Improvement and automation of cleaning processes in the Pharmaceutical Industry

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Thesis to obtain the Master of Science Degree in

Chemical Engineering

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December 2020

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“Aquele que anda com os sábios será sábio; o que acompanha os insensatos tornar-se-á mau como eles.”

– Provérbios 13,20

"Progress cannot be generated when we are satisfied with existing situations."

– Taiichi Ohno

Agradecimentos/Acknowledgements

A realização desta Dissertação de Mestrado só foi possível graças a determinadas pessoas e entidades, às quais quero de seguida agradecer.

Primeiro, aos meus orientadores da The Company, o Eng. Tiago Faria e o Dr. Pedro Felizardo, por, no meio de todas as atividades e agendas apertadas dos seus cargos, terem tido sempre tempo para esclarecer todas as minhas dúvidas e ouvir todas as minhas ideias.

À Engª Mafalda Rodrigues, por toda a paciência dispensada a conduzir-me pelas instalações e abertura para ouvir as minhas sugestões. Às Engªs Inês Fabela e Mónica Duarte, pelas formações sobre metodologias A3 e tipos de mapeamentos. Não me esqueci de nada.

Aos diretores e líderes de equipa das reuniões mensais, José Melo, Jorge Pastilha, Felipe Vicente e Claúdio Rebelo pelas sugestões e conselhos fornecidos. À colega da equipa de excelência operacional, Bruna Cunha, pela iniciativa própria em me elucidar sobre as metodologias usadas pela empresa.

À minha antiga colega de curso, Catarina Reis, por se ter esforçado para que eu me integrasse sem atritos na cultura e modo de funcionamento da empresa. Este estágio foi uma extraordinária experiência em grande parte devido a esse seu esforço inicial. Ao Diogo Marques e Diogo Matias por terem sido uma companhia indispensável no meio de uma pandemia e situação social sem precedentes, tornaram o meu estágio simultaneamente produtivo e agradável.

Ao meu mentor Sebastião Thomaz, pelas inúmeras reuniões sobre o meu futuro como jovem engenheiro e o mercado de trabalho. É em grande parte pelos frutos dessa amizade formada que esta oportunidade pode ser aproveitada.

À empresa The Company, pelo incrível padrão que estabelecem como multinacional portuguesa. Consegui sentir o seu orgulho e ambição durante todos os cinco meses do estágio. A dedicação mostrada em me integrar fez-me sentir um membro da equipa desde o primeiro dia. Espero ter contribuído.

Ao Instituto Superior Técnico, pelos 5 anos de maior crescimento pessoal e educativo da minha vida, pelas amizades e ensinamentos. À minha orientadora Profª. Dra. Cristina Fernandes, que forneceu um contributo inestimável para a produção desta tese. A qualidade da sua orientação é um reflexo vivo do estatuto da nossa universidade.

Por último e acima de tudo, aos meus pais por tudo o que sacrificaram para eu poder estar onde estou. Ao meu pai, pelas oitenta horas semanais de trabalho para me possibilitar estudar onde estudei e pelas inúmeras conversas e lições de vida ao longo dos anos. À minha mãe, por todo o carinho desde criança e por me ter incutido de uma autoestima intuitiva que só alguém com uma enorme virtude maternal consegue incutir.

Abstract

The cleaning process in-between production batches in multi-purpose pharmaceutical industries is an ongoing challenge since it represents downtime where value is not being produced to the customer.

This thesis aimed to provide tools which promote the continuous improvement of the cleaning process of a specific spray-dryer unit, SD1.

The Standard Work Methodology was applied, and the Cleaning Procedures were investigated to uncover the Top 3 Time-Consuming Operations and the Top 3 Sources of Variability. A Register Sheet was coupled with a Swimlane Map Continuous Improvement Tool to allow for the proper quantification of the cleaning operations and provide an automatic treatment of the collected data. A Suggestions Sheet was created to allow the operators to give feedback regarding the inaccuracies in the Cleaning Procedures and propose suggestions for improvement.

A Continuous Improvement Loop was developed based on the two tools provided, the Register Sheet and the Suggestions Sheet, to tackle both of the identified problems: the impossibility of quantification of the cleaning operations and the lack of opportunity for the operators to give feedback regarding the Cleaning Procedures.

The study on the potentiality of automated cleaning processes revealed that a decrease in the lead time of 36% could be achieved due to the parallelization of operations and the use of an extra CIP Tank. The Master Batch Recipe also promotes variability reduction since the control system performance is not relying on the operator's proficiency with DeltaV which leads to a positive impact on predictability.

Keywords: CIP, Swimlane Map, Standard Work, Automation, Pharmaceutical Industry

Resumo

O processo de limpeza entre os lotes de produção em indústrias farmacêuticas multiproduto é um desafio contínuo, pois representa tempo de inatividade em que não se produz valor para o cliente.

Esta tese teve como objetivo fornecer ferramentas que promovam a melhoria contínua do processo de limpeza de uma instalação específica de spray-drying, SD1.

O Standard Work foi aplicado e os Procedimentos de Limpeza foram investigados para descobrir as Top 3 Operações Consumidoras de Tempo e as Top 3 Fontes de Variabilidade. Uma Folha de Registo foi acoplada ao Mapeamento Swimlane para permitir a quantificação das operações de limpeza e automatizar o tratamento dos dados. Criou-se uma Folha de Sugestões para permitir que os operadores deem feedback sobre as imprecisões nos Procedimentos de Limpeza e proponham sugestões de melhorias.

Um Loop de Melhoria Contínua foi desenvolvido com base nas duas ferramentas fornecidas, a Folha de Registo e a Folha de Sugestões, para resolver ambos os problemas identificados: a impossibilidade de quantificação das operações e a falta de oportunidade para os operadores darem feedback sobre os Procedimentos de Limpeza.

O estudo da potencialidade da automação do processo de limpeza revelou que uma redução no lead time de 36% poderia ser alcançada devido à paralelização das operações de limpeza e ao uso de um Tanque CIP extra. A automação também promove a redução da variabilidade, uma vez que o desempenho do sistema de controle não depende da proficiência do operador com o DeltaV o que conduz a um impacto positivo na previsibilidade.

Palavras-chave: CIP, Mapeamento Swimlane, Standard Work, Automação, Indústria Farmacêutica

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List of Acronyms

API – Active Pharmaceutical Ingredient

BVA – Business-Value-Added

CBB – Cleaning Between Batches

CDMO – Contract Developing and Manufacturing Organization

CIP – Clean-In-Place

COL – Change of Line

COP – Clean-Out-Of-Place

CV – Coefficient of Variation

FDA – U.S. Food and Drug Administration

GMP, cGMP – (current) Good Manufacturing Practice

HEPA – High-Efficiency Particulate Arrestance

JIT – Just-In-Time

NVA – Non-Value-Added

OEE – Overall Equipment Effectiveness

PSD – Particle Spray-Dryer

QA – Quality Assurance

QC – Quality Control

R – Reactor

SD – Spray-Dryer

SLR – Systematic Literature Review

SMED – Single Minute Exchange of Die

TPS – Toyota Production System

VA – Value-Added

VSM – Value-Stream Map

1 Introduction

1.1 Relevance

The cleaning of equipment in chemical processes is an essential part of every multi-purpose industry for economic and legislative reasons, even more so in the pharmaceutical industry, where the regulation and implementation of GMPs, Good Manufacturing Practices, are more demanding than in other industries.

The Company sells products and services, operating as a CDMO – Contract Developing and Manufacturing Organization – providing service to lab-scale companies to convert their drug substance, an API (Active Pharmaceutical Ingredient), into a drug product (a pill or an inhalable powder, for example) in large scale. In this situation, The Company charges the service for days of the occupation of their equipment.

The longer the product takes to be developed in The Company's installations, the costlier it will be for the client. The Company also sells its products developed from the API until the drug product. In this case, The Company sells a product and not a service. The cost is directly related to the amount of product produced that translates into the amount of product sold, and not days of the occupation of the equipment. The more time is spent cleaning the installation; the less time is available to produce.

With this perspective, the importance of having an effective and efficient cleaning process becomes apparent. When it comes to productivity and profit, the cleaning time is downtime.

Besides the economic motives, there are other imperative standards to maintain that require an effective cleaning process. Among them, maintaining product quality, for which the cleaning process contributes by removing trace ingredients from the previous batch and preventing them from contaminating the next batch, a crucial reason for multi-purpose installations.

The cleaning process also prevents equipment malfunction caused by an accumulation of solid residues; it provides a clean surface for sanitization – sterile filth is as desirable as unsterile filth [1] – since surfaces cannot be sanitized if they are not thoroughly cleaned first. Moreover, it enhances worker safety by providing a clean working environment and smoothly functioning equipment.

1.2 Scope

It was within the scope of this thesis the mapping of the cleaning process for a specific spray-drying unit, SD1, and to provide insights on how the cleaning operations could be improved.

One of the most significant challenges to be overcome by The Company is the reproducibility of the cleaning process, in other words, to eliminate the variability in the lead time of different cleaning processes and the sequencing of the cleaning operations. As such, The Company is striving towards automation. By reducing the human interaction with the equipment, the variability between cleaning processes is reduced.

Due to this, the last goal of this dissertation was to design the ideal standardized sequence of how to perform the cleaning operations, taking into consideration the advantage of an automated cleaning system, leading to process improvement and variability reduction, which leads to a positive impact on predictability.

1.3 Chapters Overview

This dissertation is organized as follows:

- **Chapter 2 – Literature Review:** a systematic literature review on the history of Lean Manufacturing and Continuous Improvement Tools which aid the present work is exhibited;
- **Chapter 3 – Spray-Drying Cleaning Process and Current Situation:** presents a brief description of the Spray-Drying Production Process, Cleaning Methodology and Cleaning Documentation; highlights the current situation – lead time and variability – of the cleaning process of SD1;
- **Chapter 4 – Investigation and Improvement of the Cleaning Process:** shows the conducted investigation on the SD1 operator's feedback regarding the cleaning operations, as well as the conclusions drawn after extracting data from the Cleaning Documentation; exhibits the developed Swimlane Map Continuous Improvement Tool that automatically treats the collected data and identifies the Top 3 Time-Consuming Operations and the Top 3 Sources of Variability; along with the proposed Continuous Improvement Loop to promote the SD1 operators and engineer's engagement with the improvement of the cleaning process' operations;
- **Chapter 5 – Cleaning Process – Auto-Mode vs Batch-Mode:** an evaluation of the potential of parallelization of the cleaning operations leading to a shorter lead time with an automated cleaning system is performed;
- **Chapter 6 – Conclusions and Future Work:** the main conclusions obtained in this work and recommendations for future work are exposed.

2 Literature Review

This dissertation was produced in a corporate context; as such, the majority of the tools and subjects were taught in training or were available in The Company's manuals.

Nonetheless, a literature review was conducted to assess the work that researchers and practitioners have done in the related fields that could help discover new methods which may apply to the present work.

The following topics will be covered in order: the systematic literature review principle followed during the research, lean manufacturing, lean tools, process mapping, Good Manufacturing Practices, types of cleaning and automation.

2.1 Structure of the Review

The systematic literature review (SLR) principles were adopted to promote an effective literature review [2]. In which is included: a careful planning of the review and searching the literature, and an adequate screening process considering the scope of the dissertation.

2.1.1 Planning the Review

The literature search included articles and books. The most efficient way of searching the literature is using electronic databases [3]. Therefore, the search relied on search engines such as Elsevier Science Direct, Emerald, Google Scholar and Google Books. For articles, the search was conducted using the set of primary keywords indicated in Table 2.1. A set of secondary keywords was combined with the set of primary keywords using the Boolean connector "AND" to achieve narrower results. To get a recent picture of the state-of-the-art only papers between 2010 and 2020 (both inclusive) were researched.

Table 2.1: Structure of the literature review for articles.

Period of Publication	Electronic Databases	Primary Keywords	Secondary Keywords
2010 – 2020	Elsevier Science Direct Emerald Google Scholar	Lean manufacturing Continuous improvement SMED Pharmaceutical Industry Clean-In-Place Automation	Pharmaceutical Industry Change-over Sources of variability Process mapping

Once articles were reviewed, other cited articles were added following the principle of snowballing [4].

Since books provide a more comprehensive explanation regarding each subject, it was not necessary to categorize the keywords into primary and secondary sets, Table 2.2.

Table 2.2: Structure of the literature review for books.

Period of Publication	Electronic Databases	Keywords
All-time	Google Books Elsevier Science Direct	Toyota lean Clean-in-place SMED Process mapping Automation

2.1.2 Screening

Research articles were examined by title, abstract and keywords. The review determined research inclusion and exclusion criteria to ensure reliability and comprehensiveness. These criteria are critical to the quality assessment of papers [5]. By this means, all articles that met the inclusion criteria were selected.

Articles or books not belonging to the following areas of research were excluded: management, manufacturing, industrial engineering and operations research.

2.2 Lean Manufacturing

2.2.1 Historical Context

To better understand the concept of lean manufacturing, an historical analysis of the Toyota Production System (TPS) – Toyota's manufacturing system and the lean manufacturing precursor – must be done.

Toyota's story started in 1926 when Sakichi Toyoda founded the Toyoda Automatic Loom Works. Toyoda wanting to relieve his family of the punishing labour of the spinning and weaving with manual looms set out to develop power-driven wooden looms. Toyoda's relentless tinkering and inventing resulted in sophisticated automatic power looms [6][7]. A mechanism to automatically stop a loom whenever a thread broke would evolve into a broader system called Jidoka that became one of the two pillars of the TPS [6]. Jidoka can be described as "autonomation": automated machines capable of detecting a single defective part and immediately fix the problem or stop themselves while sending an alarm [8]. Jidoka allows workers not to be tied to machines and frees them to perform value-added work [6].

In 1937, Kiichiro Toyoda, Sakichi's son, established The Toyota Motor Corporation as an independent fork of his father's company [9]. Influenced by the United States of America supermarket system of replenishing products on the shelves just in time as customers purchased them, Kiichiro's contribution to the TPS would be the Just-in-time (JIT) principle: delivering what the customer wants, when it is wanted, and the amount it is wanted [6].

After World War II, a collapse in sales forced Toyota to end a large part of the workforce. After a tour to U.S plants, Toyota's president Eiji Toyoda gave plant manager Taiichi Ohno the task to improve Toyota's manufacturing process productivity to match that of Ford [6]. Given Japan's post-war economy and its auto market smaller consumer demand, Toyota could not afford to mimic Ford's mass production system; it needed to adapt Ford's manufacturing process to achieve simultaneously flexible, high quality, low cost and with short production times.

Taiichi Ohno's solution to this problem was the absolute elimination of waste in the manufacturing process. Contrary to the U.S. plants approach of enhancing productivity by producing faster, Ohno realized that there were activities in the processes that did not add any value to the final product, for example, overproduction and waiting times. In the TPS, taking out Non-Value-Added, NVA, activities – that is, activities the customer is not willing to pay for – is much more important than speeding up individual Value-Added, VA, activities – that is, activities the customer is willing to pay [9].

With this, the basis for the TPS becomes clear: founded out of necessity, seating in the Jidoka and JIT principles laid by Sakichi and Kiichiro, an approach designed to provide a flexible, high-quality system aimed at reducing all Non-Value-Added activities through the attentiveness in the shop floor and creating a culture of continuous improvement.

In 1988, John F. Krafcik coined the term "lean" in his article *Triumph of the Lean Production System* [10]. The term would be made popular in the two best-selling books *The Machine That Changed the World* [11] and *Lean Thinking* [8].

2.2.2 Lean Wastes

In the original Japanese, *Muda* refers to any activity that does not add value to the customer. Ohno was the first to identify the seven major types of NVA activity:

1. **Overproduction:** producing items for which there is no order. It results in overstaffing and storage. Taiichi Ohno considered that overproduction was the organic waste since it causes the other types of waste [12].
2. **Waiting:** this waste affects both goods and workers. Involves standing around waiting for the next processing step or workers merely having no work because of equipment downtime or lot processing delays, for example.
3. **Unnecessary transport:** carrying work in progress for long distances, moving materials or finished goods in or out of storage.
4. **Over-processing:** taking unnecessary steps to process the parts. Inefficient processing due to inadequate tools and process design.
5. **Excess inventory:** excess raw material, work in progress or finished goods causing longer lead times, transportation and storage costs. Extra inventory also hides problems such as production imbalances, equipment downtime and long setup times.

6. **Unnecessary movement:** any wasted motion the employees have to perform during their work. Walking is a waste.

7. **Defects:** production of defective parts is waste. It implies wasted material, repair actions, inspection handling and effort.

Some literature referencing lean manufacturing has included an 8th waste: the unused talent and creativity of workers [8]. It is essential to note that this 8th waste is not part of the TPS due to not being directly connected to the production process.

2.2.3 Lean Tools

There is a myriad of tools at disposal to identify, quantify and eliminate waste in a process [13].

The most relevant to the scope of this thesis are:

- **A3 Problem Solving:** a method to succinctly and precisely describe an entire project in an A3 sized page (hence the name). A problem-solving A3 can concisely state the problem, document the current situation, assess the root cause, propose alternative solutions, and have a cost-benefit analysis. This was the tool used to present the monthly status of the work to The Company's Operational Excellence Team;

- **Gemba Walks:** Japanese for "the place where the work gets done". In manufacturing, Gemba is the factory floor. The reasoning behind Gemba Walks is that the engineer must go to the shop floor to get an accurate and realistic understanding of the processes and problems of a given plant;

- **OEE:** abbreviated from "Overall Equipment Effectiveness", a framework for measuring the efficiency and effectiveness of a process. The OEE is calculated by multiplying its three constituent components: the equipment's availability, performance and production quality.

$$OEE = Availability \times Performance \times Quality$$

  The OEE provides a standardized method of benchmarking progress. It identifies the percentage of manufacturing time that is genuinely productive. An OEE of 100% implies manufacturing only decent parts, as fast as possible with no stop time; it means 100% quality, 100% performance and 100% availability. The improvement of the cleaning process increases the availability of the equipment;

- **SMED:** abbreviated from "Single-Minute Exchange of Die", and deeply discussed in [14]. It started with Shigeo Shingo challenge to reduce setup times to a single-digit time, that is, less than 10 minutes. SMED's brilliance involves converting internal tasks (performed while the equipment is stopped) to external tasks (performed while the equipment is running);

- **Standard work:** standardized work is the safest, easiest and most waste-free way of performing a process that we currently know. Its reasoning consists in organizing operations in the best

sequence to make the most out of human resources, equipment tooling and materials. As such, the standard work methodology is the baseline of continuous improvement. It is implemented by having standardized instructions and a commitment between the leader and team members to follow the given instructions [15]. There are several layers to the implementation of standard work, based on the level of detail of the procedure (see Figure 2.1);

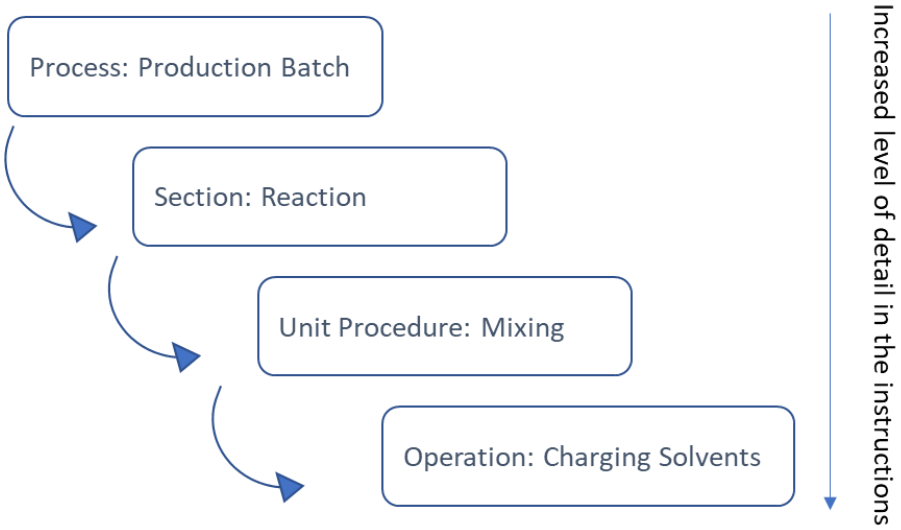

Figure 2.1: Example of application of the Standard Work methodology.

