output.

3.3.3 Statistical Tests in Multivariate SPC

Principal component analysis of a data table gives vectors of scores, with values t_{ia}, which summarize all the variables entering the analysis. It is customary to calculate two or three **score** vectors, and then plot them against each other (tt-plots). This gives a picture that is a good summary of the process behavior over time. In this plot we can see trends, unusual behavior and other things

of interest. The standard SPC hypothesis that tests whether a process is within or out of statistical control is extended to multivariate processes through in the form of different statistical tests. These tests evaluate the resultant output of PCA by defining a single test statistic that incorporates all variables and their correlations. Below is a brief review of these statistical tests:

1. **Hotellings T^2 test:** the Hotelling's T^2 statistic is a multivariate generalization of the univariate student t-statistic for testing the hypothesis on the mean of a distribution. It is proportional to the F-distribution. Mathematically, "if the observation vectors $X_1, X_2, \dots, X_n$ are independent normally distributed random vectors with mean vector ϑ and a covariance matrix Σ, then the statistic

$$T^2 = n \cdot (\bar{X} - \mu)' \cdot S^{-1} \cdot (\bar{X} - \mu)$$

where

$$\bar{X} = \frac{1}{n}\sum_{i=1}^{n} X_i$$

and

$$S = \frac{1}{n-1} \cdot \sum_{i=1}^{n} (X_i - \bar{X}) \cdot (X_i - \bar{X})'$$

has a Hotelling's T2 distribution with $(n-1)$ degrees of freedom." [49]. The random variable $((n-k+1)/nk) \cdot T^2$ has an F distribution with k and $(n-k+1)$ degrees of freedom [49]. In case of a multivariate process, the Hotelling's T^2 test is applied to a test statistic crated from the underlying observation vectors of process variables to test for the hypothesis of statistical control. Confidence level similar to the α value in a univariate SPC are defined and the statistical test is conducted.

2. **Distance from ModX:** The PCA also gives residuals, deviations between the data and the principal component model, named *DModX*. When these residuals are large, this indicates an abnormal behavior in the process. Plots of the residual standard deviation, DModX (residual distance, root mean square) are made to observe these abnormal behaviors. Observations with a DModX larger than the DCrit are outliers. When DModX is twice DCrit they are strong outliers. This indicates that these observations are different from the normal observations with respect to the correlation structure of the variables.

3.3.4 Applications of Multivariate Statistical Process Control (SPC)

Multivariate SPC has found widespread applications in several industries some of the more important ones being manufacturing processes involving chemical reactions such as pharmaceutical industry as well as complex biologics manufacturing processes. As explained earlier, these processes have high quality demands and involve large number of variables which are often correlated. Several applications have been explored by Uwe Kruger and Lei Xie in their introductory book "Statistical Monitoring of Complex Multivariate Processes: With Applications in Industrial Process Control" [43].

One application discussed is that of the manufacturing process for manufacturing two solvent chemicals through complex exothermic reactions involving five different reactants and five parallel fluidized bed reactors. The process involves control variables such as feed rates of input materials (to maintain ratio of output of the chemical processes), temperature of the reaction mixture (to control feed rates and cooling processes), oil recirculation rate (to remove heat from the system), reactor pressure (to achieve constant catalyst fluidization) etc. Since any disturbance leads to alterations in reacting conditions and hence temperatures, the temperature sensors recording temperature in different parts of the equipment chain were used as key monitoring variables. PCA is applied to variables representing each of the thermocouples in the system and principal components were identified on the basis of the Eigenvalues for each component.

Another study shows the implementation of multivariate statistical modeling to continuous pharmaceutical manufacturing processes with the specific example of paracetamol [48]. This study lays out a generalized process for the implementation of Multivariate SPC which is composed of three steps namely data organization, exploratory data analysis and comprehensive data analysis.

Soh, Wang, et. al. studied the "utility of multivariate analysis in modeling the effects of raw material properties and operating parameters on granule and ribbon properties in roller compaction" [50]. This experiment studies how inclusion of raw material properties as input variables improved the goodness of fit and model predictability of the PCA and PLS models.

Mark Polizzi and Salvador Garcia-Muñoz applied a new two-step multivariate modeling method, called the weighted scores PLS to enable simultaneous process understanding and prediction of powder properties using a database of physical properties of pharmaceutical powders developed by the Pfizer Materials Assessment Laboratory [51]. "The physical properties for each individual component were first transformed using a PCA technique to place them in a multivariate

design space and capture property correlations. The scores from these PCA models were then weighted by the blending ratios prior to PLS regression versus actual measured blend properties" [51]

3.4 Chapter Summary

SPC is a highly effective method for monitoring and controlling processes through its critical input variables to ensure desired quality in the output. SPC is one of the most powerful quality improvement tools that quantifies process understanding to highlight possible deviations from desired output through visual and easy to use control charts that monitor the required process parameters during the manufacturing process. Statistical tests like the student t test for hypothesis testing of whether a process is within or out of statistical control are probabilistic in nature and are subject to Type I and Type II errors. Univariate SPC is a good tool to identify Type I errors which helps eliminate false alarms. However, in case of processes that involve several input and output variables which are possibly correlated, univariate control charts can be cumbersome. Moreover, univariate SPC does not take correlation among variables into account increasing probability of Type II errors making out of control processes difficult to detect. Multivariate Statistical Process Control methods such as Principal Component Analysis and Partial Least Squares are increasingly being implemented to account for the correlations among variables to improve the ability to detect process deviations. This thesis presents work that was done to implement process control using univariate SPC and automated control to improve the effectiveness of cleaning processes. It goes further to pilot a multivariate model for the cleaning process on a single equipment and proposes implementation of multivariate SPC once enough data becomes available.

4. Hypothesis Development

4.1 Cleaning Process Stabilization

The cleaning cycles executed on the equipment during the engineering run were a part of the cleaning cycle development process. During cycle development, cleaning process developed on lab scale as part of the QbD approach is converted into an equivalent commercial scale recipe for the particular equipment on site and fine-tuned through iterations and learning from failures. As a result, lack of performance in cleaning cycles can be a result of the ineffectiveness of the recipe or due to a lack of repeatability in the execution of an effective cleaning recipe. Figure 13 shows the current status and the focus of research to improve the effectiveness of cleaning.

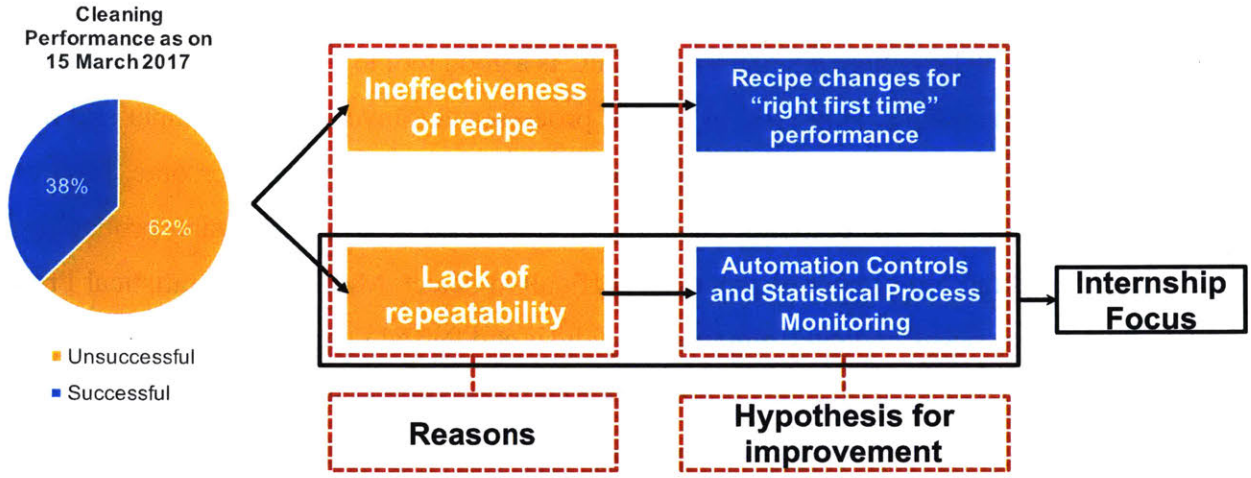


Figure 13: Hypothesis for Improvement of Cleaning performance

Given the intermittent success of cleaning cycles executed in the first ten weeks, process data from historical execution of the cleaning cycles was looked into to understand possible reasons for lack of repeatability. In order to identify the relevant data sources from the system, the cleaning process for each equipment was examined to come up with a list of critical process parameters. While each equipment had its own cleaning recipe which was based on the worst-case soil handled in that equipment, it was identified that each recipe consisted of a different permutation and combination of steps from a standard list of cleaning steps defined for the site. The differences in recipes for the equipment depended on their individual worst-case soil information. This is a consequence of the Clean-In-Place (CIP) systems incorporated in the design of the facility. Below is a list and a brief description of these process steps:

1. **Solvent Manifold Cleaning:** The solvents required for process steps were fed to equipment through a solvent manifold that connects the solvent tank farm to the equipment. The solvent manifold consists of several connections and valves that allow transfer of solvent from any tank to any equipment. Due to multiple connection points and multiple solvents, this step is used to remove traces of alternate solvents from the connection that will be used to feed cleaning solvent to the equipment. This is done by flushing the relevant connections in the solvent manifold with the cleaning solvent to remove traces of past solvents that have passed through the valve and pipe combination that will be used for the cleaning process.
2. **Once through Flush of the CIP loops** – the system design consisted of several circuits for the flow of materials between the equipment. Since these circuit loops were in contact with either raw material, solvents or intermediates or final product in the course of the manufacturing process, these are classified as product contact areas and hence must be cleaned to avoid contamination. These circuit loops were designed to be cleaned by flushing them using cleaning solvents (in this case methanol, ethanol or water). This step was designed to take advantage of the dissolution properties of the residual drug in these solvents at room temperature as well as mechanical action from the turbulence of the solvent flow to eliminate residual drug from the loops. The routing of the once through flush starts at the source of the solvents (the solvent manifold) and ends inside the vessel being cleaned in the recipe before being disposed.
3. **Vessel Fill Boil:** This step is used as the key cleaning step for the reactor and dryer vessels and used the dissolution properties of the key ingredients to be cleaned. This step follows the once through flush because the once through flush is expected to leave some residues from the loops in the equipment on the way to disposal. In this step, the vessel being cleaned is filled with a cleaning solvent to a predetermined level and then heated to boil. Once in the boiling phase, the vapor is allowed to condense on the walls of the defined vessel boundary to dissolve traces of the residual drug. This is followed by a reflux phase for circulation of the vapor in relevant CIP loops and a distillation phase to distill the dissolved residual drug out to a distillate receiver.
4. **Recirculation of the CIP Loops**: In this step, cleaning solvent is circulated through the CIP loops at high temperature to dissolve residual drug that might be left in the CIP loops post the once through flush. This step takes advantage of the dissolution properties of the residual drug

in the solvent at high temperature as well as mechanical action caused by the turbulence of the flow of solvent through the loops. The recirculation is done for a specified duration depending on the extent to which a particular loop is expected to contain residues. The solvent used in this step is the heated solvent from the vessel fill and boil step.

5. **N_2 Blowdown of CIP Loops:** Once the CIP loops have been recirculated with solvents, nitrogen is blown through the loops at high pressure for a specified period of time to mechanically remove traces of the solvent from the walls of the CIP loops. During this step, the vessel still contains the heated solvent with dissolved residues and the nitrogen blow pushes the solvents on the walls of CIP loop pipes towards the vessel.
6. **Vessel Draining:** Post the nitrogen blow, the aggregate solvent in the vessel is drained from the system. Safety procedures at the site require disposal to be at room temperature and hence this step is designed to ensure that the solvent solution drained is at room temperature.
7. **Rinse Sampling:** This step is designed to collect a sample from the vessel post a cleaning recipe has been executed. In this step, a designated quantity of fresh solvent is filled in the vessel and a predetermined quantity of the solvent is taken as a representative sample and tested for quantity of residual drug against the maximum allowable carryover (MAC) defined taking into account limits for avoiding contamination in the next manufacturing steps.
8. **Vessel Drying:** This step is used to eliminate traces of the cleaning solvent from the equipment vessel prior to the visual inspection and subsequent start of the next manufacturing step. In this step, drying action is carried out by creating a vacuum in the vessel and then increasing the temperature to the boiling point of the solvent at that absolute pressure.
9. **Process Solvent Flush:** Once the residual drugs are removed from the equipment and chemical train, the equipment must be made ready for the start of the next manufacturing step that will be performed on it. For this, the equipment and its CIP loops are flushed with the solvent used in the upcoming manufacturing step. This ensures removal of the cleaning solvent which might be undesirable for the upcoming manufacturing step. This step uses mechanical action in the form of spraying the required solvent in the equipment using a spray ball and high pressure. The mechanical action from turbulence is used to clean the CIP loops of the cleaning solvent.

Table 3 describes the cleaning recipe of each equipment in terms of these component steps (the number in the table represents the serial number of the step as described in this section)

Table 3: Cleaning recipe of each equipment in terms of the component steps (complete table)

Representative Cleaning Recipe	Equipment			
	A	B	C	D
	1	1	1	2
	2	2	2	3
	3	3	3a	4
	4	4	4	5
	5	5	5	6
	6	6	6	3
	3	3	3a	4
	4	4	4	5
	5	5	5	6
	6	6	6	8
	8	8	8	VI
	VI	VI	VI	7
	7	7		RST
	RST	RST		8
	8	8		
	9	9		

Legend

1. Solvent Manifold Cleaning
2. Once Through Flush of CIP Loops
3. Vessel Fill Boil / 3a.Vessel Fill Heat
4. Recirculation of CIP Loops
5. N_2 Blowdown of CIP Loops
6. Vessel Draining
7. Rinse Sampling
8. Vessel Drying
9. Process Solvent Flush

VI Visual Inspection

RST Rinse Sample Testing

Once the cleaning recipes were broken down into these component steps which served as building blocks for the cleaning processes, the Critical Process Parameters (CPP) for each of these component steps were defined. As described earlier, the Critical Quality Attributes (CQA) for the cleaning process are visual cleanliness and drug residue level post cleanliness. Process parameters that are expected to impact these CQAs were defined as the Critical Process Parameters. **Table 4** shows the list of CPPs defined for each of these component steps.