- **Continuous Improvement Loop:** abbreviated “CI Loop”, recurring meeting to assess the current status of the process, analyze the most critical operations and discuss possibilities of improvement;
- **5S:** useful to create and maintain an organized, clean, safe and high-performance workplace. It consists of applying five steps in order: sort, set in order, shine, standardize and sustain. Useful for the organization of tools;
- **5 Whys:** first described by Taiichi Ohno [12]. It consists of asking why five times when a problem arises. By asking why five times the apparent symptoms can be overridden, and it is possible to uncover the root cause.

2.2.4 Process Mapping

Process mapping is an essential lean tool to identify and quantify the most time-consuming tasks and sources of variability in a process. These tools help to diagnose and improve work by the identification of the current workflow. Due to its relevance for this dissertation, a separate section is dedicated to this tool.

The two most relevant types of process maps for the scope of this dissertation are presented: the Value-Stream Map (VSM) and the Cross-Functional Map.

Value-Stream Map (VSM)

The Value-Stream Map, VSM, captures all vital flows of work, information and materials in a process, as well as essential process metrics to aid in the assessment of the Value-Added activity, VA, and the Non-Value-Added activity, NVA. An example of a VSM is displayed in Figure 2.2.

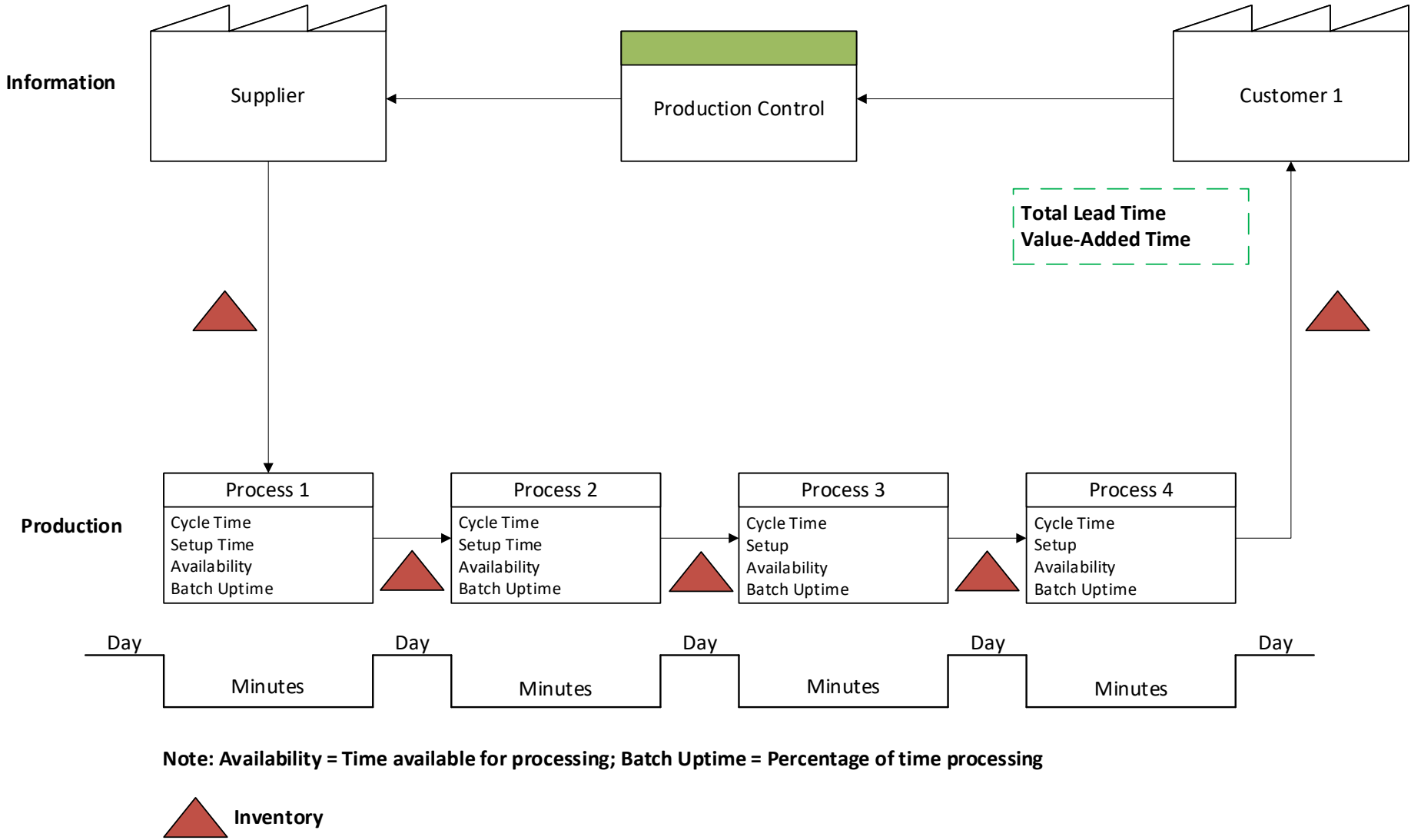

Figure 2.2: Generic example of a Value-Stream Map.

The VSM covers the process starting with the customer's ordering until the delivery of the order to the customer.

The production control receives the demand from the customer and orders the raw materials necessary from the supplier. After receiving the raw materials, these will undergo several processes until they become the delivered product the customer ordered. In each of those processes, the following metrics are typically measured:

- **Cycle Time:** the time each process needs to produce one unit of the product;
- **Setup Time:** the time between the end of processing one product to start producing a different product. For example, the time necessary to set up the equipment;
- **Availability:** the time or percentage of time in which the machine is available to produce;
- **Batch Uptime:** the time the machine spends processing without producing defective units;
- **Lead Time:** the time it takes to prepare the material, produce the product and transport it to the customer [13].

The VA time corresponds to the activities of the VSM that the customer is willing to pay for, and that process the inventory correctly in the first time.

Cross-Functional Map

The Cross-Functional Map illustrates the workflow in organizations. Displays the set and series of interrelated work activities and resources that follow a distinct path as work inputs (resources) get transformed into valuable outputs (items). The name "cross-functional" is given since the workflow "crosses" several functions or organizational entities. An example of a Cross-Functional Map is exhibited in Figure 2.3.

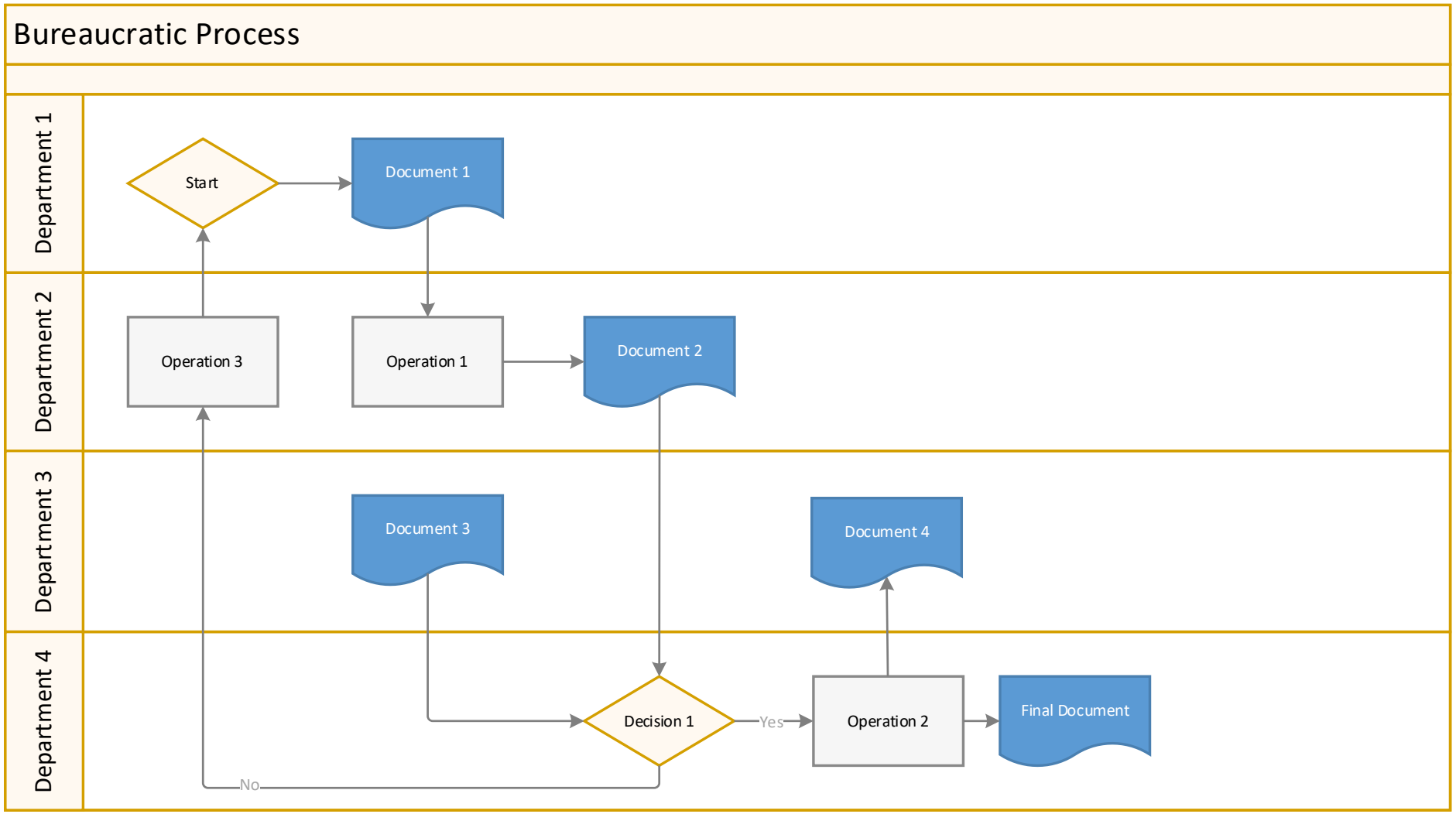

Figure 2.3: Generic example of a Cross-Functional Map for a Bureaucratic Process.

In Figure 2.3, a generic example of a Cross-Functional Map illustrates the interaction of the workflow with the different functions.

The Cross-Functional Map also receives the nickname "Swimlane" Map due to the pattern of the horizontal bands resembling the lanes of a swimming pool. The nickname "Swimlane" is used more often to refer to maps of manufacturing procedures, where "Cross-Functional" is mostly used to describe bureaucratic process maps.

2.3 Good Manufacturing Practices (GMPs)

Good Manufacturing Practices, GMPs, or current Good Manufacturing Practices, cGMPs, are the regulations imposed by authorities (e.g., FDA) to ensure the quality, safety and efficacy of the products and to minimize the risks involved in the pharmaceutical production in any step of the process and distribution [16].

GMPs comprehend support to manufacturing, frequent sanitization, in-process controls to safeguard quality and reliability, validation of samples, well-defined documentation, frequent inspections and audits, among others.

The main goal is to avoid possible external contamination or cross-contamination to prevent problems in product quality and consumer health.

In pharmaceutical processes, even a small change can be GMP relevant, which results in the involvement of various stakeholders beyond operation, an example being the Quality Assurance Department, abbreviated QA. These regulations make it challenging to implement lean practices and are a considerable constraint that slows down the continuous improvement of the processes.

2.4 Cleaning Process

The cleaning process goal is to remove previous product traces of the equipment before the start of the next production batch. As such, the cleaning process should not be approached as the last step of a batch manufacturing process since the cleaning has no impact on the quality of the batch for which the cleaning is performed [16]. Instead, it is the first step in the manufacture of the next product since it can considerably impact safety and efficacy.

2.4.1 Types of Cleaning

When it comes to cleaning processes, two types of cleaning are available: Clean-Out-of-Place (COP) and Clean-In-Place (CIP).

COP – Clean-Out-of-Place

Clean-Out-Of-Place (COP) or manual cleaning is accomplished by disassembling the equipment to perform manual washing and rinsing. It is not useful for large installations, and it is susceptible to variation due to the inherent variability of the human factor.

CIP – Clean-In-Place

CIP means that the cleaning of the equipment occurs with the installation setup has it is, where water, detergent solutions or solvents flow through the pipes and equipment with a predetermined pressure, velocity and sequencing in a way that is intended to guarantee effective cleaning.

In CIP, while operator training is essential, it is secondary to the process equipment and design [17].

The cleaning process at The Company is a hybrid between CIP and COP. The core of the cleaning process is performed in-place, but certain parts of the equipment, require disassembly to perform manual cleaning.

2.4.2 Business-Value-Added Activity

In the previous chapters, the concept of Value-Added and Non-Value-Added activity has already been presented. Now, the third type of activity is exhibited: Business-Value-Added activity. A BVA activity does not provide value to the customer, but it is necessary to keep the business going, we could describe it as a necessary waste. A summary of the three types of activity is presented in Figure 2.4.

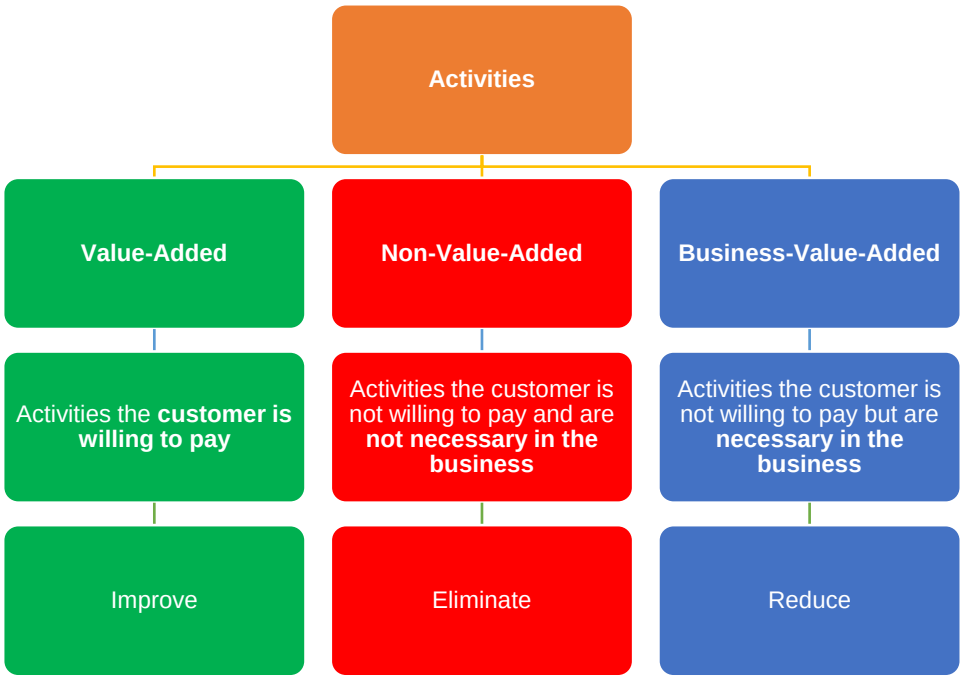

Figure 2.4: Depiction of the type of activities: VA, NVA and BVA.

In Figure 2.4, the improvement methods are also exhibited: a VA activity should be improved, a NVA activity should be eliminated, and a BVA activity should be reduced. The cleaning process is a BVA activity.

2.5 Automation

2.5.1 Overview

We can define automation as the technology by which a process is performed without human assistance [18]. Nonetheless, humans may be present as observers or even participants, but the process itself operates under its self-direction.

An automated system consists of three necessary components: power, a set of instructions and a control system.

1. **Power:** the most used form of power is electricity since it can easily be converted into mechanical, hydraulic or thermal power. It can be used at low power levels for function such as signal processing and communication, and it can be stored in life-long batteries.
2. **A set of instructions:** the program of instructions defines a sequence of activities required to do during the work cycle.
3. **A control system** executes the program of instructions. Two types of control systems can be distinguished: closed-loop and open-loop. A closed-loop system, also known as a feedback control system, requires a controller that compares the value of the output variable with the value of the input parameter (set-point). Depending on the value of the deviation from the set-point, the controller sends a signal to an actuator. The actuator manipulates another process variable, which influences the value of the output variable to drive its value towards the set point. [18]. In Figure 2.5, an example of a closed-loop system is displayed.

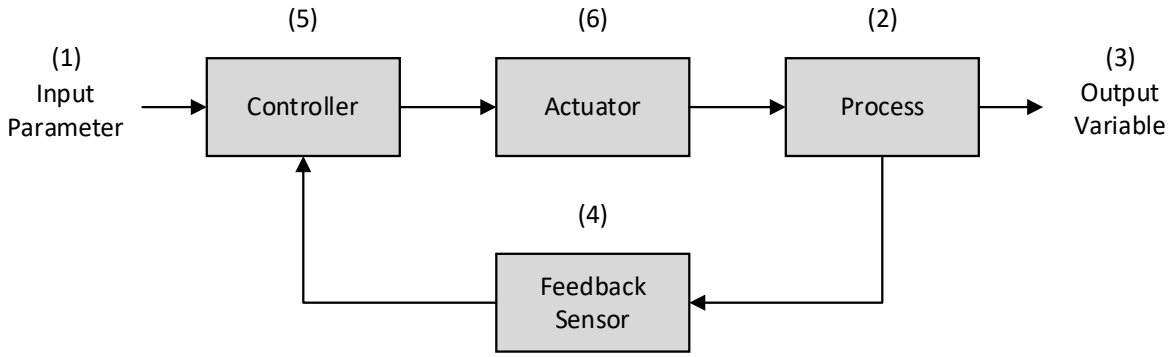

Figure 2.5: Example of a closed-loop system (Adapted from [18]).

There is a mandate to apply automated CIP, if the cleaning process cannot be executed in a robust and reproducible way, the production of biopharmaceutical products — a growing trend in the pharmaceutical industry [19] — is impossible [1].

2.5.2 Control Program – DeltaV

The control system at The Company is run and monitored with a program called DeltaV, developed by a company called Emerson [20].

There are three modes in which DeltaV can operate the process:

1. **Manual-Mode:** the operator will need to open and close all the valves. The Company never uses it in their production or cleaning processes;

2. **Auto-Mode:** the operator must choose “Modules” in the control system, like “Charging Solvent”, “Discharge”, “Heating” and the necessary valves open automatically. The operator also needs to insert the process parameters set-points into the system;

3. **Batch-Mode:** the system executes operations following a set of instructions which is elaborated by The Company's Automation Department. At The Company, this set of instructions is referred to as a “Batch Recipe”. When predetermined conditions are met, the system proceeds to the next operation. If there is an operation that cannot be automated and has to be performed infield, the program will stop and only proceed forward after the operator’s order. In Batch-Mode, this is called an “Operator Check” and is the only interaction the operator has with the program.

At The Company, all cleaning processes are run on Auto-Mode at the moment, which consumes one human resource (one operator) that continually needs to be operating the system on a DeltaV Workstation, see Figure 2.6.

Figure 2.6: Operator on a DeltaV Workstation (a situation similar to the one at The Company [21]).

Besides consuming one operator's attention, this situation also makes the lead time of the cleaning process dependent upon the operator's proficiency with the program. As such, from the point of view of standardization and elimination of variability, this is an undesirable situation. Because of this, The Company looks forward to implementing Batch-Mode on every cleaning process. As such, I investigated

what would be the most efficient sequence of performing the cleaning operations, considering the extra human resource that is freed from the DeltaV Workstation when implementing Batch-Mode.

3 Spray-Drying Cleaning Process and Current Situation

3.1 Production Process

At any given spray-dryer installation, the same core equipment is set up: the stabilization tank, the reactor, the spray-dryer, the cyclone, the bag filter and the HEPA (High-Efficiency Particulate Arrestance) filters. In Figure 3.1, a simplified process flow diagram of the spray-drying process is shown.

The spray-drying production process was not within the scope of this dissertation. Nonetheless, a brief explanation of it will be given now.

First, we prepare the reactional mixture in the reactor with the addition of solvent, excipient and API. Organic solvents are typically used to produce spray-dried dispersions because the API tends to be poorly water-soluble. While the dissolution process is taking place, nitrogen is employed as a drying gas to provide an inert processing atmosphere, and solvent from the stabilization tank is fed into the spray-drying chamber to establish a thermal profile before the delivery of the reactional mixture to the spray-dryer.

After we establish the thermal profile, the reactional mixture is fed into the atomizer, where atomization transforms the liquid stream into fine droplets, which interact with the drying gas at a high temperature. During this drying phase, the solvent contained within the dispersion droplets is vaporized, leading to the formation of solid product particles.

Finally, the dried particles are separated from the drying medium by an appropriate device, typically a cyclone separator and a filter bag. The spray-dryer installations, like the one exhibited in Figure 3.1, are identified with the label of the spray-dryer chamber.

Table 3.1: Dimensions of the different types of Particle Spray-Dryers, PSDs.

Types of PSD	Label	Nominal Gas Flow (kg/h)
PSD 1	SDX	80
PSD 2	SDXX	360
PSD 3	SDXXX	630
PSD 4	SDXXXX	1250

The spray-dryer installation assigned to this dissertation was SD1, a PSD 1, in the Pilot Plant Department.

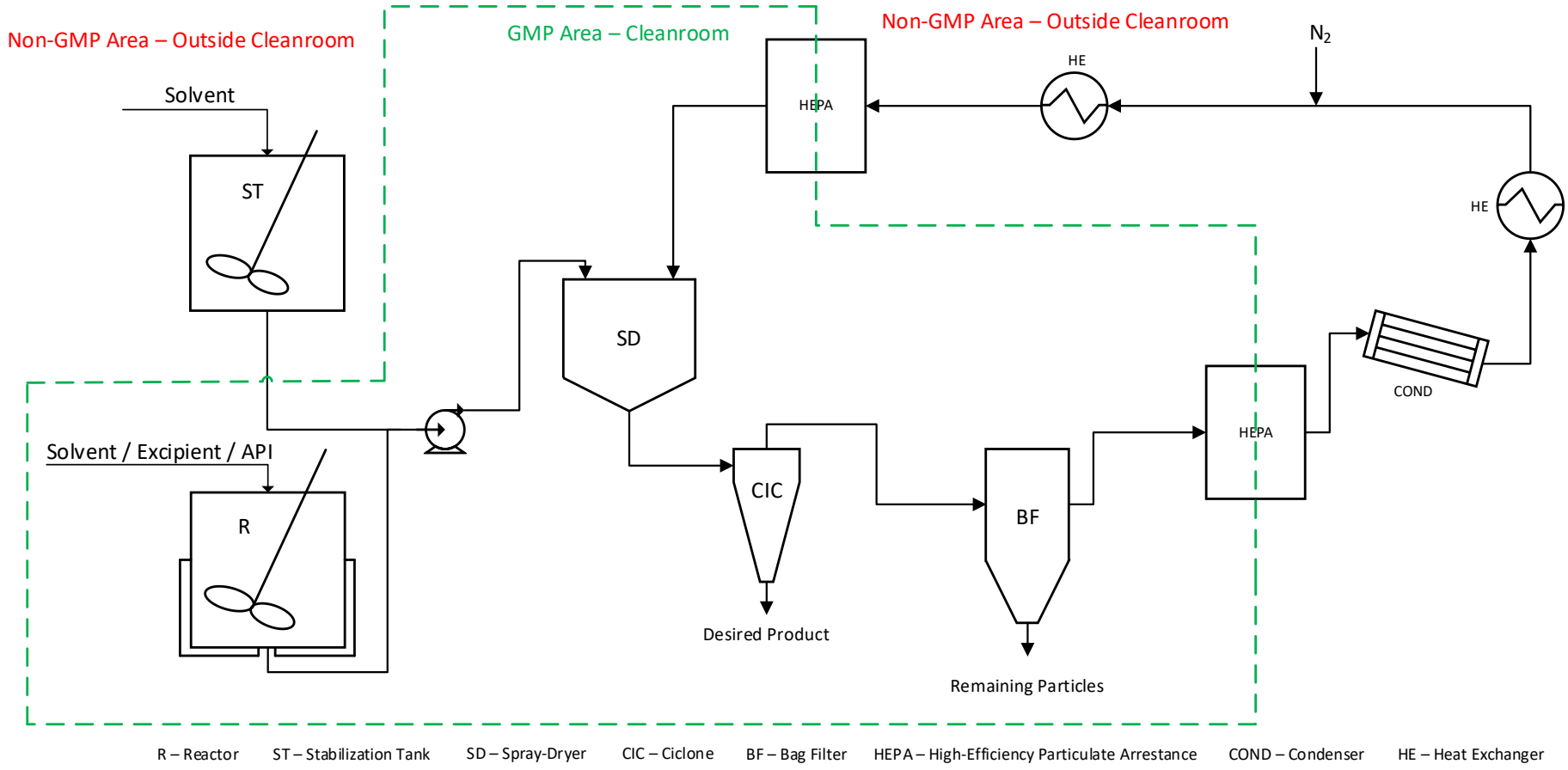

Figure 3.1: Simplified process flow diagram of a typical spray-drying process.

The HEPA filters are the separation between the cleanroom, where the GMP norms are to be followed, and the operators should be appropriately equipped, and the Non-GMP area, where the nitrogen is treated to remove traces of solvent from the gas. In the GMP area is all the equipment that comes into contact with the product. All equipment within the GMP Area is to be thoroughly cleaned, which means the reactor, the spray-dryer, the cyclone, the filter bag and the HEPA filters.

3.2 Cleaning Methodology

The cleaning process of the spray-drying installation is performed in between production batches. The degree and type of cleaning performed will depend on whether the cleaning is being performed between batches of the same product or between batches of different products. The first scenario is called "Cleaning Between Batches", abbreviated CBB, and the latter is called "Change of Line", abbreviated, COL. In Figure 3.2, we clarify the timing of each cleaning type.

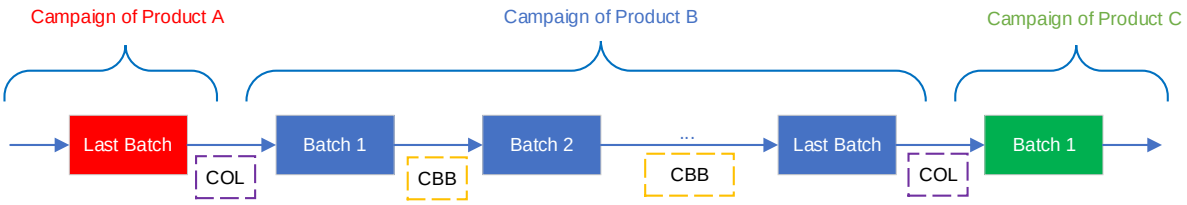

Figure 3.2: Illustration of where to apply COL or CBB.

The goal of the cleaning process is to reduce the contents of the previous product in the next product to levels that will not have adverse effects on the patient taking the medication.

At The Company, the experience gathered from years of performing cleaning processes and the existence of a team dedicated to improving its efficiency and efficacy culminated in a methodology which depicts the best-known way of performing the cleaning process (see Table 3.2).

The execution of the methodology presented in Table 3.2 will differ depending on if the cleaning process is a COL or CBB and on the Cleaning Agent. A flowchart, Figure 3.3, was developed in this work to summarize and synthetize which steps are performed in each occasion.

Table 3.2:Cleaning Process Methodology [15].

Step Number	Step Description	Function
1	Flush 1 – Rinse with Industrial Water	To grossly remove residues from the equipment.
2	Flush 2 – Cleaning with Cleaning Agent	To remove the product residues. The Cleaning Agent can be Solvent, Detergent or Deionized water.
3	Flush 3A – Rinse with Industrial Water	To remove the Cleaning Agent with industrial water.
4	Flush 3B – Rinse with Deionized Water	To remove the Cleaning Agent with deionized water.
5	Drying	To dry the equipment in order to allow a proper visual inspection and to avoid microbial growth.
6	Visual Inspection (abbreviated VI)	Visual inspection of the equipment is performed to check its cleanliness. Also prevents unnecessary sampling: if it is visually dirty, it is pointless to sample.
7	Product Removal Verification	Sample and analytical verification of product residues content are performed.
8	Cleaning Agent Removal Verification	Sampling and analytical verification of the cleaning agent removal are performed.
9	Drying	To dry the equipment in order to allow appropriate visual inspection, to avoid microbial growth and prepare the equipment for the next use.
10	Visual Inspection	A final visual inspection of the equipment is performed.

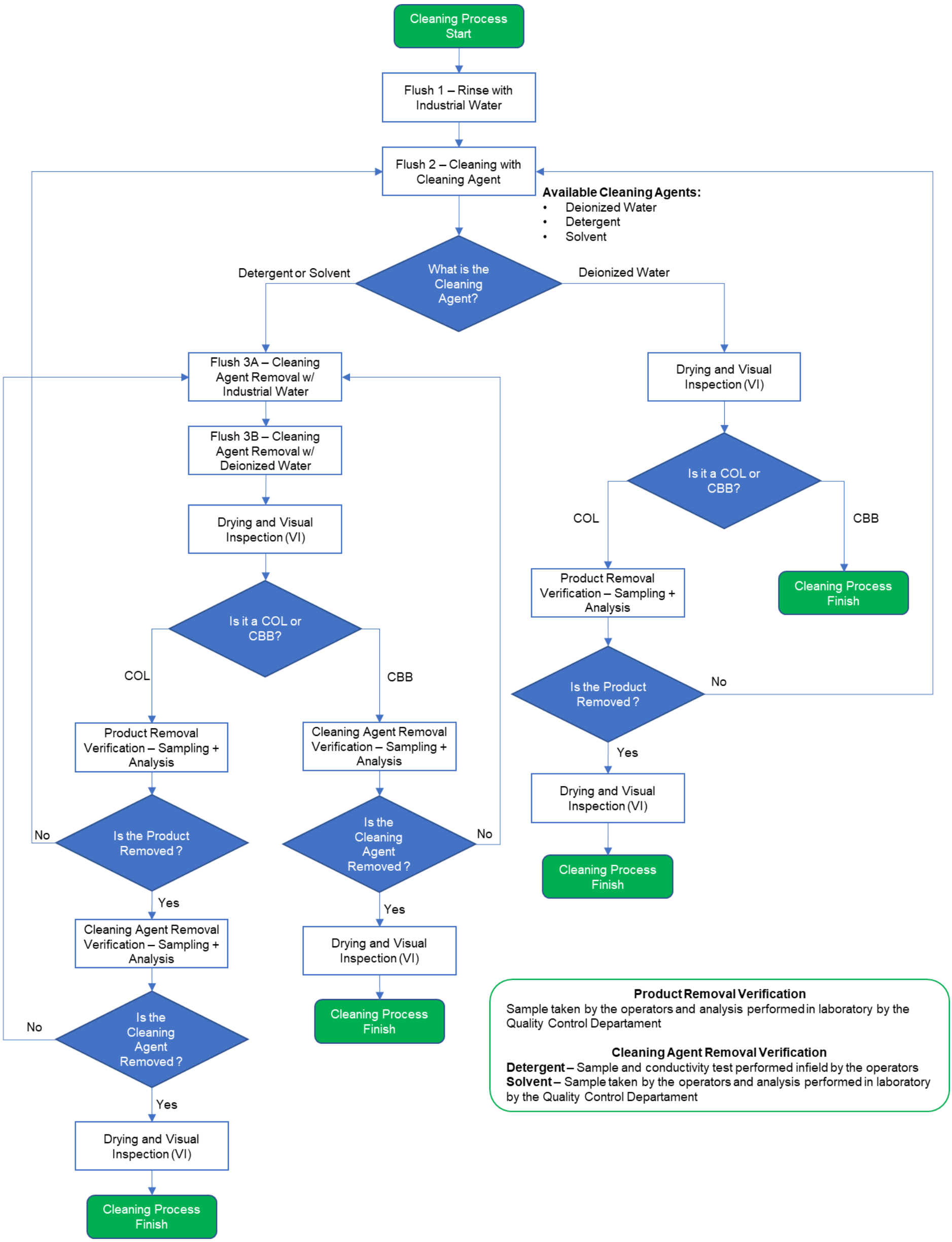

Figure 3.3: Cleaning Process Decision Flowchart for COL and CBB.

The Product Removal Verification and Cleaning Agent Removal Verification for solvent both need to be analyzed in the laboratory by the Quality Control Department, abbreviated QC. The Cleaning Agent Removal Verification of Detergent is performed infield by the operators with conductivity testing. Because of this, the time it takes to verify the Product Removal and Solvent Removal Verification is considerably more significant than the time it takes to sample and analyze the Detergent Removal Verification.

The lead time of the cleaning process exhibited in Figure 3.3 can be reduced in two ways:

1. Guarantee the selection of the appropriate cleaning agent to ensure the maximum percentage of Right-First Time cleaning and avoid unnecessary Flush repetitions;
2. Develop a standardized and improved sequence of performing the cleaning operations in order to reduce the cleaning process lead time and variability by diminishing the Lean Wastes exhibited in Chapter 2.2.2.

To achieve the first one several cleaning agents at laboratory scale are tested and validated to assess the choice of the appropriate cleaning agent. This was not within the scope of this dissertation.

The scope of this dissertation was the second alternative of reducing the cleaning lead time which makes use of the Lean Tools presented in Chapter 2.2.3 to improve the flow of operations and diminish the lead time and variability of the cleaning process.

3.3 Cleaning Zones – Spray-Dryer and Reactor

The cleaning process covers the equipment by zones to ensure that no area is left uncleaned. Regarding SD1, the zones are exhibited in the process flow diagram of Figure 3.4.

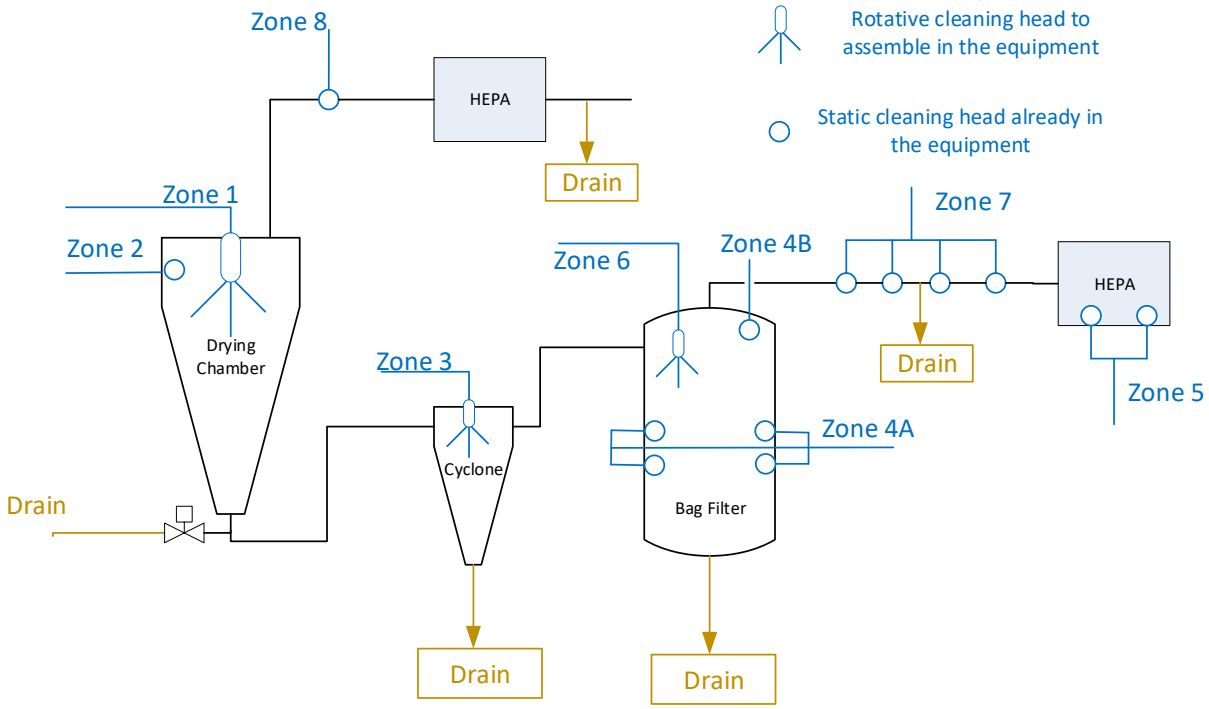

Figure 3.4: Cleaning zones of the SD1 installation (Reproduced from [15]).

The Reactor R1 is the reactor associated with the SD1 installation. In Figure 3.5, its zones are illustrated. On top of the reactor, there is a reflux condenser to cool the reactional mixture's vapours.