Table 4: Critical Process Parameters for Cleaning Processes (update this for corrections)

Process Parameters for Cleaning Process ASM2					
Generic Step Name	**Description**	**Critical Process Parameters (CPP)**	**Rationale for CPP**	**Non Critical Process Parameters (NCPP)**	**Rationale for NCPP**
Solvent Manifold Cleaning	flushing of the solvent manifold with cleaning solvent to displace other solvents before equipment cleaning	Solvent Manifold Flow Rate	flow rate will ensure consistent and adequent turbulency to ensure effective cleaning	Temperature	Effectivenenss of pipe cleaning for residual solvent by displacement is a function of Reynolds Number. Temperature is not critical for solvent displacement.
		Duration	the manifold needs to be exposed to a turbulent flow for a minimum duration to ensure effective cleaning	Solvent Manifold Totaliser / Equipment level	Is a product of flow rate and time and both are monitored.
				Concentration of cleaning agents	cleaning solvents used are Methanol, Acetone which are all used as procured without any additional cleaning agent added
				Agitator Speed	Agitation speed is not applicable for solvent manifold cleaning
Once Through Flush of loops	flushing cleaning solvent through CIP loops to remove any potential product in these lines	Solvent Manifold Flow Rate	flow rate will ensure consistent and adequent turbulency to ensure effective cleaning	Temperature	While temperature is an indicator of solubility, the once through flush is designed to utilise the solubility at room temperature for effective cleaning. The contact time and flow rate (or turbulency) are controlled to ensure effectiveness of cleaning at room temperature
		Duration of flush	the loops need to be exposed to a turbulent flow for a minimum duration to ensure effective cleaning	Solvent Manifold Totaliser / Equipment level	Solvent flow rate and time and both are monitored
				Concentration of cleaning agents	cleaning solvents used are Methanol, Acetone which are all used as procured without any additional cleaning agent added
				Agitator Speed	Agitation is not applicable for once through flush since no solvent is collected in the equipment and is all drained at once.
Fill Boil Reflux Distillation	fill the equipment with cleaning solvent, heat it to boil, reflux for a few minutes, distill volume to a desired final level, and then cool down to the temperature at which recirculation is desired. This step is used to reach the entire inner surface of the equipment through reflux and distillation	Equipment fill level	effective mixing is combination of ensuring sufficient immersion of impeller and the optimum agitation speed without generating vortex effect. Initial fill level is defined to ensure this. Moreover, the fill boil step has a distillation phase which	Concentration of cleaning agents	cleaning agents used are Methanol, Acetone which are all used as procured without any additional cleaning agent
		Jacket Temperature	The boiling, reflux and distillation phases of the fill boil require a constant temperature difference between jacket and batch (Tjacket>Tbatch) to ensure constant heat transfer for phase change. This is achieved through a set point of jacket temperature. Changes in the jacket temperature only affect the rate of boiling and do not impact the efficacy of cleaning as long as the jacket temperature is higher than the batch temperature.		
		Agitation Speed	agitation is important to ensure that the soil does not settle down in the equipment and also to increase solubility of the soil by increased mechanical action. It also aids cleaning of the agitator itself.		
		Reflux duration	a minimum duration of reflux post boiling is needed to ensure the cleaning of inner surfaces above the fill level through the condensate of the cleaning agent		

Generic Step Name	Description	Critical Process Parameters (CPP)	Rationale for CPP	Non Critical Process Parameters (NCPP)	Rationale for NCPP
Recirculation of loops	Recirculation of the loops with cleaning agent in the equipment at a higher temperature and for a longer duration to further clean possible traces of product in the loops. Higher temperature gives better solubility properties for	Batch Temperature	Constant batch temperature will ensure all loops are exposed to cleaning solvent at the same high temperature and hence uniform	Concentration of cleaning agents	cleaning agents used are Methanol, Acetone which are all used as procured without any additional cleaning agent
		Agitation Speed	agitation is important to ensure that the soil does not settle down in the equipment and also to increase solubility of the soil by increased mechanical action. It also aids cleaning of the agitator itself.		
		CIP Pump Flow rate	flow rate will determine if the flow is turbulent enough to ensure cleaning		
		Duration of recirculation	the loops need to be exposed to a turbulent flow for a minimum duration to ensure effective cleaning		
N2 Blow of loops	Post recirculation of solvent, high pressure N2 blow is used to push traces of cleaning solvent in the loops back into the equipment. This ensures that the loops are dry of any cleaning solvent	Duration of N2 Blow	the loops must be exposed to pressurized N2 blow for a minimum duration to ensure enough contact to push all the residual cleaning agent (left post recircuation) back into the equipment	Air Flow	Pressure is used as indicator of flow
		Absolute pressure of N2 line	the N2 header pressure is monitored against a minimum pressure requirement to ensure there is enough force to push the cleaning solvents out of the loop and into the equipment. The site wide safety alarms for the nitrogen pressure are used as control limits.		
		Agitation Speed	agitation is important to ensure that the soil does not settle down in the equipment and also to increase solubility of the soil by increased mechanical action. It also aids cleaning of the agitator itself.		
Equipment Draining	This is a safety requirement to ensure that the temperature of any drain is ~ 25 deg C	Batch Temperature	need to ensure that the batch temperature meets safety norms before draining to waste	Flow Rate	bottom valve is opened to drain the vessel using gravity. No cleaning action performed during step
				Duration	bottom valve is opened to drain the vessel using gravity. No cleaning action performed during step
				Agitator Speed	Agitation speed is not critical for draining phase
				Concentration of cleaning agents	cleaning agents used are Methanol, Acetone which are all used as procured without any additional cleaning agent
				Volume	All volume inside the vessel is emptied (irrespective of how much it is)
Vessel Drying	drying of the vessel is done at the end of the cleaning process to ensure no traces of cleaning agent are left behind before visual inspection	Jacket Temperature	improved effectiveness of drying by vaporisation	Concentration of cleaning agents	no cleaning agent used in step
		Vacuum pressure	steady vacuum is maintained to ensure boiling point is lower that atmospheric pressure. This vacuum in combination with jacket temperature achieves the drying action.	Agitator Speed	Equipment is empty; requires drying
		Drying Duration	for consistent effectiveness of drying by vaporisation	Flow Rate	no flow occurs during step
				Volume	no flow occurs during step. Vessel is empty and no charging / recirculation
Rinse Sampling	Rinse sample for testing	Solvent Manifold Totalizer	Residual soil needs to be dissolved in fixed solvent quantity to compare against standard Quality limits and Maximum Allowable Carryover (MAC) values	Flow Rate	step not designed to perform any cleaning action. Only fixed quantity of cleaning agent is required to be charged
				Agitator Speed	nothing to agitate in equipment
				Concentration of cleaning agents	cleaning agents used are Methanol, Acetone which are all used as procured without any additional cleaning agent
				Duration	no cleaning action in this step hence duration not critical
				Temperature	no cleaning action performed in this step. Ambbient temperature used since sampling stnadards are defined at ambient temperature

Generic Step Name	Description	Critical Process Parameters (CPP)	Rationale for CPP	Non Critical Process Parameters (NCPP)	Rationale for NCPP
Process Solvent Flush	Flushing of equipment with the process solvent of the upcoming step to ensure removal of cleaning agent. This step involves charging the process solvent in the equipment and then recirculating it to the loops	Duration of Charging	To have a minimum duration for which impingement of process solvent occurs on the walls of the equipment	Concentration of cleaning agents	cleaning agents used are Methanol, Ethyl Acetate and DCM which are all used as procured without any additional cleaning agent
		Solvent Manifold Flow Rate	Equipment surfaces are cleaned of the cleaning agent through impingement of process solvent through the spray ball. Flow rate is critical to achieve the required impingement on the walls of the equipment	Temperature	One cleaning solvent used to push out another cleaning solvent. No solubility requirement making temperature irrelevant
		Recirculation duration	Minimum duration of the CIP recirculationof the Process Solvent to each loop to ensure effective removal of cleaning solvent	Volume	It is a product of duration and flow rate which are both monitored as CPP
		CIP Pump Flow rate	flow rate will determine if the flow is enough to ensure displacement by turbulency		
		Agitator Speed	agitation is important to ensure that there is appropriate mixing and no separation / settling down in the equipment. It also aids cleaning of the agitator itself and equipment contact surface with mechanical action.		

Once CPPs were identified and their target values were obtained from the recipe, data available from the historical cleaning cycles was analyzed to identify sources affecting repeatability of the cleaning processes. For this analysis, values of the critical process parameters were plotted on a time series chart to check for adherence to the target value defined in the recipes. Several cases were identified where the actual value deviated significantly from the target value for the parameter set in the recipe. **Figure 14** shows a sample time series plot for a Vessel Fill Boil step that was executed on Equipment A as a part of a cleaning cycle. This figure shows how the target set point for the temperature of the jacket on equipment A was not achieved till quite late in the process. The actual temperature values have been removed from the chart per guidance from Amgen. The deviation from the set point visible in the first half of the chart would prevent boiling of the cleaning solvent used and hence the reflux and distillation which can possibly lead to an unsuccessful cleaning cycle since residual drug on the walls of the vessel that is not exposed to the solvent might not be dissolved and cleaned effectively which can be expected to show up in the testing of the rinse sample taken post the cleaning process.

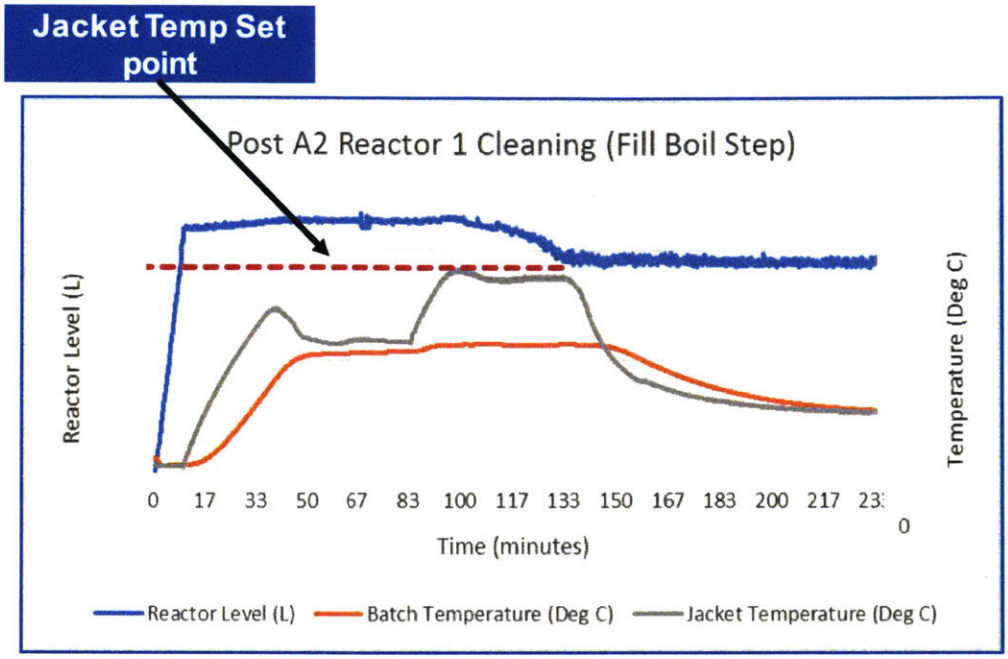


Figure 14: Time series plot for Vessel Fill Boil Step for Equipment A

This along with several other incidents were identified in which the process deviated substantially from the designed recipe. A select few of the cases from different cleaning cycles are shown in **Appendix A**. Another key insight was obtained from analysis of the alarms generated during the execution of the cleaning cycles. The cleaning recipes had provision for control limits for process parameters but existing values were found to be dummy values that would allow execution of the recipes without alarms associated with control limits of process parameters. Hence, these deviations from target values of CPPs were not accompanied by alarms during the execution of the process. It was found that the automation control logic that defines the action taken in case of deviation from the control limits needs review. Given the extent of variation of CPPs and the lack of alarms highlighting these variations during execution, it was hypothesized that consistent execution of the cleaning cycle through implementation of appropriate process controls will improve the repeatability and hence the overall performance of the cleaning process.

5. Implementation of Statistical Process Control

5.1 Methodology of Implementation

In order to test the hypothesis of improved effectiveness of cleaning processes through appropriate process controls, it was decided to identify the control limits for CPPs for each component step for each equipment cleaning recipe and implement these process controls. This was executed in four stages:

1. *Data Availability* – Each piece of equipment had undergone a different number of cleaning cycles for each manufacturing step and the cleaning recipe used evolved over time. As a result, it is critical to differentiate data that can be used for calculation of control limits vis-à-vis data that is not relevant.
2. *Control Limits Calculation* – Once representative sample data is available, control limits for all CPPs were calculated using appropriate statistical tools. For cases where limited data was available, a first principles approach was used to identify reasonable control limits.
3. *Implementation of Control Limits* – With control limits for all CPPs known, automation control logics in the system were modified appropriately to ensure action is taken through the system or call for a manual action is initiated within a reasonable time frame in case of deviation from defined process controls
4. *Offline Testing and Go Live* – Control limits and automation logic implemented in the system were tested for different cases of deviations on an offline system before implementation on live process.

The following sections explain these steps in detail as followed for Equipment D. Each equipment underwent a similar process of identification of control limits and implementation of statistical process control in the recipe.

5.2 Data Availability

As described in **4.1 Cleaning Process Stabilization**, any cleaning recipe is a permutation and combination of a limited number of component steps, sometimes repeated multiple times in a recipe. Process control limits will have to be calculated for each CPP of each component step in the recipe. Given the evolving state of recipes, the current state of recipe cannot be used to calculate the number of times each component step was utilized over all the cleaning cycles. Hence,

depending on the cleaning cycles used for calculating the control limits, the number of occurrences of each component step will differ.

In a validated state of the cleaning processes, the control limits used would be derived from a sufficient sample size of validated cleaning cycles that have been successful at cleaning the equipment. Given the limited success in cleaning cycle development so far, if only the successful cycles are considered for the calculation of control limits, the status of available data for equipment D is shown in **Table 5.**

Table 5: Step by Step data availability from successful cleaning cycle for Equipment D

	Step Description	No. of Samples from successful cycles (Equipment D)
1	Solvent Manifold Cleaning	0
2	Once Through Flush of CIP Loops	8
3	Vessel Fill Boil	5
4	Recirculation of the CIP Loops	5
5	N2 Blowdown of CIP Loops	11
6	Vessel Draining	14
7	Rinse Sampling	3
8	Vessel Drying	1
9	Process Solvent Flush	0

As is clear in **Table 5**, if only successful cleaning cycles are considered, most component steps will have a limited sample size which may not be sufficient for calculating control limits with a reasonable degree of confidence. Hence, it was decided to explore all other cleaning cycles for relevant data in an attempt to increase the sample size.

All cleaning cycles were analyzed separately to identify the sample size available for each component step which is represented by the number of times that component step has been used for cleaning of the equipment. Equipment D was cleaned a total of 10 times from January 2017 to April 2017 in the course of the engineering run. **Table 6** shows the data of sample size of each component step available for cleaning of Equipment D

Table 6: Step by Step data availability of from past cleaning cycles for Equipment D

	Step Description	No. of Samples available (Equipment D)
1	Solvent Manifold Cleaning	0
2	Once Through Flush of CIP Loops	15
3	Vessel Fill Boil	21
4	Recirculation of the CIP Loops	21
5	N2 Blowdown of CIP Loops	27
6	Vessel Draining	36
7	Rinse Sampling	14
8	Vessel Drying	13
9	Process Solvent Flush	0

The changes done to the cleaning recipe during the engineering run can be classified under three categories

1. Changes in set points of Process Parameters
2. Change in order and sequence of operations in a cleaning recipe
3. Change in the frequency of cleaning step in a recipe

In case of change in process parameter value, all following runs will have a mean shift in the value of that particular variable for that cleaning operation. Hence, for characterizing a particular cleaning step, it is important to use the data from all the runs that occur after the last time the set point of a CPP was changed. A change in the sequence of operations might change the impact that cleaning operation has on the overall clean ability of the equipment. However, since no process parameter is changed, characteristically the operation remains the same. Additionally, in case of a change in the number of times a particular step is performed in the cleaning recipe, the system actually generates more data for the characterization of that CIP operation. Hence any such data is used for the characterization of the cleaning operation.