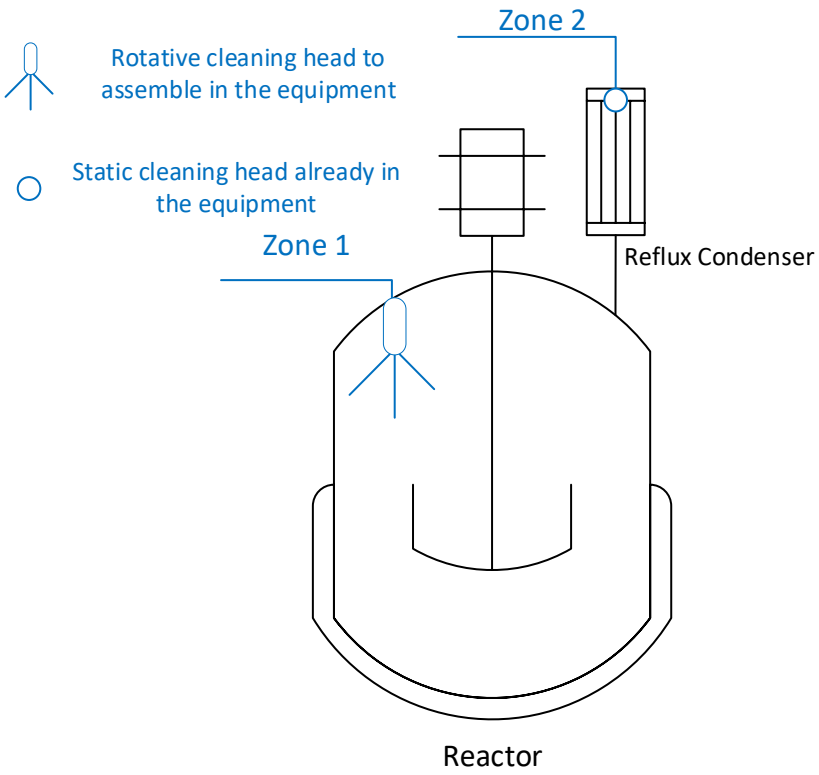

Figure 3.5: Cleaning Zones of the R1 installation (Reproduced from [21]).

Each of the Flushes mentioned in Chapter 3.2 has to be performed in all zones of the equipment. The cleaning heads are specific devices attached to a CIP spear which are installed on the equipment to perform the cleaning of its internal surfaces. The Static Cleaning Heads are already in the equipment, and the Rotating Cleaning Heads have to be set up to perform the cleaning process.

3.4 Cleaning Agent Preparation – CIP Tank

The three cleaning agents available: Deionized Water, Detergent and Solvent are prepared in a tank called “CIP Tank”, a tank dedicated only to the preparation of the different cleaning agents (see Figure 3.6).

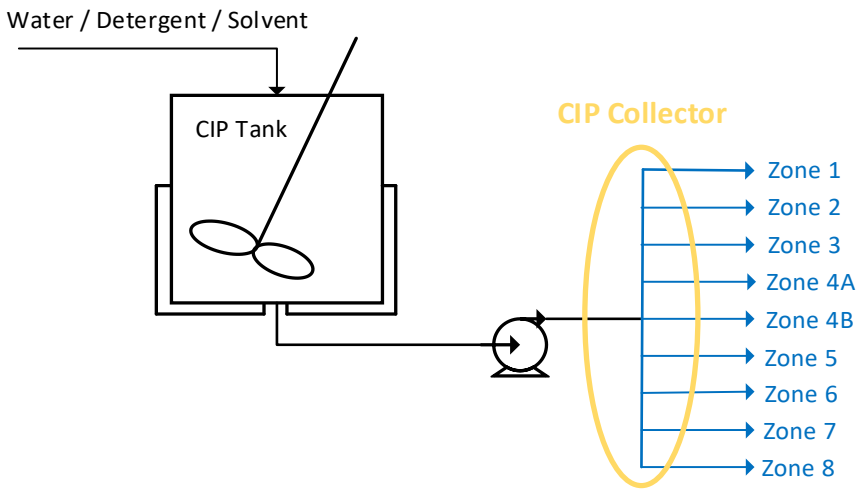

Figure 3.6: CIP Tank connection to the different Zones.

At downstream of the CIP Tank, the pipe branches into the multiple zones of the spray-dryer installation. That branching is called the "CIP Collector".

3.5 Documentation – Cleaning Procedures

To perform the cleaning, the operators follow two Cleaning Procedures: one regarding the reactor, and one regarding the spray-dryer and its downstream equipment: the cyclone, the bag filter and the HEPAs. The Cleaning Procedures are very detailed documents that can go over fifty pages in length and obey every GMP and Quality Assurance requirement.

The typical page layout of a Cleaning Procedure is presented in Figure 3.7. The Cleaning Procedure's page includes the Date and Start Time of each step.

Cleaning Procedure

Date: _____

Step: Prepare the CIP Tank Start Time: _____

- Check Instrumentation
- Fill CIP Tank
- Etc…

Step: Flush 1 – Rinse with Industrial Water Start Time: _____

- Setup the cleaning heads
- Start Flush 1
- Etc….

Figure 3.7: Example of a typical Cleaning Procedure page layout.

The reactor's Cleaning Procedure instructions and the spray-dryer's Cleaning Procedure instructions are independent of each other. The cleaning of the spray-dryer is never mentioned in the reactor's Cleaning Procedure and vice-versa.

3.6 Assessment of the Current Situation

Since the goal of this internship was to reduce the high lead time and variability of the cleaning process of SD1, it is first necessary to assess the current status of the cleaning process and the continuous improvement initiatives the Pilot Plant Department might have already started.

The data readily available at the Pilot Plant Department regarding the cleaning process of SD1 was scarce and dated back to 2017 and 2018. It is exhibited in Table 3.3 and Table 3.4.

The Pilot Plant Engineers had already categorized the cleaning process time in the following sections:

- **1st Cleaning Execution Time:** the time is referring to the execution of the cleaning process except for the Product Removal Verification. It includes the setups, performing the flushes, and all other operations carried out by the operators;
- **1st Product Removal Verification:** the time is referring to the sampling time performed by the operators and the analysis time of the samples performed by the Quality Control Department;
- **2nd Cleaning Execution Time:** if the sample result indicates that the amount of product residues in the equipment is unacceptable, the cleaning execution will have to be repeated, which consumes additional time;
- **2nd Product Removal Verification:** this will be time consumed during the second sample and laboratory analysis;
- **Total COL Time:** the time is referring to the Change of Line. It includes the Cleaning Execution Time + Product Removal Verification;
- **Total CBB Time:** the time is referring to the Cleaning Between Batches of the same product. It includes only the Cleaning Execution Time since it is not required to verify the Product Removal in CBBs.

Since the available data did not make a distinction between what Cleaning Agents and Analysis Methods were used, I investigated those parameters in the company's cleaning guidelines, see Table 3.3 and Table 3.4. It was essential to investigate that data, because, as can be seen in the flowchart exhibited in Figure 3.3, we should not expect that a cleaning process performed with Deionized Water in a CBB, should last as long as a cleaning process performed with Solvent in a COL (the worst-case scenario, since it involves depending on the Quality Control Analysis both for the Product and Cleaning Agent Removal Verification).

Table 3.3: Raw data from the COLs performed in SD1 during the years 2017 and 2018.

COL Breakdown (Parameters in days)							
Batch	**1st Cleaning Execution**	**1st Product Removal Verification**	**2nd Cleaning Execution**	**2nd Product Removal Verification**	**Total COL Time**	**Cleaning Agent**	**Analysis Method**
Batch 1	4.5	1.5	-	-	6	Detergent	HPLC
Batch 2	3	3	-	-	6	Detergent	HPLC
Batch 3	0.5	3	1.5	1	6	Deionized Water	TOC
Batch 4	3.5	1.5	-	-	5	Deionized Water	TOC
Batch 5	3	1.5	-	-	4.5	Deionized Water	TOC
Batch 6	2.5	1	-	-	3.5	Detergent	HPLC
Batch 7	1	1	-	-	2	Deionized Water	HPLC
Batch 8	2	1	-	-	3	Detergent	HPLC

— Data available from the Pilot Plant
— Data I investigated

Table 3.4: Raw data from the CBBs performed in SD1 during the years 2017 and 2018.

CBB Breakdown (Parameters in days)			
Batch	**Cleaning Execution = Total CBB Time**	**Cleaning agent**	**Analysis Method**
Batch 9	1	Detergent	HPLC
Batch 10	2	Detergent	HPLC
Batch 11	1	Detergent	HPLC
Batch 12	2	Detergent	HPLC
Batch 13	1	Detergent	HPLC
Batch 14	5	Detergent	HPLC
Batch 15	5	Detergent	HPLC
Batch 16	3	Detergent	HPLC
Batch 17	3	Detergent	HPLC
Batch 18	2	Detergent	HPLC
Batch 19	1	Deionized Water	HPLC
Batch 20	1	Deionized Water	HPLC
Batch 21	1	Deionized Water	TOC

— Data available from the Pilot Plant
— Data I investigated

The Cleaning Agent used was either Deionized Water or Detergent, and the analysis method used was either HPLC (High-Performance Liquid Chromatography) or TOC (Total Organic Carbon).

Several statistical manoeuvres were performed on the available data to determine the meantime and the standard error of the lead time of the cleaning process.

Since the data received is just a sample of the cleaning processes performed from 2017 to 2018, the t-student method with a 95% confidence interval is applied. The t-student method is appropriate when the sample size is small (less than 30 samples [22]), and the standard deviation of the population is not known, which is the case, given that the Pilot Plant Department does not have that data.

For the normality test to assure the applicability of the t-student method, the Q-Q Plot method was used. It provides a quick, visual assessment of the normality of the distribution. The graphics obtained can be consulted in Appendix A.1. As can be seen from the visual assessment of the Q-Q Plots, it is reasonable to assume the data points follow a normal distribution and the t-student method is applicable.

The graphics obtained from this calculation can be consulted in Appendix A.2, and the obtained results are summarized in Table 3.5, Table 3.6 and Table 3.7.

Table 3.5: Mean times with error for detergent as cleaning agent using the t-student method.

Detergent			
Parameters in days	Cleaning Execution | 14 Measures	CBB | 10 Measures	COL | 4 Measures
Mean Time	2.6	2.5	4.6
Standard Deviation	1.4	1.5	1.6
Standard Error	0.8	1.1	2.5
Mean ± Standard Error	2.6 ± 0.8	2.5 ± 1.1	4.6 ± 2.5
Mean ± Standard Error (%)	2.6 ± 30 %	2.5 ± 43 %	4.6 ± 55 %

Table 3.6: Mean times with error for water as a cleaning agent using the t-student method.

Water			
Parameters in days	Cleaning Execution | 7 Measures	CBB | 3 Measures	COL | 4 Measures
Mean Time	1.6	1.0	4.4
Standard Deviation	1.2	0.0	1.7
Standard Error	1.1	0.0	2.7
Mean ± Standard Error	1.6 ± 1.1	1.0 ± 0.0	4.4 ± 2.7
Mean ± Standard Error (%)	1.6 ± 69 %	1.0 ± 0 %	4.4 ± 62 %

Table 3.7: Mean times with error for the two analysis methods using the t-student method.

Sampling + Analysis Method		
Parameters in days	HPLC | 5 Measures	TOC | 3 Measures
Mean Time	1.5	2.0
Standard Deviation	0.9	0.9
Standard Error	1.1	2.2
Mean ± Standard Error	1.5 ± 1.1	2.0 ± 2.2
Mean ± Standard Error (%)	1.5 ± 72 %	2.0 ± 108 %

By analyzing the data, it is, in fact, clear, that examining at the Cleaning Execution alone, the cleaning process performed with detergent is longer than the one performed with water by one day. What is perhaps more worrying is the fact that a cleaning process performed with just water, even being a simpler cleaning, is just as variable as cleaning with detergent [Standard Error (Cleaning Execution w/ Detergent) = 0.8 VS. Standard Error (Cleaning Execution w/ Water) = 1.1].

The values of the Standard Deviation, Standard Error and Mean + Standard Error, are written in red to highlight the occasion in which the Standard Error is greater than the Standard Deviation. This is a red flag that symbolizes the misapplication of the t-student method with a 95% confidence interval. It means that it is not possible to extrapolate from the sample of the COLs performed in 2017 and 2018, that 95% of the values for the cleaning processes of the population (in this case, it would be all years) are within that Standard Error. In simple terms, the COLs are too variable in 2017 and 2018 to apply a 95% confidence interval.

From Table 3.7, it is possible to see that the analysis times are the problem of the high variability of the COL times. Even though the improvement of the sample analysis time was outside the scope of this thesis, both methods were analyzed to see if it was possible to identify any of the analysis methods as the ultimate source of variability. It was found that in both scenarios, the 95% confidence interval is not applicable, which hints at managing or overburdening problem in the Quality Control Department.

4 Investigation and Improvement of the Cleaning Process

4.1 Gemba Walk – Suggestions Sheet

Even amid the Covid-19 pandemic, three Gemba Walks were performed, two before the quarantine and one during it. During the time in the shopfloor with the operators, it was a particular concern to gather their feedback regarding the cleaning process. The most heard complaint was the lack of realistically accurate instructions in the Cleaning Procedures. This appeared to be due to a lack of opportunity for the operators to give feedback to the production technicians who elaborate the Cleaning Procedures.

As such, I came up with the idea of creating a Suggestions Sheet that would act as a communication vehicle between the operators and the technician that produces the Cleaning Procedures. The Suggestions Sheet was created with two main cautions:

- Many researchers warn against the excessive use of lean methodologies, arguing that it promotes negative impacts in the mental health of the employee [23], [24], [25]. I will also add that the overuse of lean tools promotes a lack of engagement, and since one of the main promoters of sustainability is to engage the operators in the continuous improvement initiatives, it is of no interest to overburden them.
- The simple one-page character of the Suggestions Sheet was also created thinking of striving for incremental improvements. It is expected that the continuous use of the Suggestion Sheet can bring clarification to the technicians and a substantial improvement to the quality of the Cleaning Procedures can occur over time.

The Suggestions Sheet is composed of four columns:

1. **C. P. Equip.**: this is the section to introduce what Equipment Cleaning Procedure the operator is referring to;
2. **C. P. Step**: this is the section to introduce what Step in the Cleaning Procedure the operator is referring to;
3. **Doubt:** this is the place to input the problem in need of clarification, be it ambiguous instructions or operations that could be easily improved;
4. **Suggestion for Improvement:** this is where the operator includes a suggestion to eliminate the problem identified in the previous column.

Suggestions Sheet for the Cleaning Procedures of SD1 and R1

Goal: identify and clarify the instructions in the cleaning procedures that raise doubts and prevent or hinder the efficient execution of the Cleaning Operations

Example:

In Step 37 of the Cleaning Procedure of R1, "Disassembly – R1", there is an indication to disassemble the clamped parts of the reactor.

What is the problem?

Of the vary clamped parts that are assembled in the reactor, only some are meant to disassemble. This raised doubts in some of the more inexperienced operators who needed to consult with a more experienced operator to certify that they were going to disassemble the correct pieces.

All of this uncertainty translates itself into a waste of time and can be continuously improved by creating a simple and effective communication line between the operators and the technicians who write the Cleaning Procedures.

Using this same example, the suggestion of improvement, in the next table, would look like the following:

C.P. Equip.	C.P. Step	Doubt	Suggestion for Improvement
R1	37	Lack of clarity about which clamped parts to disassemble. More experienced operator consultation required.	Photo with an indication of which clamped parts is necessary to disassemble.

Thus, it is requested that whenever an instruction is not easily perceived in the Cleaning Procedure, it is recorded in the table on the next page.

CP Equip.	CP Step	Doubt	Suggestion for Improvement
R1	19	Drain discharges are tasks that take little time. Why not perform them before feeding Zone 1?	Perform the drain discharges before feeding Zone 1.
SD1	20	They are asking to check the cleaning room cloth, but they never mention when to put it on.	An instruction mentioning when to place the cleaning room cloth should be inserted.
SD1	20	They ask to place the cleaning room cloth at the bottom of the cyclone, Zone 3, in Flush 1. This way, the cleaning room cloth will always have residues.	Perform the first cleaning flush before placing the cleaning room cloth by performing the flush in Zone 3 in Step 18.
SD1	25	It is not requested to remove the drain hose from the cyclone when it is necessary to do so.	An instruction requesting the removal of the drain hose from the cyclone should be inserted.
SD1	25	In the following steps, it is asked to perform the drying. Leakage and inertization tests are necessary before performing the drying. These tests are never mentioned.	Before drying, mention leakage and inertization tests. Only then can we proceed with the drying. IMPORTANT SAFETY MEASURE.
SD1	25	For drying, it is never mentioned when to open the inlet HEPA, which is a requirement for drying.	Mention the opening of the inlet HEPA.

The exhibited example of the Suggestion Sheet was filled during the third and last Gemba Walk, where I conducted the operators through the process of filling the Suggestions Sheet.

While brainstorming with one of the more experienced operators, it was immediately possible to identify faults in the Cleaning Procedures. Important steps, like the opening of the inlet HEPA before performing the drying and the leakage and inertization tests that should always be performed before drying the equipment, a very important safety measure, are never mentioned. The cleaning room cloth is put on the drain valve at downstream of the Flush to evaluate the dirtiness in the equipment; if this is done immediately after Flush 1 it is a given that the cleaning room cloth will be dirty, and the cleaning room cloth becomes redundant.

In just one Gemba Walk, it became clear that the Cleaning Procedures were not elaborated with the operational workflow of the operators taken into consideration. As such, a schedule for the implementation of the Suggestions Sheet Tool will be proposed in Chapter 4.4.

4.2 Analysis of the Cleaning Procedures

The assessment performed in Chapter 3.6 only informs us of the high lead time and variability of the cleaning process as a whole, mainly due to the variability of the sample analysis time, but also, and more important for the work of this internship, of the lead time and variability of the cleaning execution, even in supposedly simpler cleaning processes performed with Deionized Water.

Before analyzing the cleaning process in greater detail, it is necessary to identify which are the cleaning operations in need of being tracked and quantified. To accomplish this, the Standard Work Methodology was used, and summarized through Figure 4.1.

The cleaning process can be sectioned into the Product Removal, the Cleaning Agent Removal and the Cleaning Efficacy Assessment.

The Product Removal comprises the HEPAs Assessment, where the condition of the HEPA filters is checked, the preparation of the CIP Tank, the Setup of the CIP spears and cleaning heads, together with both Flush 1 and Flush 2.

The Cleaning Agent Removal starts by cleaning the CIP Tank to prepare for Flush 3A and Flush 3B finishing with the drying of the equipment.

Finally, when assessing the cleaning efficacy, the sampling and analysis of product and cleaning agent are performed, followed by the final drying and visual inspection of the equipment.

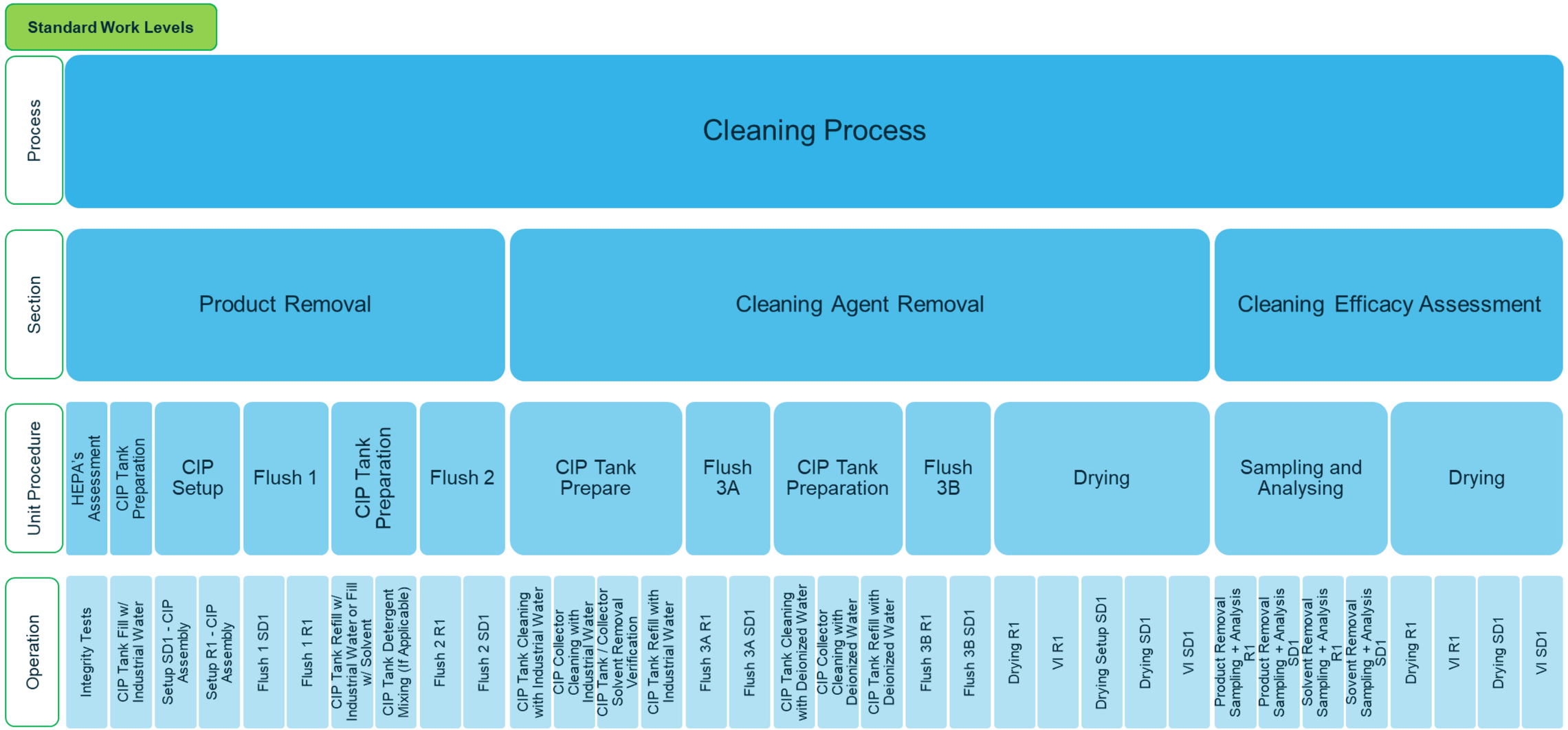

Figure 4.1: Standard Work Methodology applied to the Cleaning Process.

It is important to mention at this instant that there were no more records or historical data readily available from the Pilot Plant Department regarding the cleaning process of SD1. This creates a critical problem because it means the cleaning process is a "black box" regarding time and variability of the cleaning operations. The cleaning process is, also, not easily testable or reproducible; the number of cleaning processes I could follow infield with the operators during the internship were limited to the production schedule and got severely compromised by the Covid-19 pandemic situation.

In the face of this scenario, I came up with the idea to analyze the only record of the cleaning processes: the Cleaning Procedures.

Since there could have been improvements in the cleaning process since 2017 and 2018, the more recently filled Cleaning Procedures were utilized.

It was necessary to consult the production plan to get access to the Cleaning Procedures. After, the batch record files in the company's archives had to be investigated to find the Cleaning Procedures. The Cleaning Procedures correspondind to the last four cleaning processes were collected and examined.

I attempted to quantify the identified cleaning operations with data from the Cleaning Procedures. However, the analysis was not smooth and had a considerable associated error. If the Cleaning Procedure's layout is presented again, it is possible to see that it is impossible to know with precision when one of the steps finishes and another step begins, because in the Cleaning Procedures only the Start Time is written down.

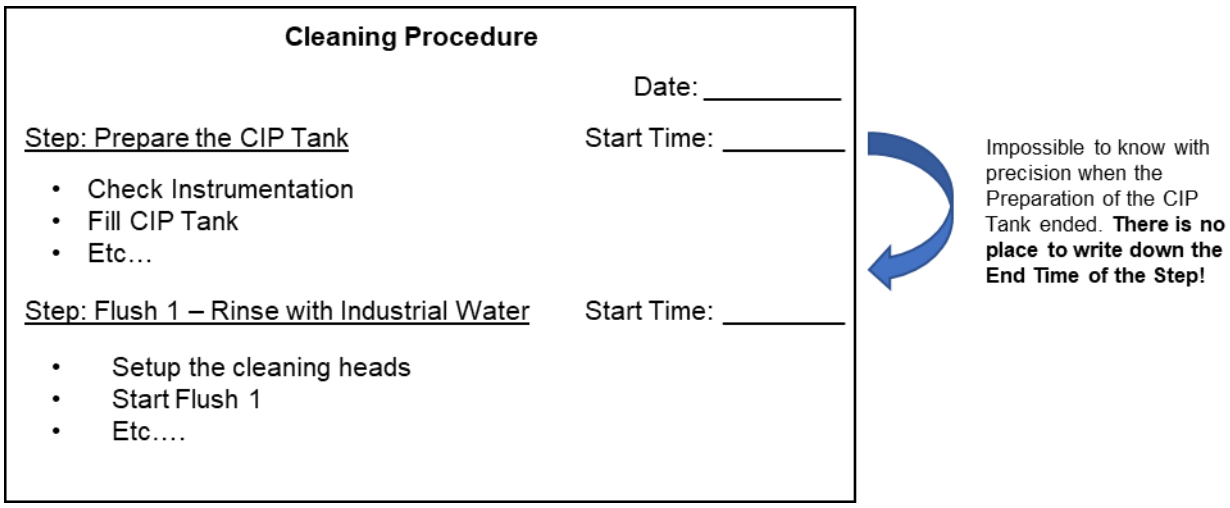

Figure 4.2: Problem with the quantification of the Cleaning Operations from the Cleaning Procedures.

Besides the associated error of the quantification of the Cleaning Procedure's steps, some of the identified cleaning operations are altogether unquantifiable, as can be seen from Table 4.1.

Table 4.1: Data extracted from the analysis of the Cleaning Procedures of the last four Cleaning Processes.

Task Duration, hh:mm					
Operation No.	**Operation Description**	**Cleaning Process 1 – CBB Cleaning Agent – Deionized Water**	**Cleaning Process 3 – COL Cleaning Agent - Detergent**	**Cleaning Process 3 – COL Cleaning Agent - Detergent**	**Cleaning Process 4 – COL Cleaning Agent - Solvent**
1	Integrity Tests	Not Applicable. Cleaning Process = CBB	10:39	01:30	04:07
2	CIP Tank Fill w/ Industrial Water	24:03	06:47	05:20	24:10
3	Setup SD1 - CIP Assembly	23:06	03:26	02:55	09:30
4	Setup R1 - CIP Assembly	04:30	02:10	00:55	02:50
5	Flush 1 SD1	05:08	01:24	01:05	03:40
6	Flush 1 R1	01:42	01:37	02:42	02:40
7	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
8	CIP Tank Detergent Mixing (If Applicable)	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
9	Flush 2 R1	00:28	01:00	00:20	04:30
10	Flush 2 SD1	01:46	11:47	06:35	01:50
11	CIP Tank Cleaning with Industrial Water	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
12	CIP Collector Cleaning with Industrial Water	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
13	CIP Tank / Collector Solvent Removal Verification	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
14	CIP Tank Refill with Industrial Water	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
15	Flush 3A R1	Not Applicable. Cleaning Agent = Deionized Water	02:30	01:34	Not Registered
16	Flush 3A SD1	Not Applicable. Cleaning Agent = Deionized Water	19:40	03:16	Not Registered
17	CIP Tank Cleaning with Deionized Water	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
18	CIP Collector Cleaning with Deionized Water	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
19	CIP Tank Refill with Deionized Water	Unquantifiable	Unquantifiable	Unquantifiable	Unquantifiable
20	Flush 3B R1	Not Applicable. Cleaning Agent = Deoinized Water	04:20	06:28	01:50
21	Flush 3B SD1	Not Applicable. Cleaning Agent = Deoinized Water	04:54	06:28	01:26
22	Drying R1	02:10	00:50	00:39	00:20
23	VI R1	00:10	00:10	00:05	00:10
24	Drying Setup SD1	Not Registered	15:28	02:25	02:43
25	Drying SD1	03:13	03:47	00:17	01:40
26	VI SD1	00:51	00:15	00:55	01:35
27	Product Removal Sampling + Analysis R1	Not Applicable. Cleaning Process = CBB	14:24	22:34	20:30
28	Product Removal Sampling + Analysis SD1	Not Applicable. Cleaning Process = CBB	30:18	35:51	17:40
29	Solvent Removal Sampling + Analysis R1	Not Applicable. Cleaning Agent = Deionized Water	Not Applicable. Cleaning Agent = Detergent Measured by Conductivity Infield	Not Applicable. Cleaning Agent = Detergent Measured by Conductivity Infield	11:20
30	Solvent Removal Sampling + Analysis SD1	Not Applicable. Cleaning Agent = Deionized Water	Cleaning Agent = Detergent Measured by Conductivity Infield	Cleaning Agent = Detergent Measured by Conductivity Infield	27:08
31	Drying R1	Not Applicable. No Sampling was Performed.	02:13	04:51	06:30
32	VI R1	Not Applicable. No Sampling was Performed.	00:10	00:07	00:05
33	Drying SD1	Not Applicable. No Sampling was Performed	04:04	06:21	05:00
34	VI SD1	Not Applicable. No Sampling was Performed	00:05	00:05	00:07
Total Cleaning Time Duration		2 Days and 23h14min	6 Days and 00h11min	4 Days and 17h18min	6 Days and 04h29min

The presented values were estimated by considering that one step ended when the next step starts, which does not take into account the time wasted in between operations, nor the possible parallelization of the execution of the Cleaning Procedure's steps. It is relevant to note that for the examined cleaning processes, the Total Cleaning Time Duration is above the values calculated in Chapter 3.6, which exhibits the lack of improvement in the cleaning process in the last couple of years.

After this investigation, I decided to calculate the meantime, the standard deviation and the coefficient of variation (or relative standard deviation) of the measured cleaning operations. With the meantime, it is possible to identify the Top 3 Time-Consuming Operations and with the coefficient of variation, the Top 3 Sources of Variability.

Table 4.2: Top 3 time-consuming tasks and sources of variability of the cleaning process of SD1.

Top 3 Time-Consuming Operations (Mean in hh:mm)		Top 3 Sources of Variability, CV	
1. CIP Tank Fill w/ Industrial Water	15:05	1. Flush 2 R1	1.25
2. Flush 3A SD1	11:28	2. Drying Setup SD1	1.08
3. Setup SD1 - CIP Assembly	09:44	3. Flush 3A SD1	1.01

It is important to note here that the analysis of the Cleaning Procedures was extremely laborious and extended beyond the timespan of the internship. As such, after its conclusion, there was no time left to investigate infield with the operators the possible inefficiencies of the Top 3 Time-Consuming Operations and Top 3 Sources of Variability. However, possible root causes and ways to tackle them will be proposed next.

When considering the focus of the continuous improvement efforts, perhaps it is more appropriate to focus on the Top 3 Sources of Variability. This is because the variability of the cleaning process impacts the planned production schedule.

Of the Top 3 Sources of Variability, two of the most variable operations are Flushes. The most critical factor here appears to be the operator’s proficiency with DeltaV, along with his availability to be constantly on the DeltaV Workstation. This is a problem that can be easily bridged with the implementation of Batch-Mode (see Chapter 5) since the operator does not have to be operating the control system.

The 2nd most variable operation and the 3rd most time-consuming operation are both setups. This is the situation that we will have to look into, and probably the 5S tool and the SMED tool will have to be implemented. In these situations, we should move towards a scenario that avoids the necessity of external departments, like the Maintenence Department. Since SD1 is a PSD1, one of the smallest spray-dryers, it might be possible to train the operators to perform the most complicated disassembles, and the variability that surges from being reliant on an external department can be altogether eliminated.

4.3 Swimlane Map – Register Sheet

Since it was impossible to extract conclusions in useful time from the analysis of the existing documentation, I decided to build a Continuous Improvement Tool using the Swimlane Map.

The Swimlane Map is useful to have a visual depiction of the sequence of steps in the cleaning process. Since the Cleaning Procedures only describe the cleaning of one equipment at a time, giving no consideration whatsoever to the sequencing of the cleaning steps inter-equipment, it is important to get a visual description of the operational workflow of the operators during the cleaning process.

The meantime, the standard deviation and the coefficient of variation were also added to the Swimlane Map. I had this coupling of VSM characteristics with the Swimlane Map in mind since the beginning and finally saw it concretized in [26].

One of the identified problems during the investigation of the Cleaning Procedures was the impossibility of accurate quantification of the cleaning operations, as such, a Register Sheet was created to be filled by the operators during the cleaning process. The proper quantification of the cleaning operations is crucial since it makes it possible to target continuous improvement efforts effectively.

The Register Sheet comprises all the identified cleaning operations with the Standard Work Methodology. With the data collected with the Register Sheet, a collection of Excel Templates was also developed to allow an automatic treatment of the data. The manual of instructions regarding the Swimlane Map Continuous Improvement Tool is presented next.

Register Sheet

Purpose: To quantify the time of the Cleaning Operations.

Instructions: Fill the Start Date and Time, and the End Date and Time of every Cleaning Operation during the Cleaning Process.

Helpful Note: Only insert the date in the beginning and whenever the day changes concerning the previous record. Otherwise, cut the date. See the illustrative example:

Operation ID	Operation	Start Date and Time	End Date and Time
1	Integrity Tests	Date: 2020 / 10 / 12 Time: 08:35	~~Date: _____ / ____ / ____~~ Time: 15:45
2	CIP Tank Fill w/ Industrial Water	~~Date: _____ / ____ / ____~~ Time: 20:45	Date: 2020 / 10 / 13 Time: 00:15

Operation ID	Operation	Start Date and Time	End Date and Time
1	Integrity Tests	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
2	CIP Tank Fill w/ Industrial Water	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
3	Setup SD1 - CIP Assembly	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
4	Setup R1 - CIP Assembly	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
5	Flush 1 SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
6	Flush 1 R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
7	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
8	CIP Tank Detergent Mixing (If Applicable)	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
9	Flush 2 R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
10	Flush 2 SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
11	CIP Tank Cleaning with Industrial Water	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
12	CIP Collector Cleaning with Industrial Water	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
13	CIP Tank / Collector Solvent Removal Verification	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
14	CIP Tank Refill with Industrial Water	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
15	Flush 3A R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
16	Flush 3A SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
17	CIP Tank Cleaning with Deionized Water	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
18	CIP Collector Cleaning with Deionized Water	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____

19	CIP Tank Refill with Deionized Water	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
20	Flush 3B R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
21	Flush 3B SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
22	Drying R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
23	VI R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
24	Drying Setup SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
25	Drying SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
26	VI SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
27	Product Removal Sampling R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
28	Product Removal Sampling SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
29	Solvent Removal Sampling R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
30	Solvent Removal Sampling SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
31	Drying R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
32	VI R1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
33	Drying SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____
34	VI SD1	Date: _____ / ____ / ____ Time: ____:____	Date: _____ / ____ / ____ Time: ____:____

Manual – Swimlane Map Continuous Improvement Tool – 1 / 4

0. Register Sheet.docx
1. Register Sheet Data.xlsx
2. Cleaning Process Map.xlsx
3. Instructions Manual.pptx

0. Register Sheet

Technician inputs the Data from the Filled Register Sheets into the Excel Spreadsheet. The Data extrated from the Cleaning Procedures is used as example.

1. Register Sheet Data

Cleaning Agent		Cleaning Agent - Water	Cleaning Agent - Detergent	Cleaning Agent - Detergent	Cleaning Agent - Solvent	Cleaning Agent ?	Cleaning Agent ?
Type of Cleaning		Cleaning 1 - CBB	Cleaning 2 - COL	Cleaning 3 - COL	Cleaning 4 - COL	Cleaning 5 - COL or CBB	Cleaning 6 - COL or CBB
Operation #	Operations	Operation Duration ([hh]:mm)	Operation Duration ([hh]:mm)	Operation Duration ([hh]:mm)	Operation Duration ([hh]:mm)	Operation Duration ([hh]:mm)	Operation Duration ([hh]:mm)
1	Integrity Tests	04:07	10:39	01:30	-		
2	CIP Tank Fill w/ Industrial Water	24:03	06:47	05:20	24:10		
3	Setup SD1 - CIP Assembly	23:06	03:26	02:55	09:30		
4	Setup R1 - CIP Assembly	04:30	02:10	00:55	02:50		
5	Flush 1 SD1	05:08	01:24	01:05	03:40		
6	Flush 1 R1	01:42	01:37	02:42	02:40		
7	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	-	-	-	-		
8	CIP Tank Detergent Mixing (If Applicable)	-	-	-	-		
9	Flush 2 R1	00:28	01:00	00:20	04:30		
10	Flush 2 SD1	01:46	11:47	06:35	01:50		
11	CIP Tank Cleaning with Industrial Water	-	-	-	-		
12	CIP Collector Cleaning with Industrial Water	-	-	-	-		
13	CIP Tank / Collector Solvent Removal Verification	-	-	-	-		
14	CIP Tank Refill with Industrial Water	-	-	-	-		
15	Flush 3A R1	-	02:30	01:34	-		
16	Flush 3A SD1	-	19:40	03:16	-		
17	CIP Tank Cleaning with Deionized Water	-	-	-	-		
18	CIP Collector Cleaning with Deionized Water	-	-	-	-		
19	CIP Tank Refill with Deionized Water	-	-	-	-		
20	Flush 3B R1	-	04:20	06:28	01:50		
21	Flush 3B SD1	-	04:54	06:28	01:26		
22	Drying R1	02:10	00:50	00:39	00:20		
23	VI R1	00:10	00:10	00:05	00:10		
24	Drying Setup SD1	-	15:28	02:25	02:43		
25	Drying SD1	03:13	03:47	00:17	01:40		
26	VI SD1	00:51	00:15	00:55	01:35		
27	Product Removal Sampling + Analysis R1	-	14:24	22:34	20:30		
28	Product Removal Sampling + Analysis SD1	-	30:18	35:51	17:40		
29	Solvent Removal Sampling + Analysis R1	-	03:16	00:19	11:20		
30	Solvent Removal Sampling + Analysis SD1	-	01:28	-	27:08		
31	Drying R1	-	02:13	04:51	06:30		
32	VI R1	-	00:10	00:07	00:05		
33	Drying SD1	-	04:04	06:21	05:00		
34	VI SD1	-	00:05	00:05	00:07		
Total Time (hour)		71:14	146:42	113:37	147:14	00:00	00:00
Total Time (days)		Day 2 - 23:14	Day 6 - 02:42	Day 4 - 17:37	Day 6 - 03:14	Day 0 - 00:00	Day 0 - 00:00
Total Time Average (days)		Day 4 - 23:41					

Note: This sequence of images is the Instructions Manual: “3. Instructions Manual.pptx”

Figure 4.3: Instructions Manual for the use of the Swimlane Map Continuous Improvement Tool (1/4).