After tracing all the change records associated with cleaning processes, it was identified that there has been no change in any of the cleaning parameters since the cleaning of equipment D that was performed on 26th January 2017. Hence, all the data generated from 26th January, 2017 to 15th April, 2017 was considered as relevant for the calculation of control limits. Within this data set, a time series plot for the CPPs in each iteration of a component step was plotted to check for

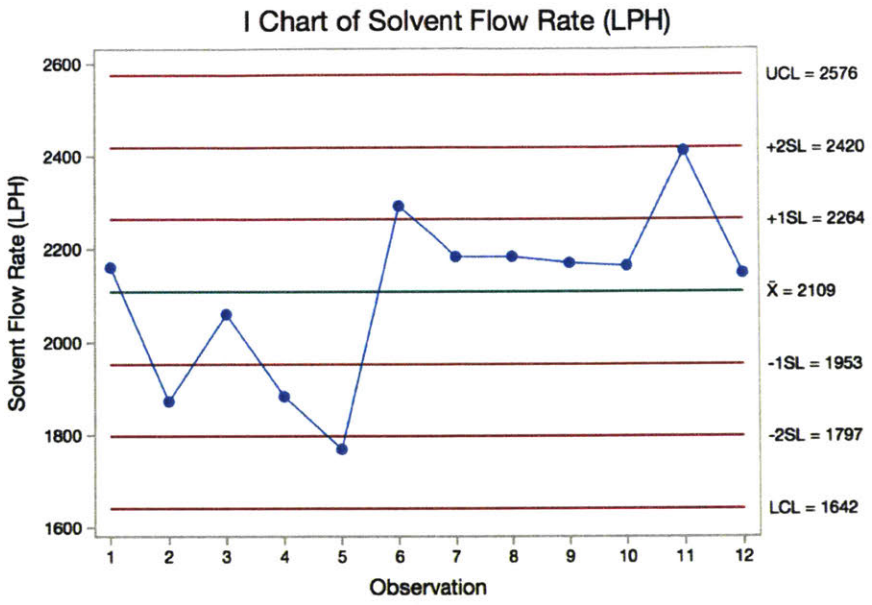
major deviations from the theoretical recipe definition. These iterations with major deviations were excluded from the final set of samples that were used for the calculation of control limits.

5.3 Calculation and Implementation of Control Limits

This section dives into the specific control limit calculations and the implementation of these control limits on the equipment for each component step. Calculation of control limits are shown for CPPs that require control limits. For every CPP that requires control limits, system controls need to be established that define actions to be taken either by the equipment or by operators to bring the CPP, and hence the process, within control. System controls defined in this section were implemented on the equipment by coding them into the automation system of the equipment.

5.3.1 Once Through Flush of CIP Loops

The CPPs for once through flush of CIP loops are flowrate at the solvent manifold and contact time. We wish to achieve enough contact time of the cleaning solvent with the loops at a flowrate that is turbulent enough to take advantage of the mechanical action for removal of any residues in the loops along with the dissolution properties for removal of drug residue. In order to identify the control limits on the flowrate, data from the previous cleaning cycles was taken and an I chart was created for flowrate. **Figure 15** shows the I chart for the flowrate for one loop with control limits. It must be noted that the flushing of the loops involves a ramp up and ramp down of flow of the solvent. The control limits were calculated after removing the ramp up and ramp down of the flow rate since the controls will be applied for the duration for which the flow is stable. Since a higher flow rate means more turbulence and hence better quality of cleaning, only a lower control limit was implemented for this step.



Method

Length of moving range: 2

Parameters

Mean	StDev
2108.7	155.6

Both parameters estimated

Tests for Special Causes

Results for I Chart

Test	Description	Failed Observations
1	1 point > 3 standard deviations from the center line	None
2	9 points in a row on the same side of the center line	None
3	6 points in a row, all increasing or decreasing	None
4	14 points in a row, alternating up and down	None
5	2 out of 3 points > 2 standard deviations from the center line (all on the same side)	None
6	4 out of 5 points > 1 standard deviation from the center line (all on the same side)	None
7	15 points in a row within 1 standard deviation from the center line (on either side)	None
8	8 points in a row > 1 standard deviation from the center line (on either side)	None

Figure 15: I-Chart for Flow rate for one loop of Once Through Flush

The CPP of contact time was a parameter defined in the recipe as the time for which the valves would be open and the pump would be in the switched-on mode. In order to ensure adherence to this parameter, it is essential that the time for which the loop sees stable flow within the control limits is equal to or greater than the contact time defined. The contact time can be ensured by automation control logic for this step that takes automatic action or notifies the operator to take action in case the flow rate goes outside the control limit. **Figure 16** shows the control logic that had been programmed into the system. In this control logic, the system timer starts once the valves are open and the loop is clear for the cleaning solvent to flow and after the system timer reaches the contact time required, the valves are closed and the phase ends.

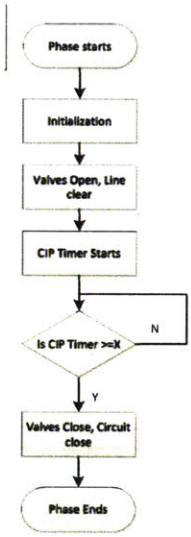


Figure 16: Automation Control Logic for Once Through Flush

Two major flaws were identified with this logic

1. This logic does not account for the ramp up and ramp down time of the flow rate once the valves are open. As a result, the specified contact time may not be achieved if the ramp up and ramp down is slow
2. This logic does not monitor the flow rate during the phase and hence does not indicate through alarms or take appropriate action in case the flow rate goes below the control limits identified.

In order to tackle these limitations, an alternate automation control mechanism was defined. **Figure 17** shows the new logic that was implemented. This logic introduces a hold timer and a stabilization timer that monitor flow rate until it reaches the minimum flow rate per the control

limits and stabilizes above that. Only after stabilization of flow rate the phase timer starts. Additionally, once the CIP timer starts, the flow rate is continuously monitored and in case flow rate drops below the control limit, appropriate actions are programmed.

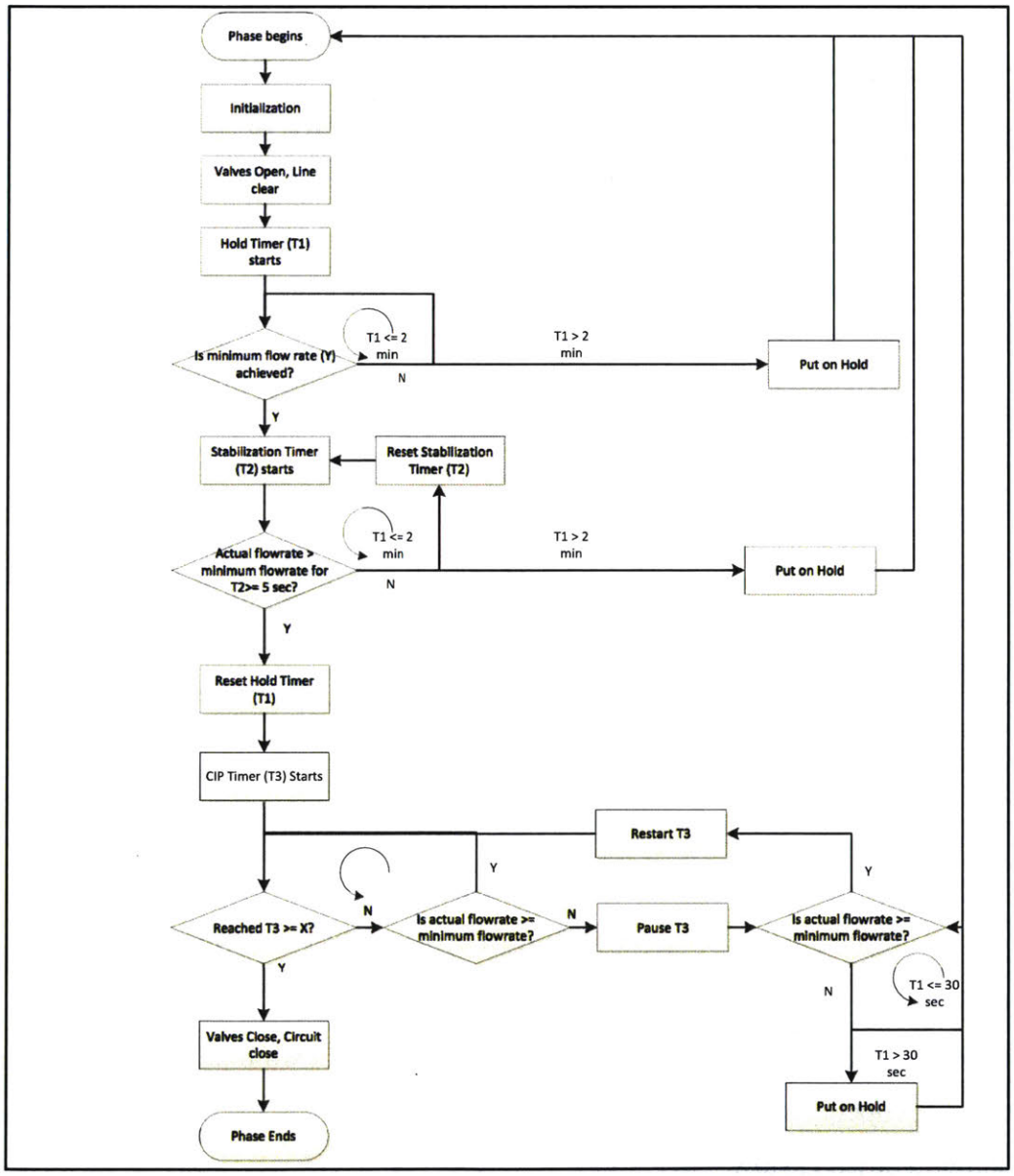


Figure 17: Revised Automation Control Logic for Once Through Flush of CIP Loop

5.3.2 Solvent Manifold Cleaning

The CPPs for Solvent Manifold Cleaning are also solvent flowrate and contact time. As a result, similar analysis was carried out to come up with a lower control limit for the step. This was done for equipment A, B and C. The cleaning recipe of Equipment D did not contain a solvent manifold cleaning step.

5.3.3 Vessel Fill, Boil, Reflux, Distillation

This step requires monitoring and control of several CPPs. Each of these CPPs was handled differently on the basis of their role in the cleaning process.

1. *Equipment Fill Level:*

   The required initial fill level was defined on the basis of the level to which the equipment is filled during the manufacturing process. It was decided to submerge the equipment up to a certain level above the level to which it is submerged during manufacturing. This parameter is controlled by the level sensor of the equipment and the recipe proceeds to the boiling phase only once the level sensor indicates the required minimum level of cleaning solvent has been achieved. This parameter, though important, is hard coded in the recipe in a way that the recipe does not move to the next step until the required initial fill level is achieved. Similarly, the end of the vessel fill boil phase happens with distillation. During the distillation phase, the solvent vapors are distilled out into the distillate receiver. The distillation step is carried out up to the point when a predetermined amount of solvent has been distilled out. This is monitored using the level sensor of the equipment. Distillation is deemed complete once the final fill level is lower than the initial fill level by the predetermined amount of distillate. This value is also hard coded in the recipe with no possible variance. This means that the recipe would continue to the next phase only after this final equipment fill level is achieved. Hence, controlling jacket temperature and agitation speed along with a monitoring of the level is sufficient for this part of the phase. As a result, no additional controls were established for the equipment level.

2. *Equipment Heating Jacket Temperature:*

   The equipment heating jacket temperature is important to ensure the boiling of the solvent inside the vessel (done at atmospheric pressure). The speed of achieving the boiling temperature is not key since it does not affect the dissolution of the residual drug. Hence, it is critical to ensure that the temperature of the heating jacket is sufficiently above the boiling point of the cleaning solvent in the equipment. The recipe already contained set points for the jacket temperature which were defined to be above the boiling points of individual cleaning solvents. The lower control limits for this parameter were defined at 5°C above the boiling point of the cleaning solvent. **Table 7** shows a list of the control

limits defined for the jacket temperature. Upper control limit is not required for this parameter since a higher temperature would mean quicker boiling.

Table 7: Control Limits / Alarm Limits for Jacket Temperature in Vessel Fill Boil by cleaning solvent

Cleaning Solvents used in Fill Boil	Boiling point (basis TRPT)	Current Jacket Set Point (basis system recipe)	Proposed Low Alarm limit for Jacket Temperature	High Alarm Limit for Jacket Temperature
Water	100°C	105°C	103°C	Basis safety
Acetone	56°C	75°C	61°C	Basis safety
Methanol	66°C	90°C	71°C	Basis safety

In case the jacket temperature goes sufficiently below the control limit defined here, the boiling action will be halted. This could mean less condensation of cleaning solvent on the unsubmerged walls of the equipment and hence ineffective cleaning of the vessel. Hence, appropriate control logic and automated actions or call for manual actions will be needed in case the temperature stays below the control limit for a longer duration. **Figure 18** shows the proposed automation control logic for equipment jacket temperature. This logic informs the operator to take action in case the jacket temperature goes below the minimum required temperature defined by the alarm limit.