The previously inputted data is automatically treated in the same Excel Spreadsheet measuring the Mean, the Standard Deviation and the Coefficient of Variation.

The Top 3 Time-Consuming Operations and the Top 3 Sources of Variability are automatically highlighted with Excel's Conditional Formatting Functionality.

1. Register Sheet Data

		TOP 3 TIME-CONSUMING OPERATIONS	NOT IN OUR CONTROL	TOP 3 SOURCES OF VARIABILITY
Operation #	**Cleaning Operations**	**Mean ([hh]:mm)**	**Standard Deviation ([hh]:mm)**	**Coefficient of Variation**
1	Integrity Tests	05:25	04:42	0.87
2	CIP Tank Fill w/ Industrial Water	15:05	10:26	0.69
3	Setup SD1 - CIP Assembly	09:44	09:23	0.96
4	Setup R1 - CIP Assembly	02:36	01:29	0.57
5	Flush 1 SD1	02:49	01:55	0.68
6	Flush 1 R1	02:10	00:35	0.27
7	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	No Data Available	No Data Available	No Data Available
8	CIP Tank Detergent Mixing (If Applicable)	No Data Available	No Data Available	No Data Available
9	Flush 2 R1	01:34	01:58	1.25
10	Flush 2 SD1	05:29	04:45	0.87
11	CIP Tank Cleaning with Industrial Water	No Data Available	No Data Available	No Data Available
12	CIP Collector Cleaning with Industrial Water	No Data Available	No Data Available	No Data Available
13	CIP Tank / Collector Solvent Removal Verification	No Data Available	No Data Available	No Data Available
14	CIP Tank Refill with Industrial Water	No Data Available	No Data Available	No Data Available
15	Flush 3A R1	02:02	00:39	0.32
16	Flush 3A SD1	11:28	11:35	1.01
17	CIP Tank Cleaning with Deionized Water	No Data Available	No Data Available	No Data Available
18	CIP Collector Cleaning with Deionized Water	No Data Available	No Data Available	No Data Available
19	CIP Tank Refill with Deionized Water	No Data Available	No Data Available	No Data Available
20	Flush 3B R1	04:12	02:19	0.55
21	Flush 3B SD1	04:16	02:34	0.60
22	Drying R1	00:59	00:48	0.81
23	VI R1	00:08	00:02	0.29
24	Drying Setup SD1	06:52	07:26	1.08
25	Drying SD1	02:14	01:34	0.71
26	VI SD1	00:54	00:32	0.61
27	Product Removal Sampling + Analysis R1	19:09	04:14	0.22
28	Product Removal Sampling + Analysis SD1	27:56	09:19	0.33
29	Solvent Removal Sampling + Analysis R1	04:58	05:42	1.15
30	Solvent Removal Sampling + Analysis SD1	14:18	18:08	1.27
31	Drying R1	04:31	02:09	0.48
32	VI R1	00:07	00:02	0.34
33	Drying SD1	05:08	01:08	0.22
34	VI SD1	00:05	00:01	0.20

Since the Product and Solvent Analysis are performed by the Quality Control Department they are not contemplated in the Top 3 Assessment.

Figure 4.4: Instructions Manual for the use of the Swimlane Map Continuous Improvement Tool (2/4).

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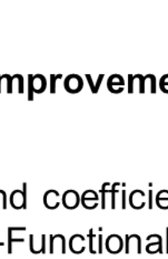
The mean, standard deviation and coefficient of variation columns are **linked** to an external Excel Spreadsheet with a Cross-Functional Flowchart functionality.

2. Cleaning Process Map

Imported		
Mean	Standard Deviation	Coefficient of variation
05:25:20	04:42:46	0,87
15:05:00	10:26:17	0,69
09:44:15	09:23:47	0,96
02:36:15	01:29:34	0,57
02:49:15	01:55:25	0,68
02:10:15	00:35:35	0,27
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
01:34:30	01:58:16	1,25
05:29:30	04:45:44	0,87
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
02:02:00	00:39:36	0,32
11:28:00	11:35:48	1,01
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
04:12:40	02:19:09	0,55
04:16:00	02:34:33	0,60
00:59:45	00:48:27	0,81
00:08:45	00:02:30	0,29
06:52:00	07:26:58	1,08
02:14:15	01:34:49	0,71
00:54:00	00:32:43	0,61
19:09:20	04:14:46	0,22
03:56:20	09:19:08	0,33
04:58:20	05:42:11	1,15
14:18:00	18:08:57	1,27
04:31:20	02:09:37	0,48
00:07:20	00:02:31	0,34
05:08:20	01:08:53	0,22
00:05:40	00:01:09	0,20



1. Register Sheet Data

TOP 3 TIME-CONSUMING OPERATIONS	NOT IN OUR CONTROL	TOP 3 SOURCES OF VARIABILITY
Mean ([hh]:mm)	**Standard Deviation ([hh]:mm)**	**Coefficient of Variation**
05:25	04:42	0.87
15:05	10:26	0.69
09:44	09:23	0.96
02:36	01:29	0.57
02:49	01:55	0.68
02:10	00:35	0.27
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
01:34	01:58	1.25
05:29	04:45	0.87
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
02:02	00:39	0.32
11:28	11:35	1.01
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
04:12	02:19	0.55
04:16	02:34	0.60
00:59	00:48	0.81
00:08	00:02	0.29
06:52	07:26	1.08
02:14	01:34	0.71
00:54	00:32	0.61
19:09	04:14	0.22
27:56	09:19	0.33
04:58	05:42	1.15
14:18	18:08	1.27
04:31	02:09	0.48
00:07	00:02	0.34
05:08	01:08	0.22
00:05	00:01	0.20

Figure 4.5: Instructions Manual for the use of the Swimlane Map Continuous Improvement Tool (3/4).

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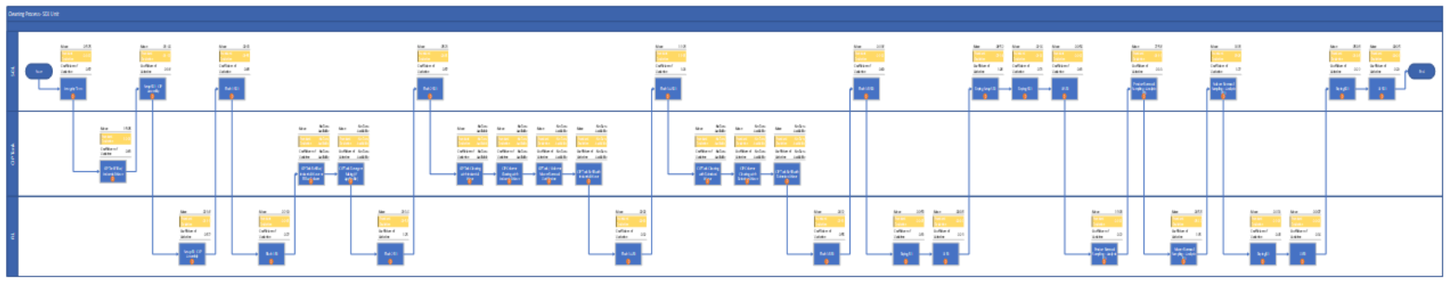
2. Cleaning Process Map

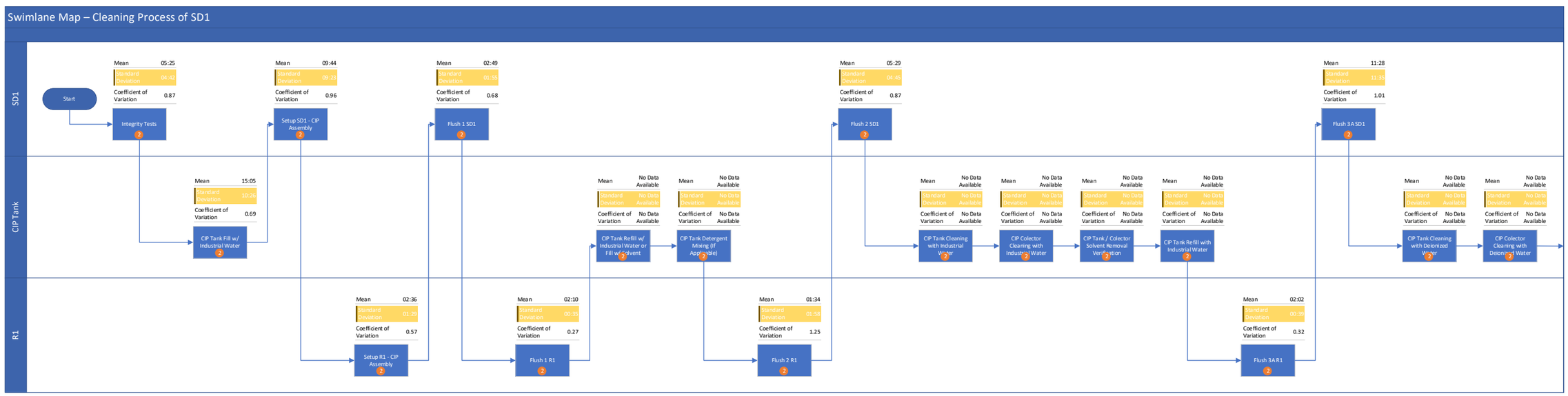
Step ID	Process Step Description	Next Step ID	Share Type	Function	Phase	Human Resources	Mean	Standard Deviation	Coefficient of Variation
1	Start	2	Start	SD1	Cleaning Process - SD1 Unit				
2	Integrity Tests	3	Process	SD1	Cleaning Process - SD1 Unit	2	05:25	04:42	0.87
3	CIP Tank Fill w/ Industrial Water	4	Process	CIP Tank	Cleaning Process - SD1 Unit	2	15:05	10:26	0.69
4	Setup SD1 - CIP Assembly	5	Process	SD1	Cleaning Process - SD1 Unit	2	09:44	09:23	0.96
5	Setup R1 - CIP Assembly	6	Process	R1	Cleaning Process - SD1 Unit	2	02:36	01:29	0.57
6	Flush 1 SD1	7	Process	SD1	Cleaning Process - SD1 Unit	2	02:49	01:55	0.68
7	Flush 1 R1	8	Process	R1	Cleaning Process - SD1 Unit	2	02:10	00:35	0.27
8	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	9	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
9	CIP Tank Detergent Mixing (If Applicable)	10	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
10	Flush 2 R1	11	Process	R1	Cleaning Process - SD1 Unit	2	01:34	01:58	1.25
11	Flush 2 SD1	12	Process	SD1	Cleaning Process - SD1 Unit	2	05:29	04:45	0.87
12	CIP Tank Cleaning with Industrial Water	13	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
13	CIP Colector Cleaning with Industrial Water	14	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
14	CIP Tank / Colector Solvent Removal Verification	15	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
15	CIP Tank Refill with Industrial Water	16	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
16	Flush 3A R1	17	Process	R1	Cleaning Process - SD1 Unit	2	02:02	00:39	0.32
17	Flush 3A SD1	18	Process	SD1	Cleaning Process - SD1 Unit	2	11:28	11:35	1.01
18	CIP Tank Cleaning with Deionized Water	19	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
19	CIP Colector Cleaning with Deionized Water	20	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
20	CIP Tank Refill with Deionized Water	21	Process	CIP Tank	Cleaning Process - SD1 Unit	2	No Data Available	No Data Available	No Data Available
21	Flush 3B R1	22	Process	R1	Cleaning Process - SD1 Unit	2	04:12	02:19	0.55
22	Flush 3B SD1	23	Process	SD1	Cleaning Process - SD1 Unit	2	04:16	02:34	0.60
23	Drying R1	25	Process	R1	Cleaning Process - SD1 Unit	2	00:59	00:48	0.81
24	VI R1	26	Process	R1	Cleaning Process - SD1 Unit	2	00:08	00:02	0.29
25	Drying Setup SD1	27	Process	SD1	Cleaning Process - SD1 Unit	2	06:52	07:26	1.08
26	Drying SD1	28	Process	SD1	Cleaning Process - SD1 Unit	2	02:14	01:34	0.71
27	VI SD1	29	Process	SD1	Cleaning Process - SD1 Unit	2	00:54	00:32	0.61
28	Product Removal Sampling + Analysis R1	30	Process	R1	Cleaning Process - SD1 Unit	2	19:09	04:14	0.22
29	Product Removal Sampling + Analysis SD1	31	Process	SD1	Cleaning Process - SD1 Unit	2	27:56	09:19	0.33
30	Solvent Removal Sampling + Analysis R1	32	Process	R1	Cleaning Process - SD1 Unit	2	04:58	05:42	1.15
31	Solvent Removal Sampling + Analysis SD1	33	Process	SD1	Cleaning Process - SD1 Unit	2	14:18	18:08	1.27
32	Drying R1	34	Process	R1	Cleaning Process - SD1 Unit	2	04:31	02:09	0.48
33	VI R1	35	Process	R1	Cleaning Process - SD1 Unit	2	00:07	00:02	0.34
34	Drying SD1	36	Process	SD1	Cleaning Process - SD1 Unit	2	05:08	01:08	0.22
35	VI SD1	37	Process	SD1	Cleaning Process - SD1 Unit	2	00:05	00:01	0.20
36	End		End	SD1	Cleaning Process - SD1 Unit				

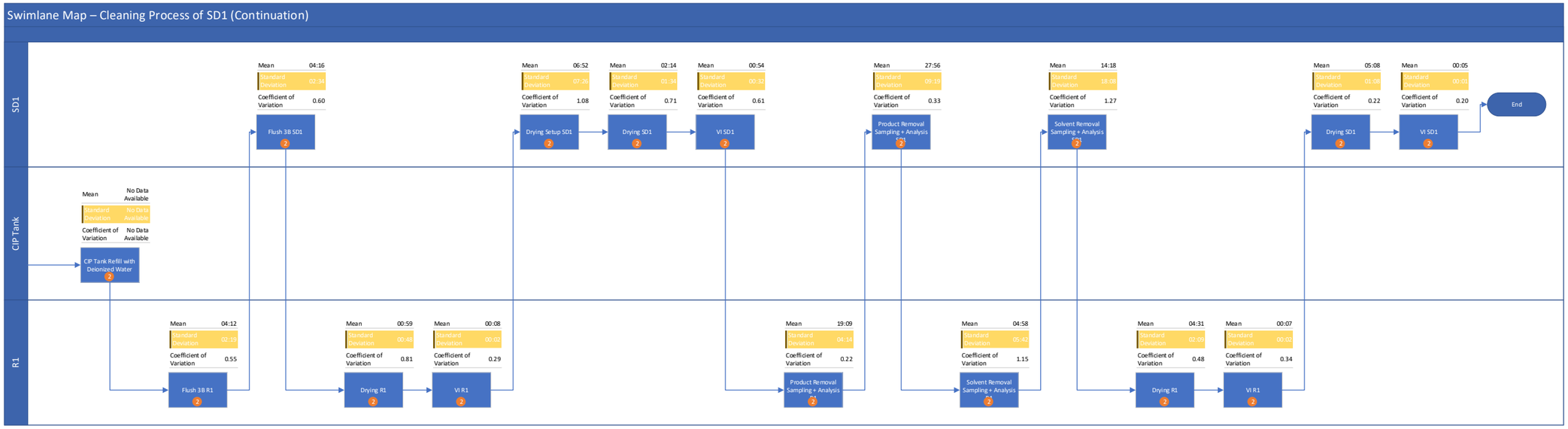
Imported		
Mean	Standard Deviation	Coefficient of variation
05:25:20	04:42:46	0.87
15:05:00	10:26:17	0.69
09:44:15	09:23:47	0.96
02:36:15	01:29:34	0.57
02:49:15	01:55:25	0.68
02:10:15	00:35:35	0.27
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
01:34:30	01:58:16	1.25
05:29:30	04:45:44	0.87
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
02:02:00	00:39:36	0.32
11:28:00	11:35:48	1.01
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
No Data Available	No Data Available	No Data Available
04:12:40	02:19:09	0.55
04:16:00	02:34:33	0.60
00:59:45	00:48:27	0.81
00:08:45	00:02:30	0.29
06:52:00	07:26:58	1.08
02:14:15	01:34:49	0.71
00:54:00	00:32:43	0.61
19:09:20	04:14:46	0.22
03:56:20	09:19:08	0.33
04:58:20	05:42:11	1.15
14:18:00	18:08:57	1.27
04:31:20	02:09:37	0.48
00:07:20	00:02:31	0.34
05:08:20	01:08:53	0.22
00:05:40	00:01:09	0.20



Final Result: Swimlane Map with Quantification and Variability of the Cleaning Operations

Figure 4.6: Instructions Manual for the use of the Swimlane Map Continuous Improvement Tool (4/4).





2 Number of operators

Figure 4.7: Exported Swimlane Map of the Continuous improvement Tool.

4.4 Continuous Improvement Loop

A Continuous Improvement Loop was developed to tackle both of the identified problems: the lack of quantification of the cleaning operations and the notorious detachment between the Cleaning Procedures prepared by the process engineers and the actual workflow of the cleaning operations in the shopfloor.

Table 4.3: Continuous Improvement Loop.

Cleaning Process	Continuous Improvement Tool
Cleaning Process 1	Register Sheet
Production Batch 1	
Cleaning Process 2	Suggestions Sheet
Production Batch 2	
Cleaning Process 3	No Continuous Improvement Tool
Production Batch 3	
Cleaning Process 4	Register Sheet
Production Batch 4	
Cleaning Process 5	Suggestions Sheet
Production Batch 5	
Cleaning Process 6	No Continuous Improvement Tool
Production Batch 6	
Cleaning Process 7	Register Sheet
Production Batch 7	
Cleaning Process 8	Suggestions Sheet
Production Batch 8	
Cleaning Process 9	No Continuous Improvement Tool
Continuous Improvement Loop: **1.** Upload data to the Swimlane Map Continuous Improvement Tool **2.** Gemba Walk + Brainstorm with Operators	

The Continuous Improvement Loop was developed considering the sustainability of the initiative, so the two tools created, the Register Sheet and the Suggestions Sheet, are never meant to be used simultaneously.