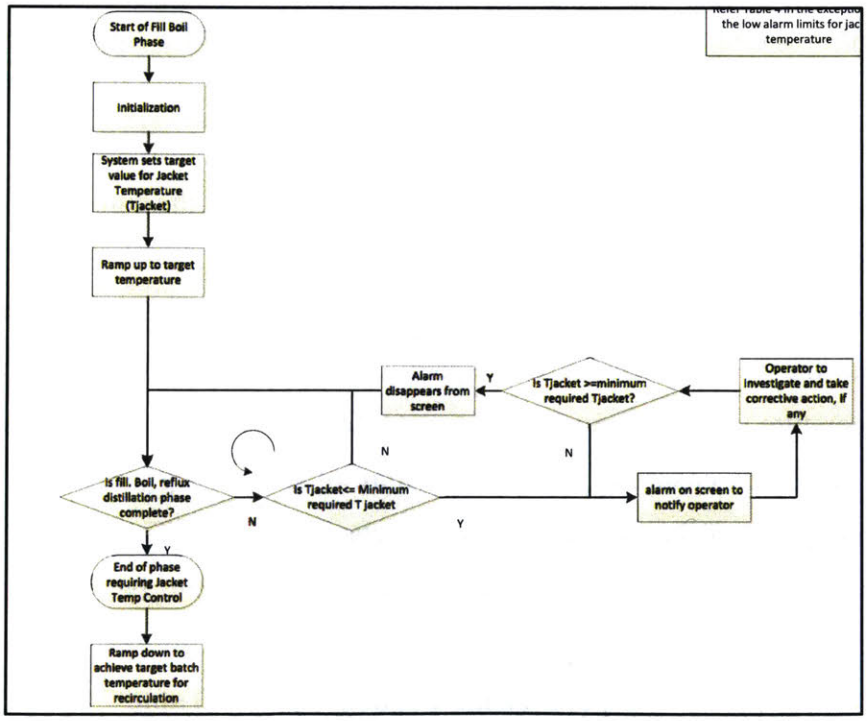
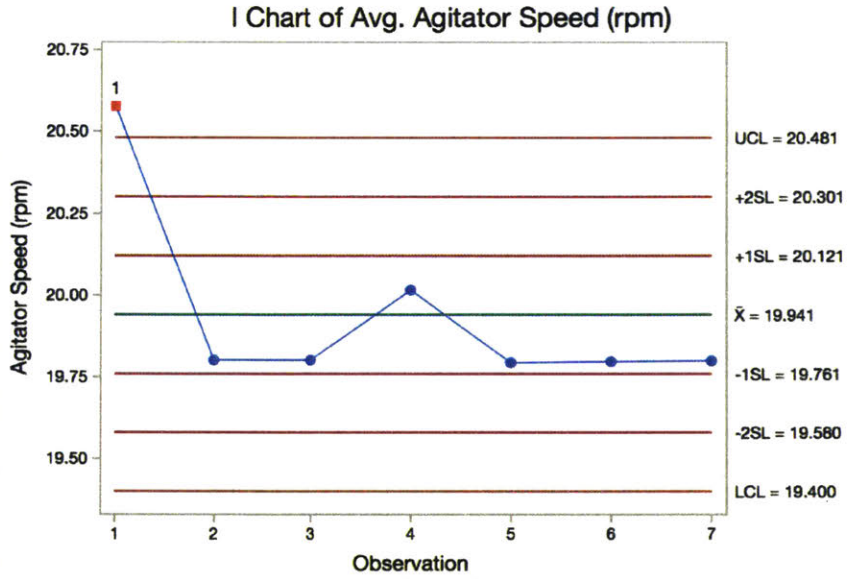


Figure 18: Automation Control Logic for Jacket Temperature

3. *Agitation Speed*

Each equipment has an agitator inside to ensure continuous mixing of the contents of the equipment and to avoid settling of particles. Agitation is critical to have continuous mixing during cleaning as well especially for the duration when the equipment is filled with cleaning solvent. The set point of the agitation speed is defined in each recipe separately depending on the capability of the agitator in that equipment. The agitator was found to have negligible standard deviation (0.285 rpm for an average agitator speed of 19.88 rpm for equipment D) around the set point once achieved. **Figure 19** shows the I Chart of the agitator speed for 14 runs of the vessel fill boil step for Equipment D. Since the action of the agitator is to continuously mix the contents of the equipment, such tight control around the mean is not as critical.

I Chart of Avg. Agitator Speed (rpm)



Method

Length of moving range: 2

Parameters

Mean	StDev
19.9408	0.1802

Both parameters estimated

Tests for Special Causes

Results for I Chart

Test	Description	Failed Observations
1	1 point > 3 standard deviations from the center line	1
2	9 points in a row on the same side of the center line	None
3	6 points in a row, all increasing or decreasing	None
4	14 points in a row, alternating up and down	None
5	2 out of 3 points > 2 standard deviations from the center line (all on the same side)	None
6	4 out of 5 points > 1 standard deviation from the center line (all on the same side)	None
7	15 points in a row within 1 standard deviation from the center line (on either side)	None
8	8 points in a row > 1 standard deviation from the center line (on either side)	None

Figure 19: I chart for Agitator speed during Vessel Fill Boil for 14 cleaning cycles

However, agitation is a critical process parameter and hence it was decided to monitor the agitation speed till the set point is achieved and continue to monitor during the process to raise alarms whenever the agitation speed is found to be less than 90% of the set point. A higher than set point agitation speed would mean better mixing action and hence the upper control limit for the parameter was defined based on safety requirements for the equipment. **Table 8** lists the control limit of agitator speed.

Table 8: Agitation Speed Control Limits for Vessel Fill Boil

Parameters for agitation speed	**Value in rpm**
Set Point during recipe	20
90% of set point (Lower Control Limit)	18
High speed limit (Upper Control Limit)	Basis safety requirements

The control limit of 90% of the set point was picked arbitrarily to highlight any major issues with the agitator. **Figure 20** shows the automation logic that was implemented for the agitator speed control.

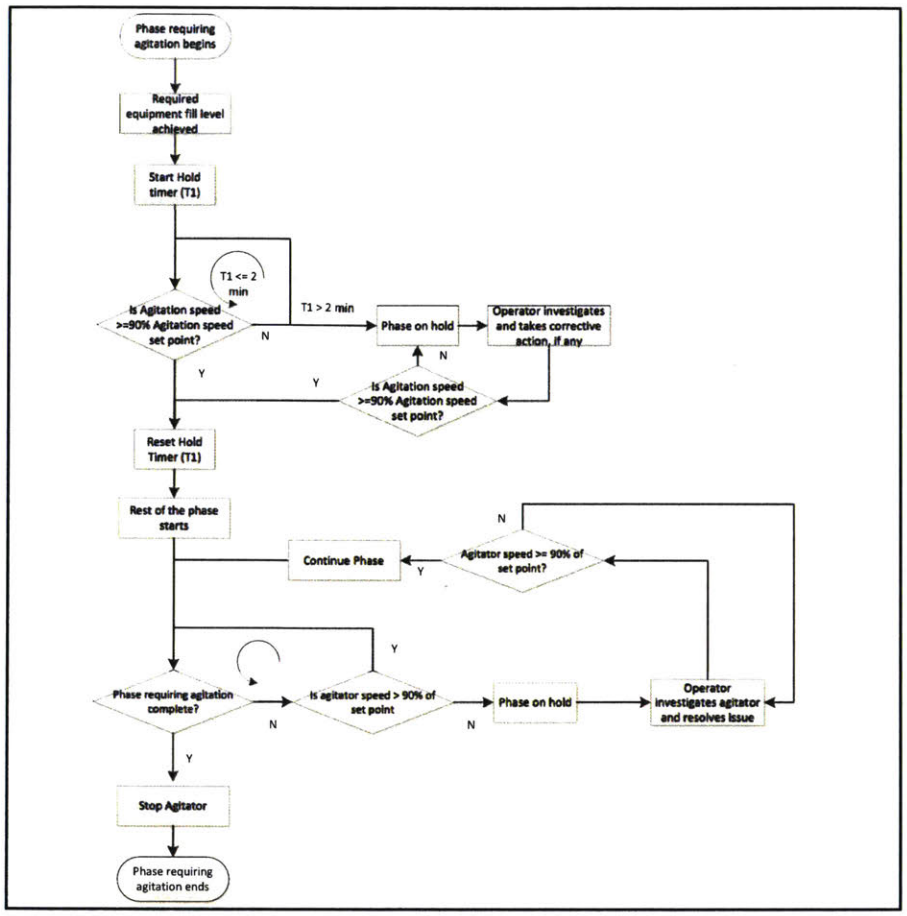


Figure 20: Automation Control Logic for Agitation Speed

4. *Reflux Duration:*

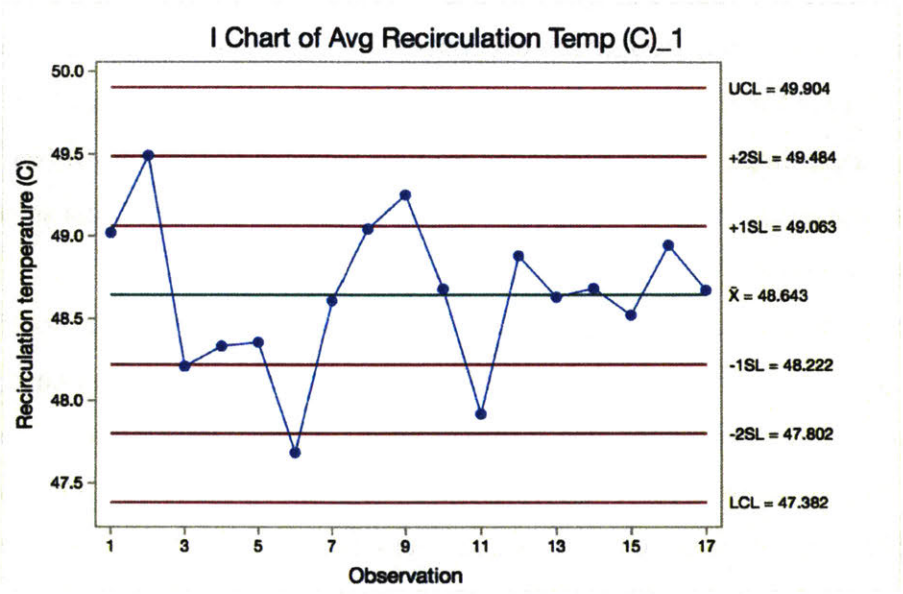
   The reflux of solvent vapors is done through opening a circular loop that brings the vapor back to the equipment. The duration of reflux is counted from the time the valves for the reflux loop are opened. At this point the phase timer also starts and the valves are closed once the phase timer reaches the duration for which reflux is planned. This CPP is thus programmed into the recipe with no possibility of deviation. As a result, no additional controls (apart from the ones explained earlier) are required for this part of the Vessel Fill Boil step.

5.3.4 Recirculation of CIP Loops

The recirculation phase takes advantage of the dissolution properties of the residual drug in the cleaning solvent at higher temperature as well as mechanical cleaning action through turbulence. For equipment D, the solvent temperature has a target set point of 48°C which is maintained with the help of the heating jacket of the equipment. This high temperature solvent is

circulated through each of the CIP loops with the help of a recirculation pump. As a result, the CPPs for this step of the cleaning process are solvent temperature (also known as batch temperature), flow rate and contact time for each loop. During this phase, the agitator is also kept on to ensure continuous mixing of the solvent inside the equipment that is not being circulated. While the cleaning action for this step is for the CIP loops, it is essential to monitor and control the agitator speed to ensure continuous mixing in the equipment. Agitator is monitored as described in the vessel fill boil stage. For batch temperature, data from past cleaning cycles was used to define the control limits. **Figure 21** shows a sample I-chart with control limits for batch temperature for one representative loop of equipment D.

I Chart of Avg Recirculation Temp (C)_1



Method

Length of moving range: 2

Parameters

Mean	StDev
48.6428	0.4204

Both parameters estimated

Tests for Special Causes

Results for I Chart

Test	Description	Failed Observations
1	1 point > 3 standard deviations from the center line	None
2	9 points in a row on the same side of the center line	None
3	6 points in a row, all increasing or decreasing	None
4	14 points in a row, alternating up and down	None
5	2 out of 3 points > 2 standard deviations from the center line (all on the same side)	None
6	4 out of 5 points > 1 standard deviation from the center line (all on the same side)	None
7	15 points in a row within 1 standard deviation from the center line (on either side)	None
8	8 points in a row > 1 standard deviation from the center line (on either side)	None

Figure 21: I Chart with Control limits for Batch Temperature

Similar analysis was carried out for each loop to come up with the control limits for batch temperature for this phase. In the process of implementing control limits for batch temperature, it was identified that the recipe design can accept only a single control limit around the set point ($\pm x\ degree\ celcius$) for all CIP loops combined. Under the situation, control limits from the CIP loop with the widest range on batch temperature was accepted as the control limit for all loops. The range of temperatures around the mean was different for each loop because of the length of each loop. For equipment D, this limit was found to be ± 3 °C.

Figure 22 shows the automation control logic that was defined for the control of the batch temperature. This logic continuously monitors the batch temperature and in case of a deviation from the control limits, pauses the phase timer and allows the temperature to come within the control limits before restarting the timer. In case the temperature is not restored for a longer duration, the phase is put on hold, operator takes actions to achieve the required temperature and the phase is started again.

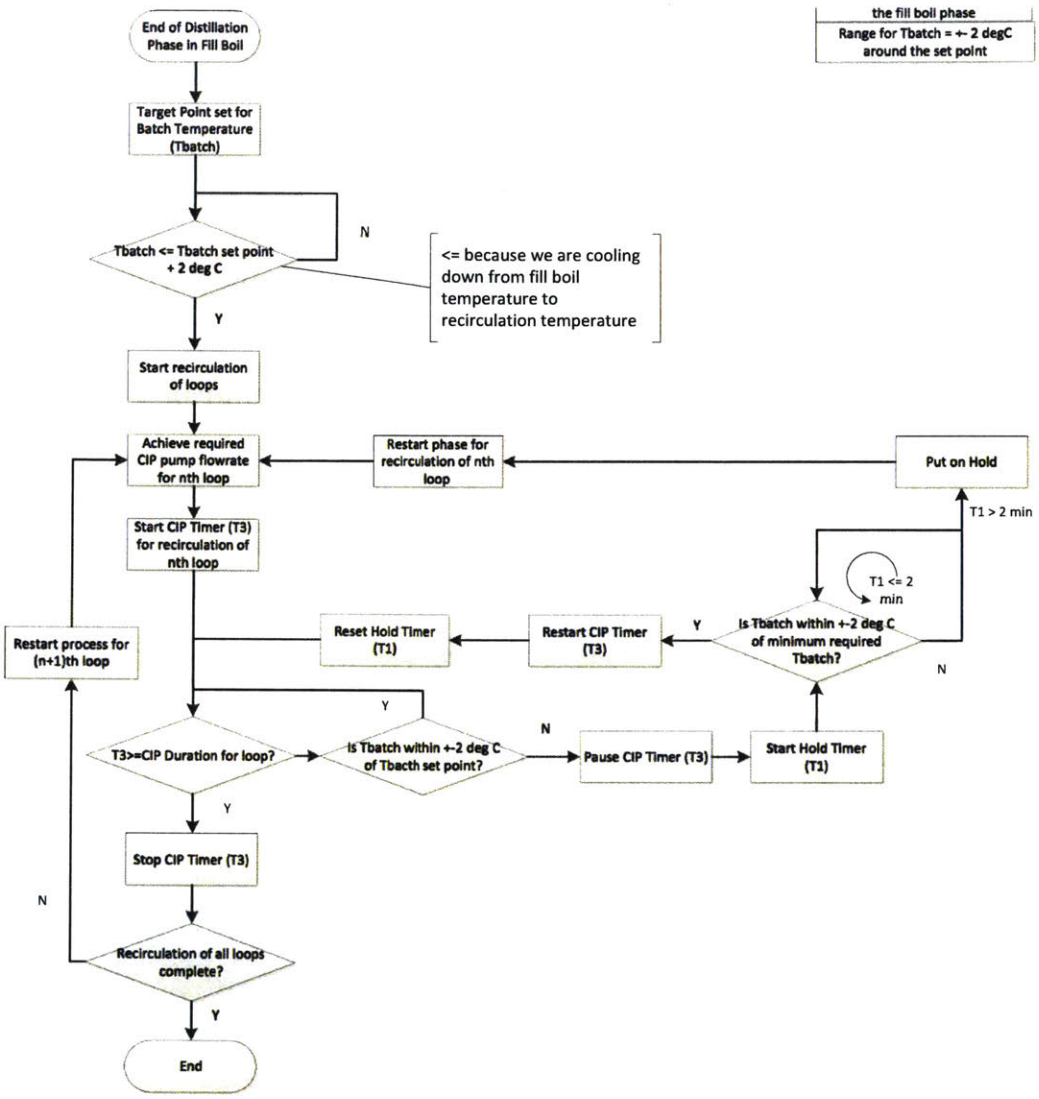


Figure 22: Automation Control Logic for batch temperature

For the flow rate, it was identified that the CIP recirculation pump flow meter has not been functional for the entire duration of the engineering trials. As a result, no data was available to find the control limits of the flow rate for the CIP recirculation. Under the situation, the specifications of the CIP recirculation pump were examined and it was identified that the pump has an operating range of $2 - 8\ {}^{m^3}/_{h}$. This operating range was used to calculate the range of Reynolds number (Re) in each CIP loop. Each CIP loop is a combination of several pipes connected in sequence. As a result, Reynolds number was calculated for the largest pipe diameter for every loop and for the lowest flow rate of the CIP pump. Lowest flow rate on the highest diameter pipe corresponds to

the lowest Reynolds number in the CIP loop. **Table 9** lists the minimum Reynolds number calculated for each loop. The Reynolds number for a circular pipe is given by the equation

$$Re = \frac{\rho \cdot \upsilon \cdot D_H}{\mu}$$

where
$\rho = density\ of\ the\ fluid\ (kg/m^3)$
$\upsilon = mean\ velocity\ of\ the\ fluid\ (m/s)$
$D_H = Hydraulic\ Diameter\ of\ the\ pipe = Diameter\ of\ the\ circular\ pipe\ (m)$
$\mu = dynamic\ viscoscity\ of\ the\ fluid\ (Pa.s)$