At the third cleaning process of the Continuous Improvement Loop, no use of any tool is demanded to to prevent the overburdening and facilitate the acceptance of the initiative from the operators and the process engineers.

5 Cleaning Process Automation

The final goal of the dissertation consisted in studying the improvements that Batch-Mode implementation over Auto-Mode could bring to the cleaning process.

5.1 Operations Sequence Variability in Auto-Mode

The implementation of Batch-Mode brings many advantages that will be shown next and also tackles one of the problems identified during the investigation of the Cleaning Procedures: the lack of a standardized sequence for the execution of the cleaning operations (see Table 5.1).

Table 5.1: Example of the variability of the cleaning operations sequence on Auto-Mode.

Different Sequencing per Cleaning Process		
Op. No.	**Cleaning Process 2**	**Cleaning Process 4**
1	CIP Tank Fill with Industrial Water	Integrity Tests
2	Setup R1 - CIP Assembly	CIP Tank Fill with Industrial Water
3	Flush1 R1	Setup R1 - CIP Assembly
4	Integrity Tests	Flush 1 R1
5	Setup SD1 - CIP Assembly	Setup SD1 - CIP Assembly
6	Flush 1 SD1	Flush 1 SD1
7	CIP Tank Refill with Industrial Water / Solvent	CIP Tank Refill with Industrial Water / Solvent
8	CIP Tank Detergent Mixing	CIP Tank Detergent Mixing
9	Flush 2 R1	Flush 2 R1
10	Flush 2 SD1	Flush 2 SD1
11	CIP Tank Cleaning with Industrial Water	CIP Tank Cleaning with Industrial Water
12	CIP Collector Cleaning with Industrial Water	CIP Collector Cleaning with Industrial Water
13	CIP Tank Refill with Industrial Water	CIP Tank Refill with Industrial Water
14	Flush 3A R1	Flush 3A R1
15	Flush 3A SD1	Flush 3A SD1
16	CIP Tank Cleaning with Deionized Water	CIP Tank Cleaning with Deionized Water
17	CIP Collector Cleaning with Deionized Water	CIP Collector Cleaning with Deionized Water
18	CIP Tank Refill with Deionized Water	CIP Tank Refill with Deionized Water
19	Flush 3B R1	Flush 3B R1
20	Flush 3B SD1	Flush 3B SD1
21	Drying Setup SD1	Drying R1
22	Drying SD1	VI R1
23	Drying R1	Drying Setup SD1
24	VI R1	Drying SD1
25	VI SD1	VI SD1

Since the Product and Solvent Verification are performed by the Quality Control Department, they cannot be automated and so are not contemplated in this study.

5.2 Identification of Automatable Operations

The first part of the study consists in identifying which operations can be fully automated, which can be automated but require human assistance and which have to be performed infield manually by the operators. This identification is exhibited in Table 5.2.

Table 5.2: Cleaning operations that are fully automatable, automatable but need human assistance and are not automatable.

Op. No.	Operation Description	Operation Time, h
1	Integrity Tests	0.5
2	CIP Tank Fill with Industrial Water	0.5
3	Setup SD1 - CIP Assembly	1.5
4	Setup R1 - CIP Assembly	0.5
5	Flush 1 SD1	1
6	Flush 1 R1	0.5
7	CIP Tank Refill with Industrial Water / Solvent	0.5
8	CIP Tank Detergent Mixing	0.5
9	Flush 2 R1	1
10	Flush 2 SD1	2
11	CIP Tank Cleaning with Industrial Water	1.5
12	CIP Collector Cleaning with Industrial Water	0.5
13	CIP Tank Refill with Industrial Water	0.5
14	Flush 3A R1	1.5
15	Flush 3A SD1	2
16	CIP Tank Cleaning with Deionized Water	0.5
17	CIP Collector Cleaning with Deionized Water	0.5
18	CIP Tank Refill with Deionized Water	0.5
19	Flush 3B R1	2
20	Flush 3B SD1	2
21	Drying R1	1.5
22	VI R1	1
23	Drying Setup SD1	1
24	Drying SD1	8
25	VI SD1	2

→ Fully automated operations | Total No. of Operations = 14 | % Operations = 56%

→ Automated operations that require human assistance | Total No. of Operations = 5 | % Operations = 20%

→ Operations that cannot be automated | Total No. of Operations = 6 | % Operations = 24%

The times exhibited in Table 5.2 correspond to the duration time of the cleaning operations if no delays or inconveniences are faced during the cleaning process, and were estimated using the experience of one of the cleaning specialists of The Company.

As can be seen, all of the Flushes, the Drying step of both the R1 and SD1, the CIP Tank and Collector Cleaning and Refill with Industrial Water are fully automatable since the operators do not have to perform any activity infield to complete these operations.

The operations in the CIP Tank involving Detergent or Deionized Water are automatable but require human assistance to perform some minor activity infield, examples being, manually connect the Deionized Water Pipeline to the CIP Tank or setup the charge of the Detergent Recipient next to the CIP Tank.

All of the Setups, CIP Assemblies or Drying, the Integrity Tests of the HEPA filters and the Visual Inspections, have to be performed manually.

By analyzing Table 5.2, it is possible to conclude that over 50% of the identified operations are automatable and represent a time where one extra human resource, one operator, is freed from the DeltaV Workstation (see Figure 2.6).

5.3 Master Batch Recipe

The implementation of Batch-Mode without any previous study can be damaging since the cleaning process can become automatically stuck to an inefficient sequencing of the cleaning operations.

It is then concluded that a previous study of what is the best execution sequence, the Master Batch Recipe, must be performed. The aim of the study should be to maximize the parallelization between the operations that are fully automatable and the operations that have to be performed manually.

Since the CIP Tank can be automatically filled with industrial water, the freed operators can simultaneously perform the integrity tests to the HEPA filters and setup the reactor for the CIP. The setup of the reactor is performed before the setup of the SD since the latter is more time consuming than the first. As such, the setup of the SD should be parallelized with the reactor's 1st and 2nd Flush.

The next opportunity to parallelize operations comes on during the drying phase of the SD. This is the most time-consuming operation, with an estimated time of 8h, and so should be the focus of the next parallelization. To maximize the parallelization during the SD's drying phase, the 3rd and 4th Flush should be performed first on the SD. By reaching the drying phase of the SD first, it is possible to simultaneously perform the 3rd and 4th Flush on the reactor, along with its drying and visual inspection.

The design sequence is shown in Figure 5.1, sectioned in the Product and Cleaning Agent Removal Stages. A symbology was inserted to show what operations are fully automatable, automatable with human assistance and not automatable.

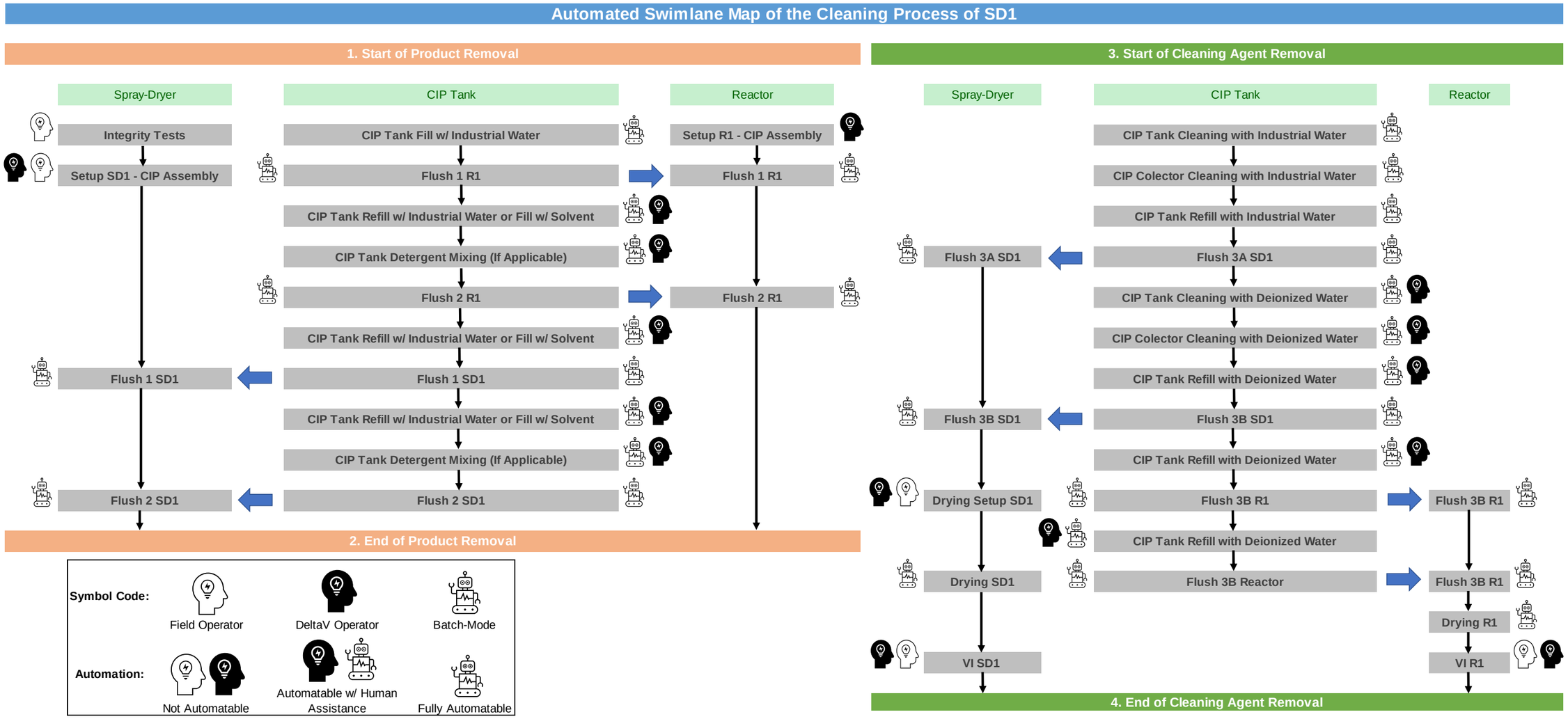


Figure 5.1: Best execution sequencing for the automated master batch recipe for the cleaning process.

Besides leading to the maximum parallelization of operations, the implementation of Batch-Mode also promotes the reduction of variability since the process is not relying on the operator's proficiency with the DeltaV program.

Since there is not, at the moment, a standardized sequence of performing the cleaning operations, when comparing Auto-Mode with Batch-Mode, no parallelization is assumed to be done in Auto-Mode. This allows us to see the sheer parallelization gains that are obtained when over 50% of the cleaning operations can be fully automated.

As can be seen in Figure 5.2, even though the number of operations performed with the Master Batch Recipe increases by four, the lead time of the cleaning process can be reduced in 21% due to the parellization of the cleaning operations.

Table 5.3: Extra time consumed with the repetition of the cleaning operations.

Repeated Cleaning Operations	Extra Time, h
2+ CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	2 × 0.5
1+ CIP Tank Detergent Mixing (If Applicable)	1 × 0.5
1+ CIP Tank Refill with Deionized Water	2 × 0.5
Total Time Added from the Extra Repetitions	**2**

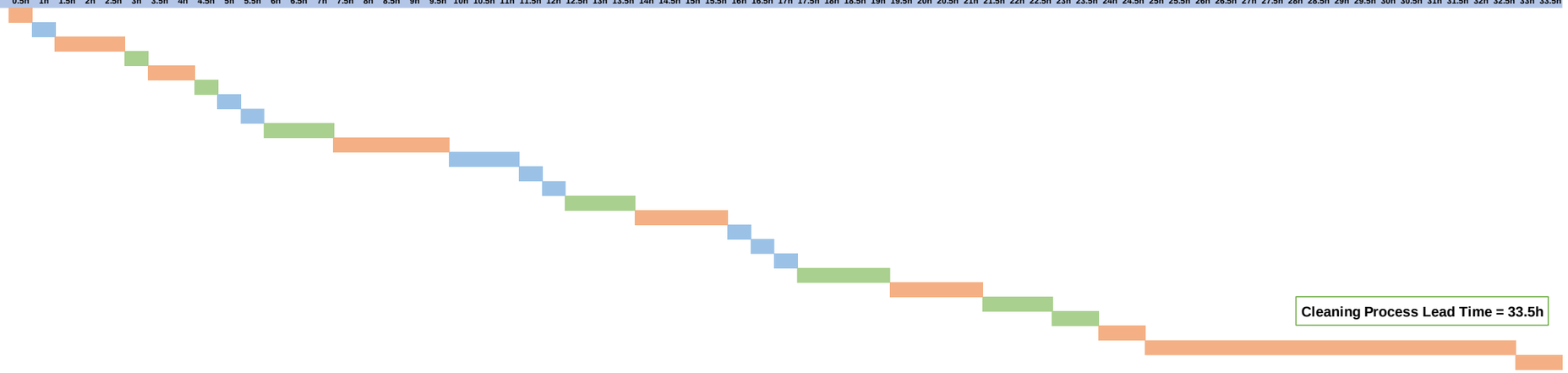
However, the repetition of the cleaning operations in Table 5.3, allows to create the parallelization focci exhibited in Figure 5.3, leading to the times in parallelization of Table 5.4.

Table 5.4: Time in parallelization of the cleaning operations and lead time reduction of the cleaning process.

Parallelization Foci	Time in Parallelization, h
1st	1
2nd	1.5
3rd	6.5
Total Time in Parallelization	**9**
Lead Time Reduction, h = 9 – 2 = 33.5 – 26.5 = 7 Lead Time Reduction = 21%	

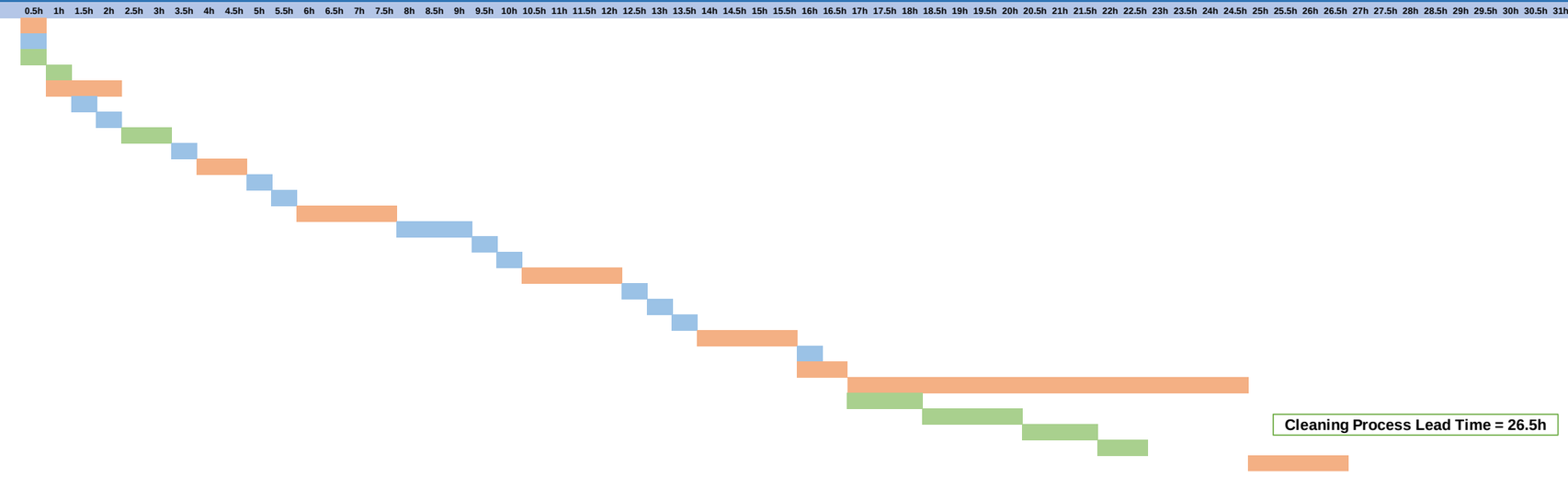
Auto-Mode

Operation #	Cleaning Operation	Operation Duration, h
1	Integrity Tests	0.5
2	CIP Tank Fill w/ Industrial Water	0.5
3	Setup SD1 - CIP Assembly	1.5
4	Setup R1 - CIP Assembly	0.5
5	Flush 1 SD1	1
6	Flush 1 R1	0.5
7	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5
8	CIP Tank Detergent Mixing (If Applicable)	0.5
9	Flush 2 R1	1
10	Flush 2 SD1	2
11	CIP Tank Cleaning with Industrial Water	1.5
12	CIP Colector Cleaning with Industrial Water	0.5
13	CIP Tank Refill with Industrial Water	0.5
14	Flush 3A R1	1.5
15	Flush 3A SD1	2
16	CIP Tank Cleaning with Deionized Water	0.5
17	CIP Colector Cleaning with Deionized Water	0.5
18	CIP Tank Refill with Deionized Water	0.5
19	Flush 3B R1	2
20	Flush 3B SD1	2
21	Drying R1	1.5
22	VI R1	1
23	Drying Setup SD1	1
24	Drying SD1	8
25	VI SD1	2



Batch-Mode

Operation #	Cleaning Operation	Operation Duration, h
1	Integrity Tests	0.5
2	CIP Tank Fill w/ Industrial Water	0.5
3	Setup R1 - CIP Assembly	0.5
4	Flush 1 R1	0.5
5	Setup SD1 - CIP Assembly	1.5
6	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5
7	CIP Tank Detergent Mixing (If Applicable)	0.5
8	Flush 2 R1	1
9	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5
10	Flush 1 SD1	1
11	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5
12	CIP Tank Detergent Mixing (If Applicable)	0.5
13	Flush 2 SD1	2
14	CIP Tank Cleaning with Industrial Water	1.5
15	CIP Colector Cleaning with Industrial Water	0.5
16	CIP Tank Refill with Industrial Water	0.5
17	Flush 3A SD1	2
18	CIP Tank Cleaning with Deionized Water	0.5
19	CIP Colector Cleaning with Deionized Water	0.5
20	CIP Tank Refill with Deionized Water	0.5
21	Flush 3B SD1	2
22	CIP Tank Refill with Deionized Water	0.5
23	Drying Setup SD1	1
24	Drying SD1	8
25	Flush 3A R1	1.5
26	Flush 3B R1	2
27	Drying R1	1.5
28	VI R1	1
29	VI SD1	2



Equipment Color Code: Spray-Dryer CIP Tank Reactor

Figure 5.2: Comparison of parallelization of the cleaning operations with Auto-Mode and Batch-Mode.