The value of density and dynamic viscosity was taken at 50°C and Reynolds number was calculated for each loop for all three cleaning solvents used in the process across manufacturing steps

Table 9: Minimum Reynolds Number for each CIP loop during recirculation (material properties from [52] and [53])

Methanol @ 50degC	Dyn. Viscosity (Cp)	0.392
	Density (kg/m3)	764
Acetone @ 50degC	Dyn. Viscosity (Cp)	0.250
	Density (kg/m3)	753.2
Water @ 50degC	Dyn.Viscosity (Cp)	0.546
	Density (kg/m3)	988.04

Equipment D						
CIP Loop	Low Flow Alarm Limit (min flow rate of CIP pump) L/H	Max pipe diameter en route inch	Velocity flow m/s	Reynold's number (Re) Methanol	Reynold's number (Re) Acetone	Reynold's number (Re) Water
CIP Loop 1	2,000	1.50	0.49	36,184	55,054	33,597
CIP Loop 2	2,000	2.00	0.27	27,138	41,291	25,197
CIP Loop 3	2,000	1.50	0.49	36,184	55,054	33,597
CIP Loop 4	2,000	1.00	1.10	54,276	82,581	50,395
CIP Loop 5	2,000	1.00	1.10	54,276	82,581	50,395
CIP Loop 6	2,000	1.00	1.10	54,276	82,581	50,395
CIP Loop 7	2,000	1.00	1.10	54,276	82,581	50,395

Since the minimum possible Reynolds Number for each CIP loop is significantly above the minimum limit for turbulent flow (for $Re \leq 2600$, flow is considered laminar), it was decided that the indicator switch for CIP pump that provides information on status of the pump (binary value on / off) will be monitored as an indicator of the flow rate. At the same time, the CIP pump flow meter was restored and it was decided to collect data during the future runs and control limits on flow rate be defined once enough data is available. The automation control logic shown in **Figure 17** was used for CIP recirculation as well with the CIP Pump status switch being monitored instead of the flow rate.

5.3.5 N_2 Blowdown of CIP Loops

Nitrogen is blown into the loops to displace the cleaning solvent possibly remaining on the walls of the pipes. This was done using either of the two central headers of nitrogen which were at a pressure of 2-bar and 6-bar. For Equipment D, the 6-bar header was used with a reducer that brings down the pressure to 2-bar before entering the loops. The measurement of the nitrogen pressure was at the header and not at any of the usage points. Moreover, for the nitrogen pressure, a site wide safety alarm is in place which over rides all processes. Hence, in case of a drop of pressure in the main header below a certain limit, all actions on the site go on hold and system is reset after the issue has been resolved. With constant pressure in the headers, the only parameter that needs to be monitored for this step is the contact time. **Figure 23** shows the automation logic that was implemented to ensure that a minimum contact time as defined in the recipe is achieved.

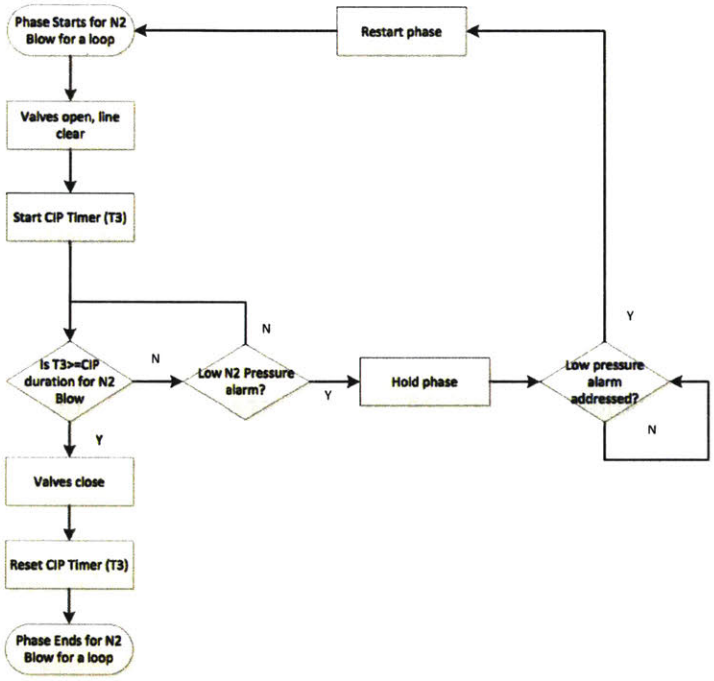


Figure 23: Automation Logic for Nitrogen blow through the CIP loops

Since the equipment is still filled with cleaning solvent, the agitator is kept on and it was decided to monitor and control it in the same way as described previously in the vessel fill-boil phase.

5.3.6 Equipment Draining

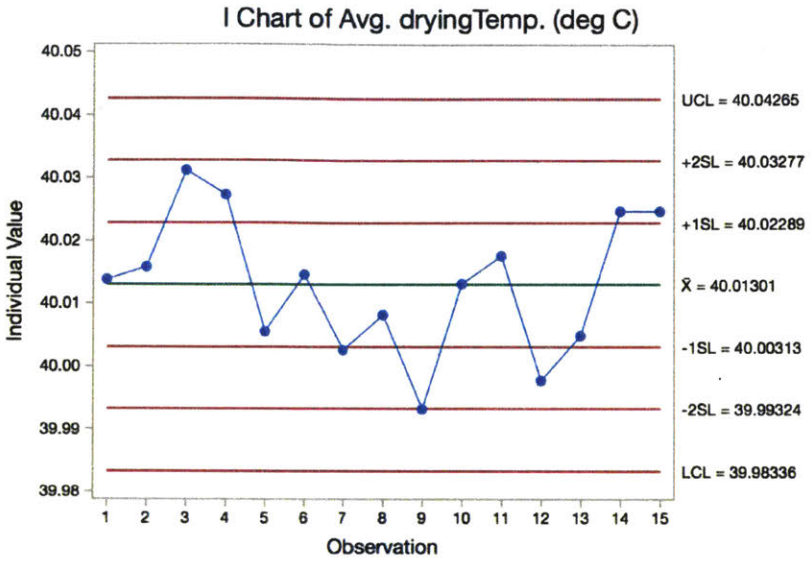
This step is used to empty the vessel post cleaning cycle. This step requires the batch temperature of the solvent being drained to be at room temperature before the drain occurs. This is a safety requirement for the site and is not critical to the quality of the cleaning process. This is

achieved by allowing cooling of the solvent to happen naturally and open the drain valves once the batch temperature reaches 25°C. The only control required for this stage is monitoring of the batch temperature and an interlock of the drain valves with the batch temperature. This exists as a safety interlock and hence no changes were done to this step.

5.3.7 Vessel Drying

Vessel drying is required at the end of the cleaning cycle to remove the residual cleaning solvent from the equipment through evaporation. For this step, the equipment is heated to a predetermined temperature with the help of the heating jacket to evaporate the solvent. The jacket temperature is required to be lower than 50°C for safety reasons. However, a steady vacuum is maintained in the equipment to lower the boiling point of the solvent. This step is followed by a visual inspection of the equipment and any traces of residual solvent visible in the equipment will lead to a failure of visual inspection. Hence, achieving evaporation of all residual solvent is critical to quality. As a result, the key parameters to be monitored and controlled for this phase are vacuum pressure and jacket temperature. For calculating the control limits for this phase, data from past cleaning cycle execution was studied and for each instance of vessel drying phase, the data for jacket temperature and equipment pressure was used for the duration for which these parameters were stable. Hence, the ramp up and ramp down of these parameters was ignored in the calculation of the control limits. A total of 15 past instances of vessel drying were identified and analyzed for the control limit calculation. **Figure 24** and **Figure 25** show the control limits for Jacket temperature and Vacuum pressure in the vessel for the vessel drying phase.

I Chart of Avg. dryingTemp. (deg C)



Method

Length of moving range: 2

Parameters

Mean	StDev
40.0130	0.009882

Both parameters estimated

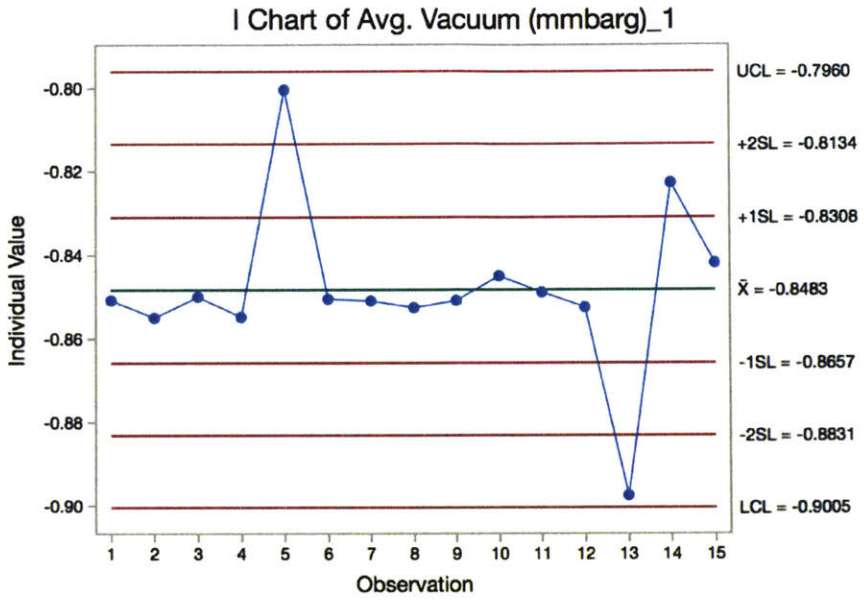
Tests for Special Causes

Results for I Chart

Test	Description	Failed Observations
1	1 point > 3 standard deviations from the center line	None
2	9 points in a row on the same side of the center line	None
3	6 points in a row, all increasing or decreasing	None
4	14 points in a row, alternating up and down	None
5	2 out of 3 points > 2 standard deviations from the center line (all on the same side)	None
6	4 out of 5 points > 1 standard deviation from the center line (all on the same side)	None
7	15 points in a row within 1 standard deviation from the center line (on either side)	None
8	8 points in a row > 1 standard deviation from the center line (on either side)	None

Figure 24: I chart with control limits for Jacket Temperature during vessel drying

I Chart of Avg. Vacuum (mmbarg)_1



Method

Length of moving range: 2

Parameters

Mean	StDev
-0.84826	0.01741

Both parameters estimated

Tests for Special Causes

Results for I Chart

Test	Description	Failed Observations
1	1 point > 3 standard deviations from the center line	None
2	9 points in a row on the same side of the center line	None
3	6 points in a row, all increasing or decreasing	None
4	14 points in a row, alternating up and down	None
5	2 out of 3 points > 2 standard deviations from the center line (all on the same side)	None
6	4 out of 5 points > 1 standard deviation from the center line (all on the same side)	None
7	15 points in a row within 1 standard deviation from the center line (on either side)	None
8	8 points in a row > 1 standard deviation from the center line (on either side)	None

Figure 25: I chart with control limits for Equipment pressure during vessel drying

Analysis of past instances of vessel drying showed a lot of variation in the drying time for which the vessel is exposed to before the drying is considered complete ($\mu = 72\ mins$, $\sigma = 62\ mins$). It was observed that the duration defined in the recipe for the drying step is supposed to be 60 mins. As a result, the automation logic was defined to ensure sufficient drying time along with appropriate process controls for the CPPs of drying. **Figure 26** shows the automation control logic defined for the vessel drying phase. Since a combination of pressure and temperature will lead to evaporation of the solvent (boiling point depends on the pressure), these two parameters are monitored simultaneously.

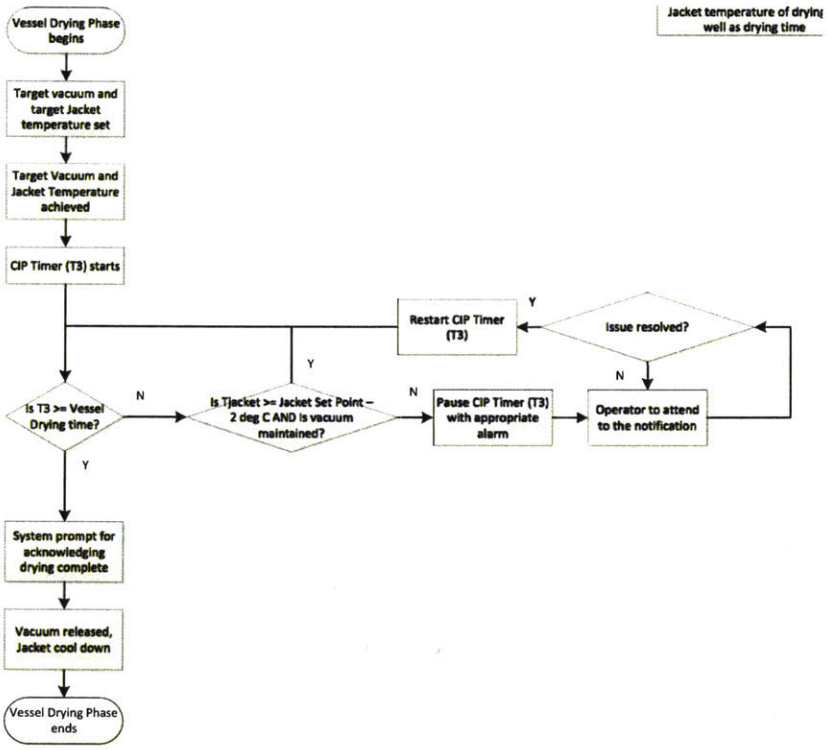


Figure 26: Automation Control Logic for Vessel Drying phase

6.3.8 Rinse Sampling

The rinse sampling requires a fixed quantity of cleaning solvent to be charged through a spray ball in the equipment to ensure that the solvent charged is a representative sample of the residues in the vessel post cleaning. This step just requires control of the volume of solvent charged into the equipment which is achieved through the solvent manifold totalizer that measures the quantity of solvent being charged. The controls for this step were already established and required no modification.

5.3.9 Process Solvent Flush

Process solvent flush is the last step performed before the equipment is considered ready for the next manufacturing step. In this step, the solvent for the next manufacturing step is flushed through the system of CIP loops and the equipment to ensure that any traces of the cleaning solvent are displaced with the solvent for the next manufacturing step. This step is critical to quality since it is required to avoid contamination by the cleaning solvent in the next step. It is performed only when the cleaning solvent is different from the process solvent for the upcoming step on the equipment. Since the cleaning action here is through displacement, it is essential to have turbulent flow in the CIP loops. As a result, similar to the once through flush of CIP loops explained in **5.3.1 Once Through Flush of CIP Loops**, flow rate and contact time were designed to be monitored and controlled through the flowchart shown in **Figure 17.** It must be noted that the CIP loops for process solvent flush are the same as that for once through flush. Equipment D is not subject to process solvent flush as a part of the cleaning recipe for any of the manufacturing steps.

5.4 Offline Testing

Once the identified control limits by step and CPP were implemented along with the requisite control logic in the recipe, a test protocol was created and offline testing was conducted to ensure that the implementation is as intended. The test protocol consisted of tests designed to check each logical decision that the equipment is required to take under conditions of deviation from the designed recipe. **Table 10** shows the test protocol for once through flush of CIP loops to test all possible cases of deviation for the phase. **Appendix B** contains the test protocols used for the automation logic implemented for each phase.

Post testing the developments offline, the automation control package was implemented in the live equipment for all upcoming cleaning cycles. The implementation of the package was completed towards the end of June, 2017. The Process Performance Qualification (PPQ) run for the site was expected to start in the first week of July. The testing of the hypothesis of improved repeatability post implementation of automated statistical process control requires several iterations of cleaning cycles on all equipment.

Table 10 : Test Protocol for Automation Logic for Once Through Flush of CIP loops

Purpose: To test the control logic for solvent flow rate during once through flush and recirculation					
Component Step: Once Through Flush (Except Bottom Vacuum Line) & Recirculation					
Step. No.	Action	Expected Result	Pass / Fail / value	Performed By	Date
1	Test Setup				
1.1	Verify the default settings for the following parameters	N/A	N/A		
	Hold Time for stabilization of flow rate	120 sec			
	Stabilization time for CIP flushing	10 sec			
	Hold Time for dip in flow rate during flushing	30 sec			
1.2	Record Cleaning Path		N/A		
1.3	Record the Cleaning Solvent Type (Water, Acetone, Methanol). Record N/A for recirculation phase		N/A		
1.4	Record the minimum solvent flow recipe value (LCL)		N/A		
2	Test Case # 1: Flow Not Established Timeout				
2.1	Simulate CIP Flow lower than the LCL. Record the value		N/A		
2.2	Run the Clean CIP phase (Once through flush or Recircul	N/A			
2.3	Verify that the pjase goes on hold after the hold time for stabilization of flow rate	N/A			
3	Test Case # 2: Flow Fluctuate Timeout				
3.1	Set the stabilization time for CIP flushing to 999 sec	N/A	N/A		
3.2	Restart the phase	N/A			
3.3	simulate the CIP flow to a value higher than minimum solvent flow recipe value (LCL). Record the value	N/A			
3.4	before the stabilization time expires, simulate the CIP flow to a value lower than the LCL. Record the value		N/A		
3.5	Verify that the phase goes on hold after the hold time for stabilization of flow rate expires	N/A			
4	Test Case # 3: Flow Establish Timer				
4.1	Set the stabilization time for CIP flushing to default value	N/A			
4.2	Restart the phase	N/A			
4.3	Simulate the CIP flow to a value lower than the LCL	N/A			
4.4	Verif that the phase waits for minimum CIP flow rate (LCL) to be achieved	N/A			
4.5	Simulate the CIP flow to value higher than LCL.	N/A			
4.6	Verify that the phase waits for stabilization timer (10 sec) before the cleaning time (CIP Timer) is started	N/A			
5	Test Case # 4: Lost flow during CIP				
5.1	Simulate the post stabilization phase and drop the value of the CIP flow rate below LCL		N/A		
5.2	Verify that the CIP Timer is paused when flow rate is less than LCL	N/A			
5.3	Before hold timer for dip in flow rate during flushing expires, set the CIP flow greater than LCL. Record the value		N/A		
5.4	Verify that the CIP timer is resumed when the CIP flow rate goes above the LCL.	N/A			
6	Test Case # 5: Loss of flow during CIP Timeout				
6.1	while the CIP flow is in progress, simulate a flow rate below the LCL. Record the value		N/A		
6.2	Verify that the phasegoes on hold after Hold time for dip in flow during flushing is exceeded	N/A			
6.3	Restart the phase and allow the phase to end normally	N/A			

6. Results and Discussion

With the control limits of individual critical process parameter implemented in the form of automation control in the cleaning recipe of each equipment, the cleaning operations were resumed at the site along with the start of PPQ runs. The qualification runs were also the first commercial runs of the product from the site. Understanding the impact of the Phase I of implementation of statistical process control in the cleaning operations was dependent on the schedule of these qualification runs. The qualification runs were started during the last month of the author's stint at Amgen. Due to proprietary data constraints, process data for cleaning runs executed during the qualification runs (i.e. post the author's duration of research at the site) is not available for analysis.

However, information about the cleaning cycles executed and their success rate was provided by Amgen for the purpose of this thesis. From the start of the qualification runs in July 2017 till February 2018, a total of 18 cleaning cycles were executed across the four pieces of equipment which were the focus of work presented in this thesis. Out of these, 15 cleaning cycles were successful in cleaning the equipment below the maximum allowable carryover of residue and with appropriate visual cleanliness. Given the success rate prior to the implementation of Phase I of SPC was 38%, this represents a significant improvement in performance. Equipment wise cleaning performance is shown in **Table 11.**

Table 11: Success rate in Cleaning post SPC implementation

	# Cleaning Cycle runs	# Successful runs	Success Rate (%)
Equipment A	5	3	60%
Equipment B	4	4	100%
Equipment C	2	2	100%
Equipment D	7	6	86%

A comparison between **Table 3** and **Table 11** shows significant performance improvement in the cleaning effectiveness for all four pieces of equipment.

With this improvement, the site took a decision to start cleaning validation protocol for the cleaning processes for Equipment A, B and D. This represents the end of cleaning cycle development requiring to the site to show three consecutive successful runs of cleaning on each

equipment without any recipe changes or manual intervention. As of December 2017, the site had completed one cleaning validation run for each of the three pieces of equipment.

This thesis presents work done to introduce Phase I of statistical process control along with automation controls to implement these in ongoing cleaning operations. The implementation showed significant improvement in cleaning effectiveness post implementation. However, as described in **3.2.2 Implementation of Control Charts,** Statistical Process Control is an ongoing quality improvement process that requires regular monitoring and review leading to continuous improvement of quality though elimination of assignable causes of variation in the process. The next section highlights opportunities for future work for Amgen to achieve reasonable level of implementation of Phase I and transition to Phase II of SPC. Additionally, it introduces work that was done to pilot real time multivariate statistical process monitoring using multivariate software SIMCA® for cleaning processes. This pilot was done only for Equipment D and shows great potential as an online monitoring tool for shop floor work force to identify deviations from designed process and identify the cause of the deviations with a sophisticated interface.

7. Recommendations and Future Work

7.1 Improvement in Control Limits

As part of the research done for this project, statistical process controls were implemented for the cleaning processes in a pharmaceutical environment. The calculation of the control limits for each critical process parameter was done using the available data from previous cleaning cycles. Given the lack of successful cleaning cycles, control limits were calculated using data from historical cycles where a component step was executed as intended based on the recipe design. While this gave a good estimation of the first cut control limits that allowed implementation of Phase I of SPC, it is essential that the control limits be updated once sufficient data from successful cleaning cycles is available. A preliminary update of control limits can be done once the cleaning validation exercise is complete since that would mean at least three consecutive successful validated runs are available along with some successful cleaning cycle development runs. Post this, control limits can be updated with a regular frequency during Phase II of SPC as more and more assignable causes are eliminated through continuous improvement.

7.2 Real-time Multivariate Statistical Process Control

The statistical process control established for cleaning processes at the site controls each CPP independently for each step. As described in **3.3.1 Motivation for Multivariate SPC** this method does not take into account the correlation among the variables. Given that most of the component steps of cleaning have more than one critical process parameter, the current SPC methodology using independent control charts for each variable assumes no correlation. Monitoring the process this way will be successful at identifying Type I errors but have a higher probability of Type II errors. As a result, Amgen can benefit from moving to a multivariate SPC methodology as it transitions from Phase I to Phase II of SPC implementation.

Given that each step of the cleaning process can be described through a combination of critical process parameters, a unique multivariate test statistic that accounts for correlation among the variables that are CPPs for that step can be used to describe the process through a single control chart. Evolution of a cleaning cycle can be monitored using a single control chart that plots the value of this test statistic against the control limits for the test statistic calculated using historical data. This reduces the number of control charts to be monitored to just one per step and also characterizes the process in a way that accounts for the correlation among process variables and

output of the process. The following section describes the multivariate model that was implemented for real time monitoring of cleaning process for equipment D.

7.2.1 Multivariate Modeling for Equipment D Cleaning Process

A trial version of multivariate model was attempted for cleaning process of equipment D. The data available as defined in **5.2 Data Availability** was used to create the multivariate model. SIMCA® by UMETRICS was used as the modeling software for the project [54]. While the model was developed for the entire process, this section is used to describe the process of building the model for a representative component step – Vessel Fill Boil. The author decided to use this step for this section because vessel fill boil has multiple CPPs and is the principal cleaning step for the equipment. Additionally, this step is the longest among the component steps covering close to 50% of the 35-hour recipe duration. A similar process was used to create models for each component step.

Data from 17 iterations of Vessel Fill Boil on Equipment D was compiled for all CPPs (agitator speed, reactor level, jacket temperature, and batch temperature) as input samples for the multivariate model. This data was uploaded on SIMCA® and several indicators from the software were looked at to identify outliers among the 17 iterations. A batch evolution model can be made on SIMCA® to show how a critical quality attribute evolves as the value of the critical process parameter and hence the underlying test statistic evolves. For the cleaning process, the CQAs are visual cleanliness and level of the residual drug. Both these attributes are measured / examined at the end of the process only and hence how these parameters evolve as the cleaning progresses is not available. As a result, it was decided to create a model that shows the evolution of the process against time. Given that contact time or duration of a phase is critical to a lot of component steps, showing evolution against time would also allow for monitoring of delays / overtime in component steps.

Figure 27 shows the Scores plot for the Vessel Fill Boil containing all batches super imposed on the same plot. The Scores plot represents the value of the test statistic (on the y-axis) over time (represented on the x-axis). As described in the figure, the dotted green line represents the mean values of the test statistic over time for all batches put together and red line represents the $\pm 3 \cdot (Std.Dev)$ around the mean. The blue arrows point to two instances of vessel fill boil that seem to be outliers. The batch represented by the black line stays beyond the LCL for quite some time during the evolution. Additionally the batch represented by the red line remains on the

same side of the mean possibly between 2σ and 3σ for a long duration which would make it an outlier as per the rules in Western Electric Handbook [55].

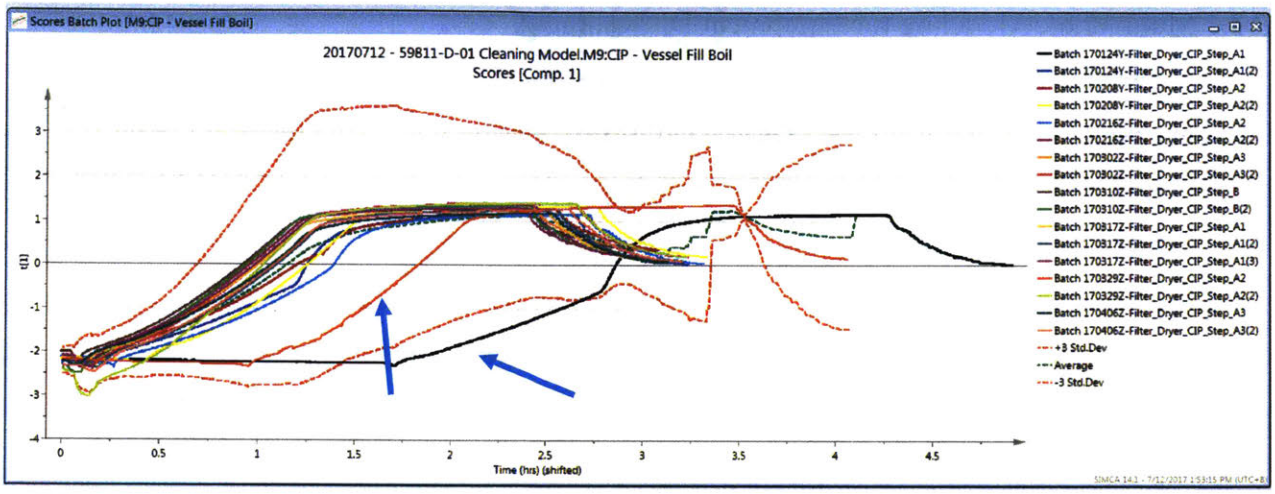


Figure 27: Scores plot for Vessel Fill Boil for Equipment D

If the cleaning processes are validated, multiple iterations of the validated process would be chosen for the model and the output of the model would be taken as is for the monitoring of the process. However, in this case, since the cleaning process evolved over time and there is limited availability of successful cleaning cycles, it was decided to scrutinize the input for outliers and use only data that is representative of the designed process for creating the model. In order to identify all outliers, the Hotelling's T squared test was performed on the model and all underlying inputs to the model. **Figure 28** represents the output of the Hotelling's T squared test on the input data. The batches identified with blue arrows represent the outliers as per the test. These outliers represent iterations where the model will not be able to predict the batch behavior to a sufficient degree of accuracy.

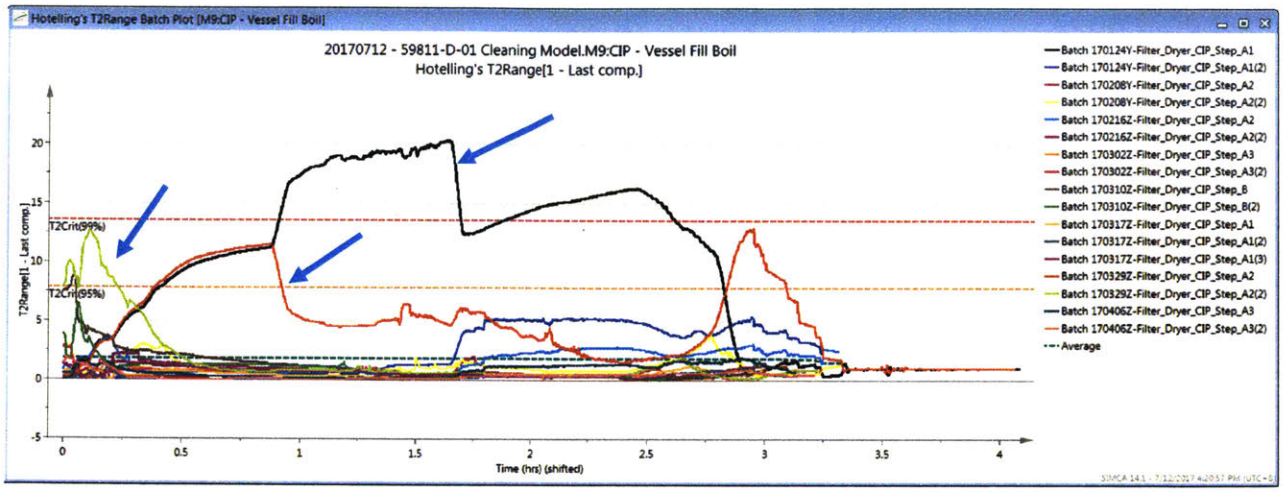


Figure 28: Hotelling's T2 Test on input batches

With the data of 17 iterations, the summary of fit for the multivariate model is shown in **Figure 29**. This plot shows an R^2 Value of 0.6.

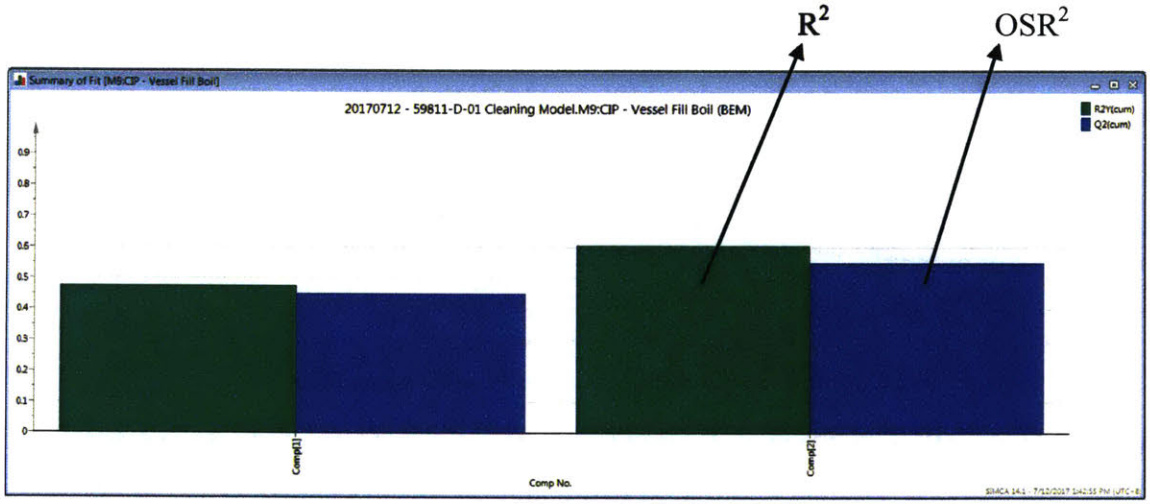


Figure 29: Summary of Fit for Multivariate model of Vessel Fill Boil

After removing the identified outliers, the model was created again and analyzed to identify more outliers, if any. After a few iterations, a best fit model was created with a scores plot as shown in **Figure 30**. It must be noted that this best fit model was eventually based on only six iterations of Vessel Fill Boil after outliers were eliminated

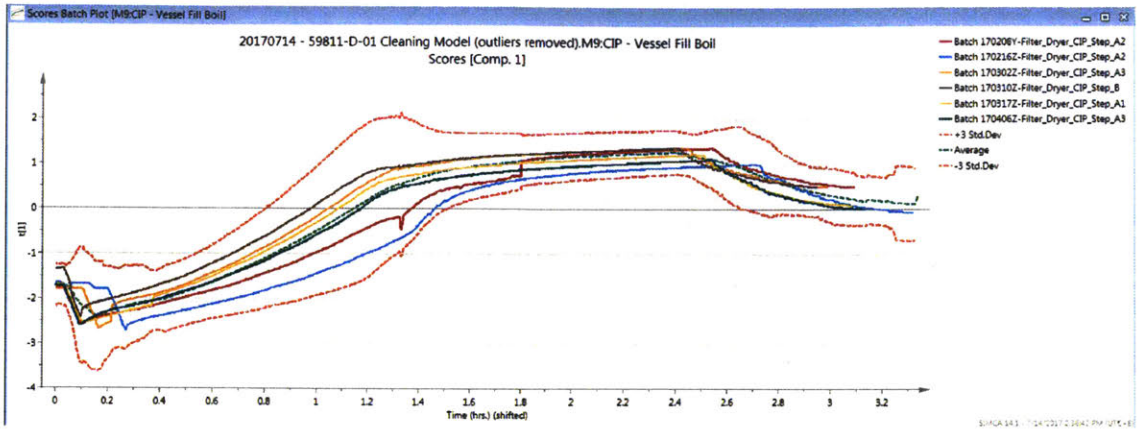


Figure 30: Scores Batch Plot after removal of outliers

The Hotelling's T^2 plot (**Figure 31**) for this best fit model showed all the underlying batches to be within T^2 Critical Range (which is equivalent to the confidence interval defined for the test).

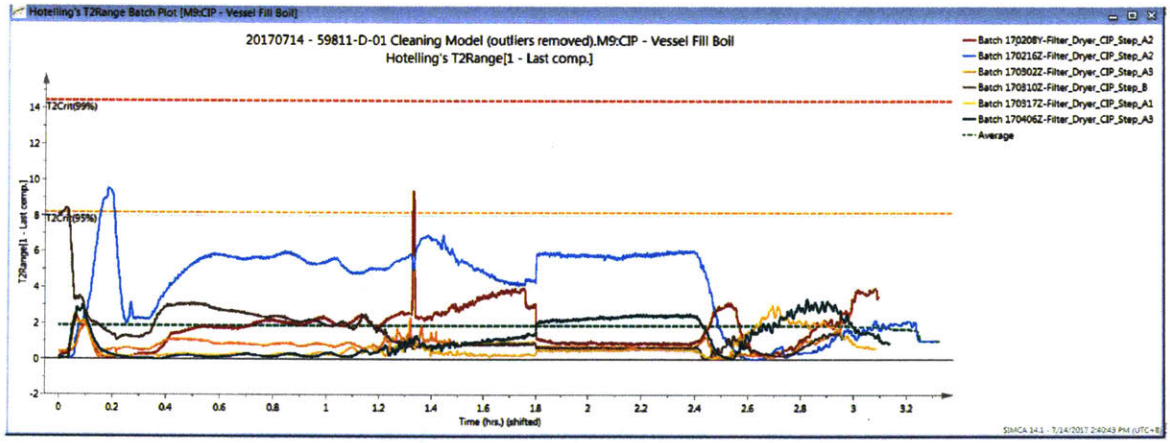


Figure 31:Hotelling's T^2 plot for model after removal of outliers

The summary of fit plot (**Figure 32**) also shows a better R^2 value (~0.72) and better predictive power over the initial model. Despite removal of many outliers, the predictive power of the model is only 70%. This shows the need for more and better-quality data to create a multivariate model with a higher goodness of fit.

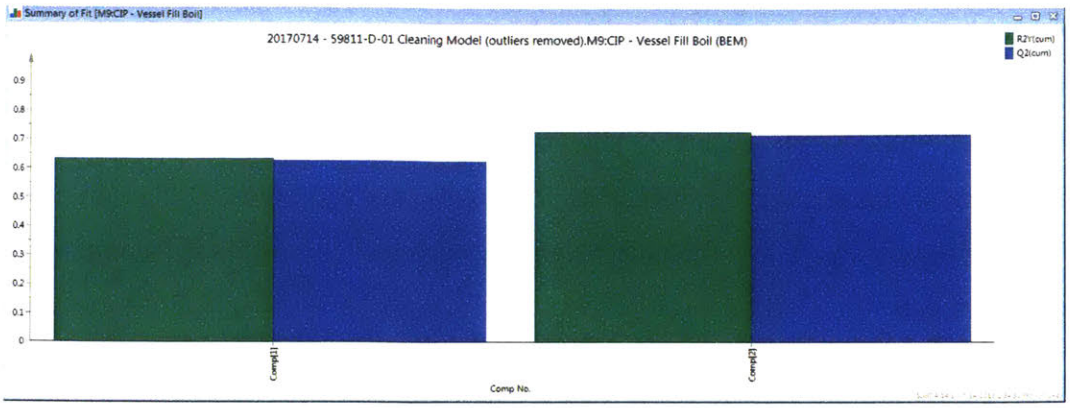


Figure 32: Summary of fit plot for revised model after removal of outliers.

Table 12 lists the coefficients of the test statistic created from the CPPs. Further, **Table 13** shows the correlation matrix for the variables of the vessel fill boil step.

Table 12: Coefficients of the CPPs in the multivariate test statistic

	1	2	3
1	**Var ID (Primary)**	**M9.CoeffCS[2](Time (hrs.))**	**2.44693 * M9.CoeffCS[2](Time (hrs.))cvSE**
2	**$constant**	1.72552	0
3	**Agitator Speed (rpm)**	-0.00540777	0.237012
4	**Filter Dryer Level (L)**	-0.317426	0.143552
5	**Filter Dryer Temp Control (deg C)**	0.716079	0.0914815
6	**Filter Dryer Jacket Temperature (deg C)**	0.111416	0.0537219

Table 13: Correlation Matrix of the CPPs for Vessel Fill boil

Correlation Matrix - M9:CI... × Workset Statistics - M9:CIP - ...

	1	2	3	4	5	6
1		Agitator Speed (rpm)	Filter Dryer Level (L)	Filter Dryer Temp Control (deg C)	Filter Dryer Jacket Temperature (deg C)	Time (hrs.)
2	Agitator Speed (rpm)	1	0.131877	0.237789	0.13911	0.141856
3	Filter Dryer Level (L)		1	-0.0263384	0.369299	-0.185138
4	Filter Dryer Temp Control (deg C)			1	0.744028	0.866048
5	Filter Dryer Jacket Temperature (deg C)				1	0.456223
6	Time (hrs.)					1

This process was repeated for all component steps to create a complete model that represents all process steps. The R^2 value of the models developed for other component steps were found to be lower than that of the Vessel Fill Boil step due to erratic execution over the cleaning cycle development which was highlighted in **4.1 Cleaning Process Stabilization.** It was identified that more and better-quality data from consistent cycle executions will be needed to create a model with better predictive capabilities. With the Phase I SPC in place, upcoming cleaning cycles will be able to provide the data needed to update the model.

Once the multivariate model was created, it was decided to pilot it on the live system where it would plot ongoing cleaning processes against the control chart created by the batch evolution model on SIMCA®. Figure 33 shows a screenshot of a batch being plotted in real time on the multivariate model created for the cleaning process for equipment D. As can be seen in the figure, the ongoing cycle was found to be within statistical control for the component steps visible on the screen.

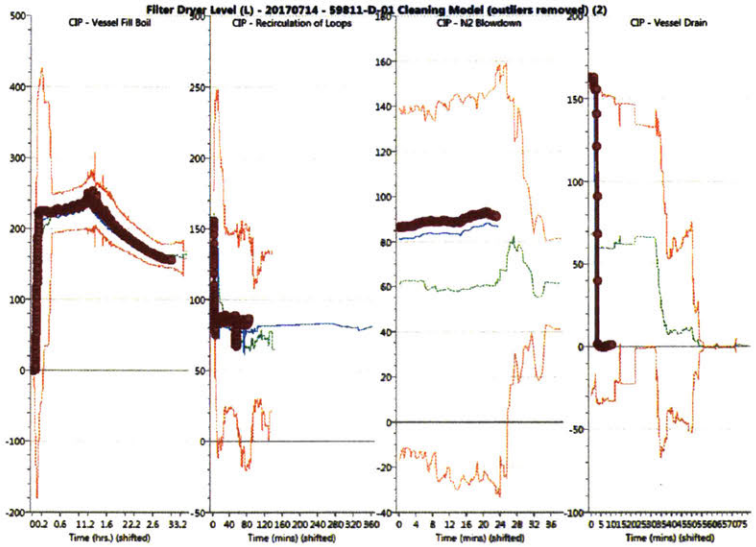


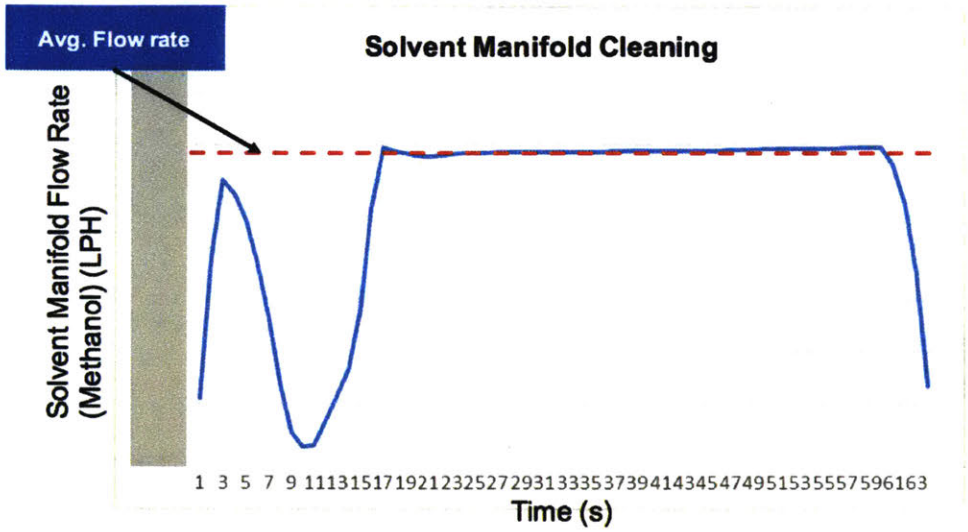
Figure 33: Real time plotting of cleaning cycle in on the multivariate control chart

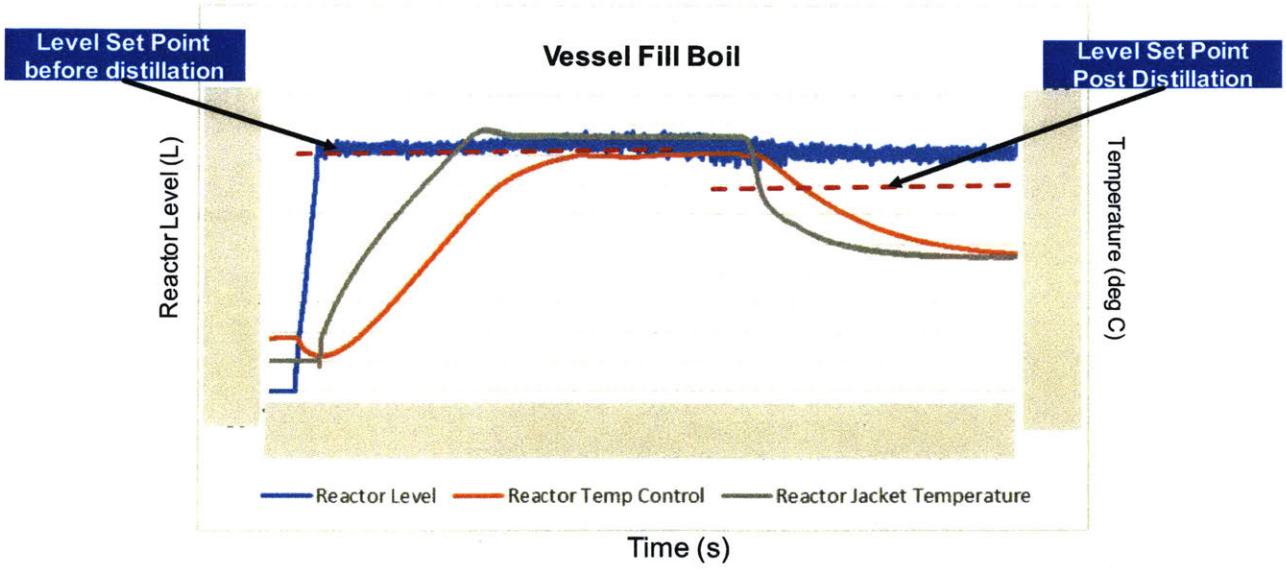
As future opportunity, Amgen should continue collecting data for cleaning cycles that operate within control limits and once sufficient data is available, remodel the process on SIMCA® and implement on the live system to introduce real time multivariate statistical process monitoring on the shop floor. This will enable the site transition from Phase I to Phase II of SPC. Multivariate modeling can be extended similarly to other sites and any manufacturing process requiring control of several critical process parameter for predictive monitoring and control of processes to ensure good quality.

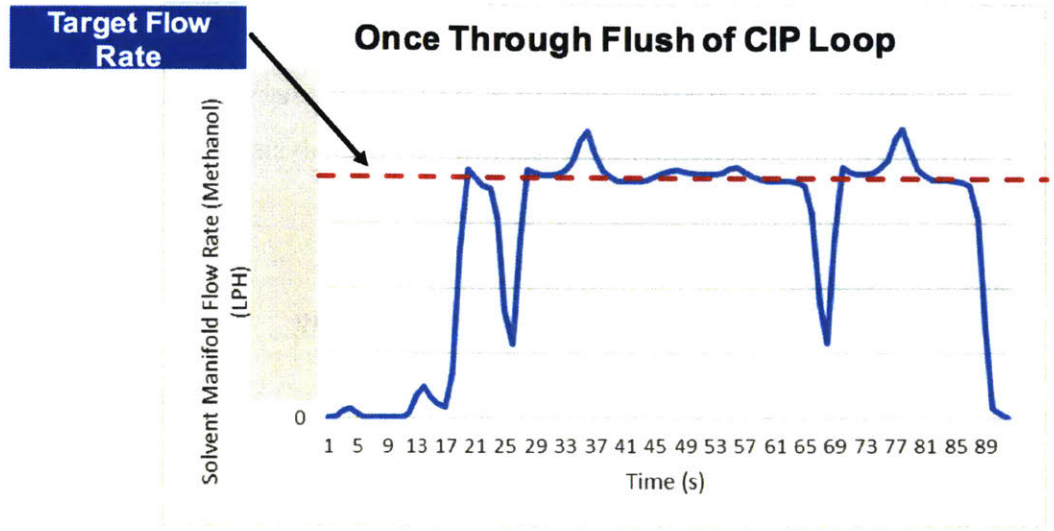
APPENDIX

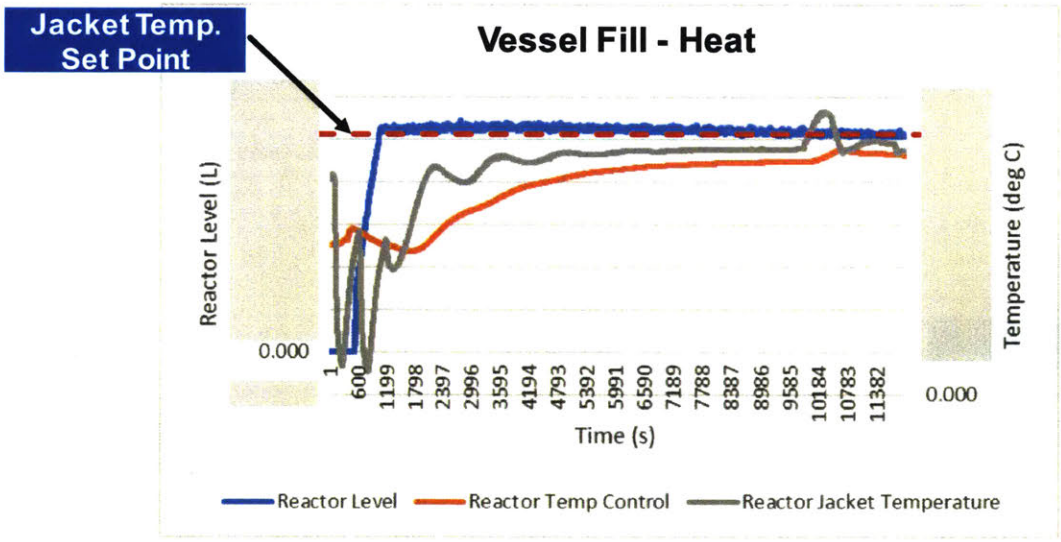
Appendix A: Sample Cases of Cleaning Process Deviation

This section shows cases of process deviation identified from analysis of data from historical cleaning cycles prior to implementation of SPC.






Target Flow Rate
Once Through Flush of CIP Loop
Solvent Manifold Flow Rate (Methanol) (LPH)
0
1 5 9 13 17 21 25 29 33 37 41 45 49 53 57 61 65 69 73 77 81 85 89
Time (s)


Jacket Temp. Set Point
Vessel Fill - Heat
Reactor Level (L)
0.000
1 600 1199 1798 2397 2996 3595 4194 4793 5392 5991 6590 7189 7788 8387 8986 9585 10184 10783 11382
Time (s)
Temperature (deg C)
0.000
Reactor Level
Reactor Temp Control
Reactor Jacket Temperature

Appendix B: Test Protocol for offline testing of implemented automation controls

Table 14: Test Protocol for Automation Logic for Jacket Temperature control during Vessel Fill Boil

Purpose: To test the Jacket Tempterature Control for Fill Boil					
Component Step: Vessel Fill Boil					
Step. No.	Action	Expected Result	Pass / Fail / value	Performed By	Date
1	Test Setup				
1.1	Record the Jacket Temperature Set Point for the phase		N/A		
1.2	Record the minimum jacket temperature for boiling		N/A		
2	Test Case # 1: Jacket Temperature Alarm warning				
2.1	Verify that the Jacket Temperature low alarm is disabled	N/A			
2.2	Set the Jacket Temperature Low alarm limit to lowest temperature		N/A		
2.3	Run the Fill Boil Phase	N/A			
2.4	Allow the phase to complete ramping up to the Jacket Temperature Set point for the phase	N/A			
2.5	Verify that the Jacket Temperature low alarm is enabled	N/A			
2.6	Verify that the Jacket Temperature low alarm is set to the minimum jacket temperature defined for boiling	N/A			
2.7	During the Fill Boil Phase, simulate the jacket temperature to go to values below the minimum jacket temperature	N/A			
2.8	Verify that the system gives a low temperature alarm	N/A			
2.9	Verify that the Jacket Temperature low alarm is enabled during reflux and distillation	N/A			
2.10	Verify that the Jacket Temperature low alarm is disabled at start of cool down	N/A			
2.11	Allow the phase to end normally	N/A			

Table 15: Test Protocol for Automation Control Logic of Agitator speed

Purpose: To test Agitation Speed Control Logic					
Component Step: Vessel Fill Boil, Recirculation of CIP Loops , N2 Blowdown of CIP Loops					
Step. No.	Action	Expected Result / current value	Pass / Fail	Performed By	Date
1	Test Setup				
1.1	Verify the default settings of the following parameters Agitator speed hold time during ramp up Agitation speed stabilization time Agitation Speed hold time during operation	N/A 120 sec 10 sec 30 sec	N/A		
1.2	Record the agitation speed set point from recipe		N/A		
2	Test Case # 1: Agitation Speed Not Established Time out				
2.1	Simulate the agitation speed to a value lower than 90% of the Agitation Speed Set point from recipe. Record the value		N/A		
2.2	Run the Fill Boil Phase	N/A			
2.3	Allow the phase to complete the filling step	N/A			
2.4	Verfiy that the phase goes on hold after the agitator speed hold time during ramp up expires	N/A			
3	Test Case # 2: Agitation Speed Fluctuation timeout				
3.1	Set the agitation speed stabilization time to 999 sec	N/A			
3.2	Restart the phase	N/A			
3.3	Simulate the agitation speed to a value greater than 90% of the agitation speed set point from recipe. Record the value		N/A		
3.4	Before agitation speed stabilization timer expires, simulate the agitation speed to a value lower than 90% of the agitation speed set point. Record the value		N/A		
3.5	verify that the phase goes on hold after the agitator speed hold time during ramp up expires	N/A			
4	Test Case # 3: Agitation Speed establish timer				
4.1	Set the agitation speed stabilization time to default	N/A			
4.2	Restart the phase	N/A			
4.3	Simulate the agitation speed to a value greater than 90% of the agitation speed set point from recipe. Record the value	N/A			
4.4	Verify that the phase timer waits for agitation speed to be achieved and stabilized before it starts	N/A			
4.5	Verify that the phase waits for agitation speed to be stabilized before heating starts for fill boil phase	N/A			
5	Test Case # 4: Loss of agitation speed during Vessel Fill and Boil				
5.1	restart the phase and allow the agitation speed to ramp up, stabilize and let the boil phase start		N/A		
5.2	Simulate the agitation speed to a value greater than 90% of the agitation speed set point from recipe. Record the value	N/A			
5.3	Verify that the phase goes on hold after the Agitation Speed hold time during operation expires	N/A			
5.4	Restart the phase and allow the phase to end normally	N/A			

Table 16: Test Protocol for Automation Control logic of Batch Temperature

Purpose: To test the automation Logic for controlling Batch Temperature					
Component Step: Recirculation of CIP Loops,					
Step. No.	Action	Expected Result / current value	Pass / Fail	Performed By	Date
1	Test Setup				
	Verify the default settings of the following parameters	N/A	N/A		
1.1	Hold timer for Temperature ramp up / ramp down process	120 sec			
	Batch Temperature stabilization timer	10 sec			
	Hold timer during recirculation	30 sec			
1.2	Record Batch Temperature Set point for recirculation		N/A		
1.3	Record the batch temperature control range around set point		N/A		
2	Test Case # 1: Batch Temperature out of limits (UCL) briefly				
2.1	Run the Clean CIP Phase	N/A			
2.2	Allow the phase to proceed to CIP recirculate and start CIP timer	N/A			
2.3	Simulate batch temperature > UCL. Record the value		N/A		
2.4	Verify that the CIP phase timer is paused when the batch temperature is out of limits.	N/A			
2.5	Before the hold timer during recirculation expires, simulate batch temperature to come within the control limits		N/A		
2.6	Verify that the CIP phase timer resumes from where it paused	N/A			
3	Test Case # 2: Batch Temperature out of limits (LCL) briefly				
3.1	Simulate batch temperature to a value < LCL. Record the value		N/A		
3.2	Verify CIP phase timer is paused when the batch temperature is out of limit.	N/A			
3.3	Before the hold timer during recirculation expires, simulate batch temperature to come within the control limits		N/A		
3.4	Verify that the CIP phase timer resumes from where it paused	N/A			
4	Test Case # 3: Loss of Batch temperature (UCL)				
4.1	Simulate the batch temperature to be > UCL. Record the value		N/A		
4.2	Verify that the phase goes on hold after hold timer during recirculation expires	N/A			
4.3	Simulate batch temperature to come within the control limits		N/A		
4.4	Restart the Phase	N/A			
5	Test Case # 4: Loss of Batch Temperature (LCL)				
5.1	Simulate the batch temperature to be <LCL. Record the value		N/A		
5.2	Verify that the phase goes on hold after hold timer during recirculation expires	N/A			
5.3	Simulate batch temperature to come within the control limits		N/A		
5.4	Restart the Phase	N/A			

Table 17: Test Protocol for Automation Control of N2 Blow of CIP loops

Purpose: To test the automation Logic for N2 blow of CIP loops					
Component Step: N2 Blowdown of CIP Loops					
Step. No.	Action	Expected Result / current value	Pass / Fail	Performed By	Date
1	Test Setup				
1.1	Record the 2 bar N2 distribution pressure indicator Low Alarm Limit		N/A		
2	Test Case # 1: Loss of N2 Pressure During CIP blow				
2.1	Ensure the 2 bar N2 distribution pressure is above low limit. Record the value		N/A		
2.2	Run the N2 Blow of CIP loops phase	N/A			
2.3	Allow the phase to start N2 Blow	N/A			
2.4	Simulate the 2 bar N2 distribution pressure to a value lower than its low alarm limit. Record the value		N/A		
2.5	Verify that the phase goes to hold immediately	N/A			
2.6	Simulate the 2 bar N2 distribution pressure to a value higher than its low alarm limit. Record the value		N/A		
2.7	Verify if the phase restarts and allow the phase to end normally	N/A			

Table 18: Test Protocol for Automation logic for Vessel Drying

Purpose: To test the automation Logic for controlling Jacket Temperature and Vacuum					
Component Step: Vessel Drying					
Step. No.	Action	Expected Result / current value	Pass / Fail	Performed By	Date
1	Test Setup				
1.1	Record the Jacket temperature set point for drying		N/A		
1.2	Record the Jacket temperature control limits around the set point		N/A		
1.3	Record the Vacuum pressure set point for drying		N/A		
1.4	Record the Vacuum pressure control limits around the set point		N/A		
2	Test Case # 1: Jacket Temperature out of limits				
2.1	Run the Vessel Drying Phase	N/A			
2.2	Allow the phase to start drying	N/A			
2.3	simulate the jacket temperature to value lower than the LCL. Record the value		N/A		
2.4	Verify that the drying timer is paused when the jacket temperature is lower than the LCL for drying	N/A			
2.5	Verify that a warning message appears to notify operator of low jacket temperature	N/A			
2.6	Simulate the jacket temperature to value higher than the LCL and within control limits. Record the value		N/A		
2.7	Verify that the drying timer resumes when jacket temperature is within control limits	N/A			
3	Test Case # 2: Loss of vacuum during drying				
3.1	Simulate the vacuum pressure to be higher than the UCL. Record the value		N/A		
3.2	Verify that the drying timer is paused when the Vacuum pressure is >UCL		N/A		
3.3	Verify that a warning message appears to notify operator of loss in vacuum	N/A			
3.4	Simulate the vacuum pressure to be lower than UCL. Record the value		N/A		
3.5	Verify that the drying timer resumes when vacuum pressure is within control limits	N/A			
3.6	Allow phase to end normally	N/A			

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