1st Focus of Parallelization			
Operation #	**Cleaning Operation**	**Operation Duration, h**	**0.5h**
1	Integrity Tests	0.5	
2	CIP Tank Fill w/ Industrial Water	0.5	
3	Setup R1 - CIP Assembly	0.5	

2nd Focus of Parallelization					
Operation #	**Cleaning Operation**	**Operation Duration, h**	**1h**	**1.5h**	**2h**
4	Flush 1 R1	0.5			
5	Setup SD1 - CIP Assembly	1.5			
6	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5			
7	CIP Tank Detergent Mixing (If Applicable)	0.5			

3rd Focus of Parallelization																	
Operation #	**Cleaning Operation**	**Operation Duration, h**	**17h**	**17.5h**	**18h**	**18.5h**	**19h**	**19.5h**	**20h**	**20.5h**	**21h**	**21.5h**	**22h**	**22.5h**	**23h**	**23.5h**	**24h**	**24.5h**
24	Drying SD1	8																
25	Flush 3A R1	1.5																
26	Flush 3B R1	2																
27	Drying R1	1.5																
28	VI R1	1																

Figure 5.3: Parallelization foci for the Batch-Mode Cleaning Operations Sequence.

5.4 Batch-Mode with Two CIP Tanks

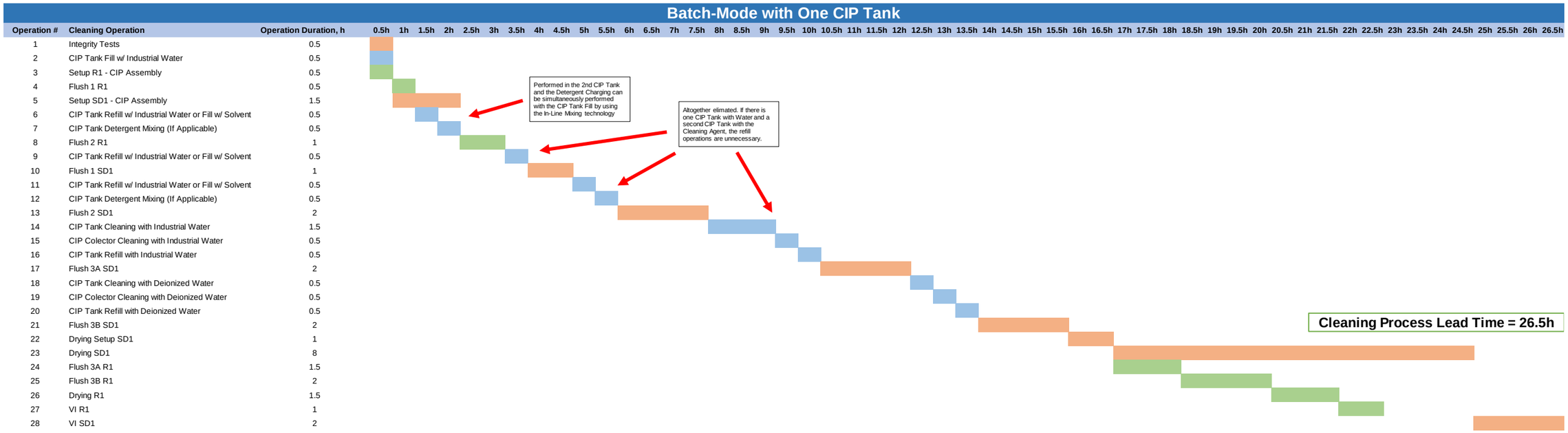
The extra added operations in Batch-Mode are performed in the CIP Tank and are either Refills or Detergent Mixing. These operations could be eliminated by adding a second CIP Tank and using the in-line mixing technology to perform the Detergent Mixing simultaneously with the CIP Tank Refill. The first CIP Tank is filled with industrial and deionized water to perform Flush 1, 3A and 3B, and the second CIP Tank is used for the preparation of the cleaning agent to perform Flush 2. The new sequence of the cleaning operations is exhibited and compared with Batch-Mode with one CIP Tank in Figure 5.4. On Table 5.5, the respective lead time for each of the three scenarios is displayed, together with the reduction that Batch-Mode brings over Auto-Mode.

Table 5.5: Lead Time for Auto-Mode, Batch-Mode with one CIP Tank and Batch-Mode with two CIP Tanks.

Mode and CIP Tanks	Lead Time, h	Reduction, %
Auto-Mode	33.5	-
Batch-Mode with One CIP Tank	26.5	21
Batch-Mode with Two CIP Tanks	21.5	36

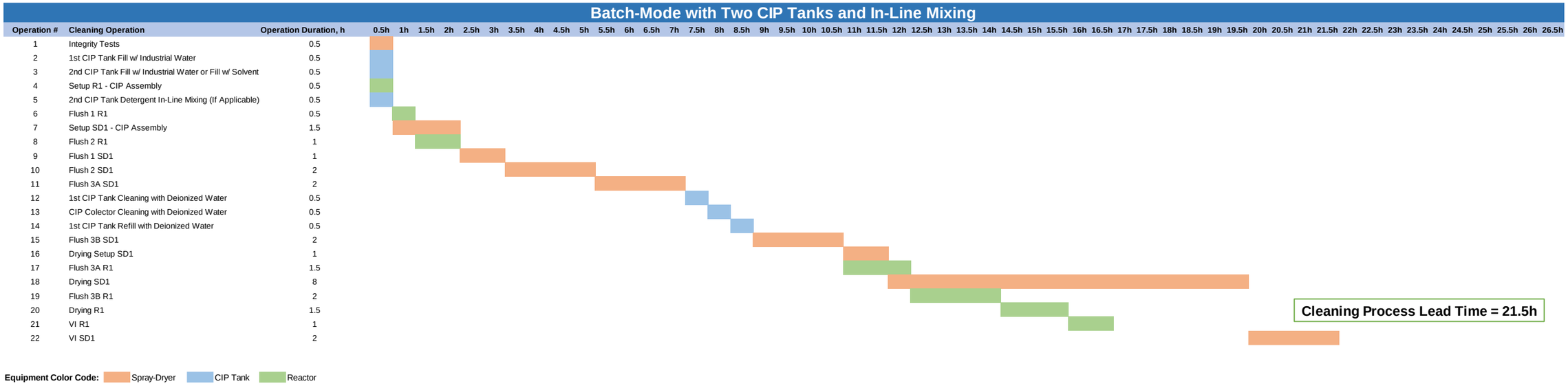
Batch-Mode with One CIP Tank

Operation #	Cleaning Operation	Operation Duration, h
1	Integrity Tests	0.5
2	CIP Tank Fill w/ Industrial Water	0.5
3	Setup R1 - CIP Assembly	0.5
4	Flush 1 R1	0.5
5	Setup SD1 - CIP Assembly	1.5
6	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5
7	CIP Tank Detergent Mixing (If Applicable)	0.5
8	Flush 2 R1	1
9	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5
10	Flush 1 SD1	1
11	CIP Tank Refill w/ Industrial Water or Fill w/ Solvent	0.5
12	CIP Tank Detergent Mixing (If Applicable)	0.5
13	Flush 2 SD1	2
14	CIP Tank Cleaning with Industrial Water	1.5
15	CIP Colector Cleaning with Industrial Water	0.5
16	CIP Tank Refill with Industrial Water	0.5
17	Flush 3A SD1	2
18	CIP Tank Cleaning with Deionized Water	0.5
19	CIP Colector Cleaning with Deionized Water	0.5
20	CIP Tank Refill with Deionized Water	0.5
21	Flush 3B SD1	2
22	Drying Setup SD1	1
23	Drying SD1	8
24	Flush 3A R1	1.5
25	Flush 3B R1	2
26	Drying R1	1.5
27	VI R1	1
28	VI SD1	2



Batch-Mode with Two CIP Tanks and In-Line Mixing

Operation #	Cleaning Operation	Operation Duration, h
1	Integrity Tests	0.5
2	1st CIP Tank Fill w/ Industrial Water	0.5
3	2nd CIP Tank Fill w/ Industrial Water or Fill w/ Solvent	0.5
4	Setup R1 - CIP Assembly	0.5
5	2nd CIP Tank Detergent In-Line Mixing (If Applicable)	0.5
6	Flush 1 R1	0.5
7	Setup SD1 - CIP Assembly	1.5
8	Flush 2 R1	1
9	Flush 1 SD1	1
10	Flush 2 SD1	2
11	Flush 3A SD1	2
12	1st CIP Tank Cleaning with Deionized Water	0.5
13	CIP Colector Cleaning with Deionized Water	0.5
14	1st CIP Tank Refill with Deionized Water	0.5
15	Flush 3B SD1	2
16	Drying Setup SD1	1
17	Flush 3A R1	1.5
18	Drying SD1	8
19	Flush 3B R1	2
20	Drying R1	1.5
21	VI R1	1
22	VI SD1	2



Equipment Color Code: Spray-Dryer CIP Tank Reactor

Figure 5.4: Comparison of parallelization of the cleaning operations with Batch-Mode with one CIP Tank and Batch-Mode with two CIP Tanks.

6 Conclusions

In this thesis, the goal was to ascertain how the cleaning process high lead time and variability of SD1 could be diminished.

The main problem identified was the inexistence of sufficient data to know what the operational root causes of this problem are, revealing the cleaning process of SD1 as a black box and making it impossible to effectively target improvement efforts.

As such, the Standard Work Methodology was used to identify what are the cleaning operations necessary to complete the cleaning process. Next, an investigation of the Cleaning Procedures was carried out to determine the meantime and coefficient of variation of the identified cleaning operations. It was concluded that the Cleaning Procedures are not the appropriated tool to extract that data: the extraction is overly laborious, and the process engineers would not have the time to provide continuity to the performed investigation. The data extracted from the Cleaning Procedures is also accompanied by a considerable error, and so the results are not entirely reliable. Nonetheless, brainstorming and proposals of improvement were provided that could help guide the process engineers to uncover the root causes of the high meantime of the Top 3 Time-Consuming Operations and the high coefficient of variation of the Top 3 Sources of Variability identified with the data from the Cleaning Procedures.

Since the Cleaning Procedures are not an efficient and effective tool to quantify the cleaning operations, a Register Sheet was created to enable the quantification of the cleaning operations, and an easily updatable Excel Spreadsheet was left prepared highlighting the Top 3 Time-Consuming Operations and the Top 3 Sources of Variability. The data collected from the Excel Spreadsheet was automatically linked with Visio's Cross-Functional Map functionality to readily allow a Swimlane Map visual representation of the collected data.

During the Gemba Walks, the feedback collected from the operators denoted an evident detachment between the Cleaning Procedures prepared by the process engineers and the actual workflow of the cleaning operations in the shopfloor. As such, a Suggestions Sheet was created to allow the operators to give feedback regarding the inaccuracies in the Cleaning Procedures and propose suggestions for improvement.

A Continuous Improvement Loop was developed based on the two tools provided, the Register Sheet and the Suggestions Sheet, to tackle both of the identified problems: the impossibility of quantification of the cleaning operations and the lack of opportunity for the operators to give feedback regarding the Cleaning Procedures. The CI Loop also takes into consideration the sustainability of the initiative, aiming for incremental improvements, and so the two Sheets are never planned to be used simultaneously, to prevent the overburdening of both the operators and the process engineers. The CI Loop should finish with a brainstorming session about the collected data, and a Gemba Walk should be done to evaluate the cleaning operations where they are performed: in the shopfloor.

Another of the identified problems regarding the cleaning process of SD1 was the lack of a standardized sequence in the performance of the cleaning operations. This promotes variability, impedes

reproducibility, and hinders the sustainability of future continuous improvement efforts since there is not a standardized way of working. To better understand this situation, an investigation on the potentiality of having batch mode implemented in the cleaning process control system was carried out in order to identify what operations could be fully automated, and, as such, free one operator from the DeltaV Workstation. With these operations identified, it is possible to design the best cleaning operations sequence that promotes the maximization of parallelization of operations leading to a reduction in the lead time of the cleaning process of 21%. It was also examined how the use of a second CIP Tank and in-line mixing technology could lead to a reduction of 36% in the lead time of the cleaning process by eliminating the time spent in CIP Tank Refill and in the Detergent Mixing operations. Automation also enables the cleaning process continuous improvement because it establishes a standardized way of performing the cleaning operations and it promotes variability reduction since the control system performance is not relying on the operator's proficiency with DeltaV, which leads to a positive impact on predictability.

6.1 Recommendations for Future Work

The most frustrating limitation of this thesis was the lack of raw data making it impossible to quantify the cleaning operations. This prevents knowing with precision if the possible implementation of certain continuous improvement tools, like the 5S and the SMED, could lead to significant improvement in the cleaning process. As such, these tools are suggested to be discussed during the brainstorming in the Continuous Improvement Loop.

The Covid-19 pandemic situation also prevented the use of more Gemba Walks, and the time spent infield with the operators got severely compromised. As such, special attention should be given to the Gemba Walk to get a more accurate depiction of what the cleaning operations actually look like.

A batch recipe should be developed following the sequence in the Master Batch Recipe; the results should be evaluated and, if positive, the Master Batch Recipe should be applied transversely.

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Appendices

Appendix A – Current Status

Appendix A.1 – Q-Q Plots for Normality Testing

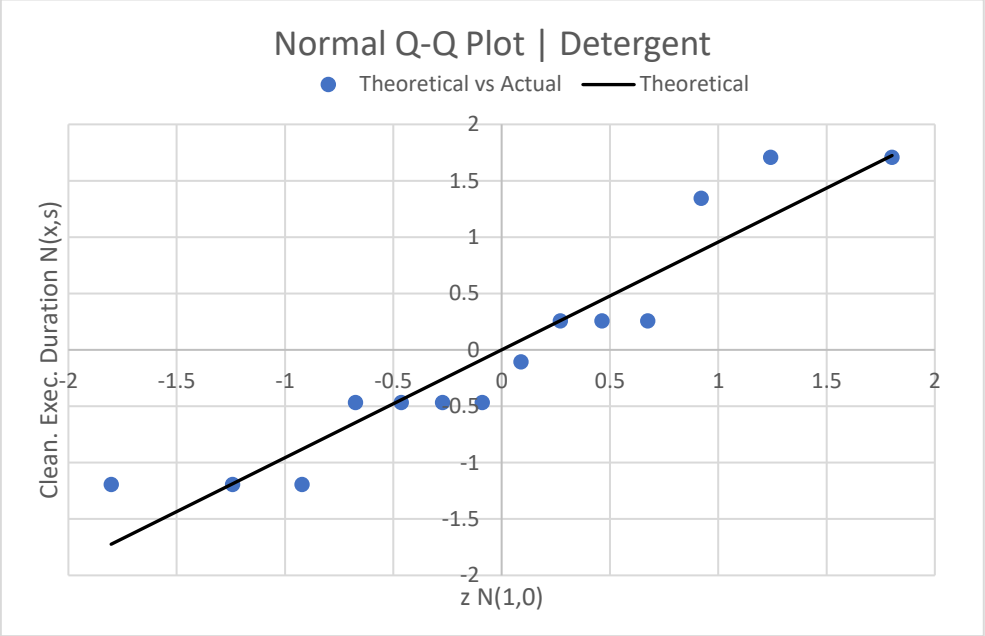

Figure A.1.1: Q-Q Plot for Cleaning Execution Duration performed with Detergent.

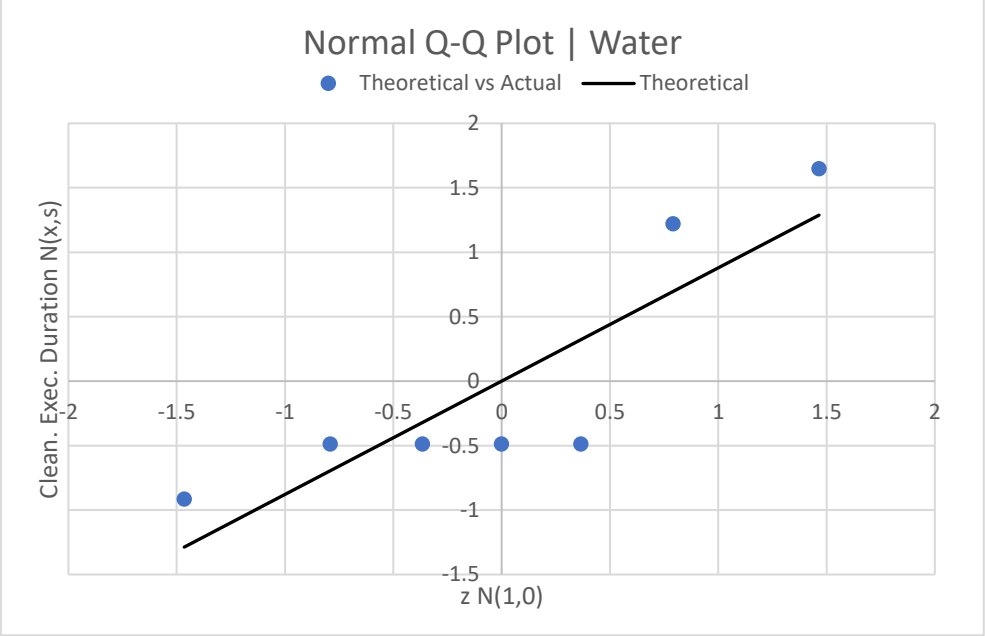

Figure A.1.2: Q-Q Plot for Cleaning Execution Duration performed with Water.

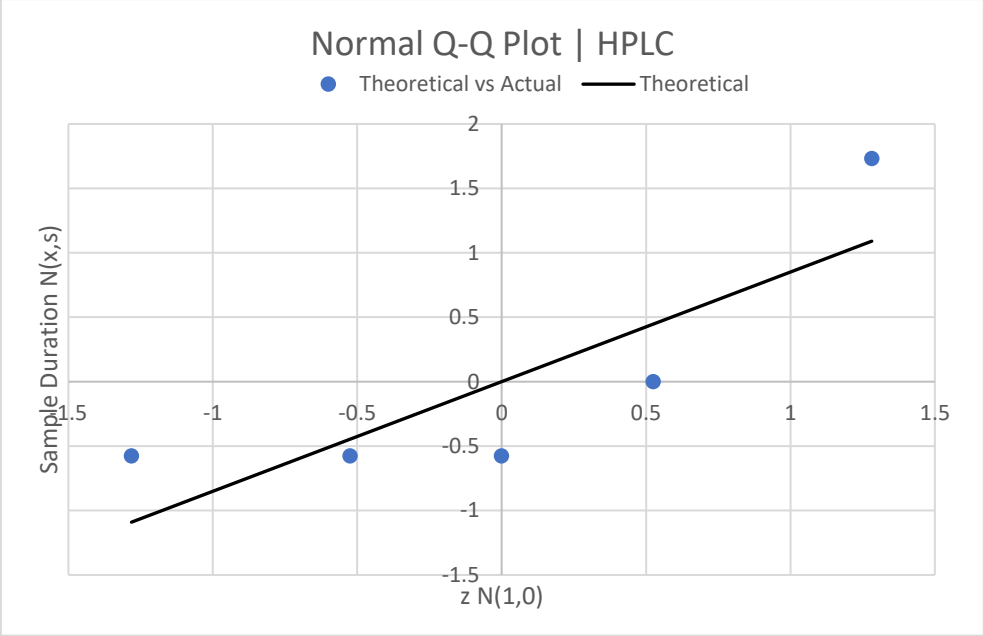

Figure A.1.3: Q-Q Plot for Sample Analysis Duration performed with HPLC method.

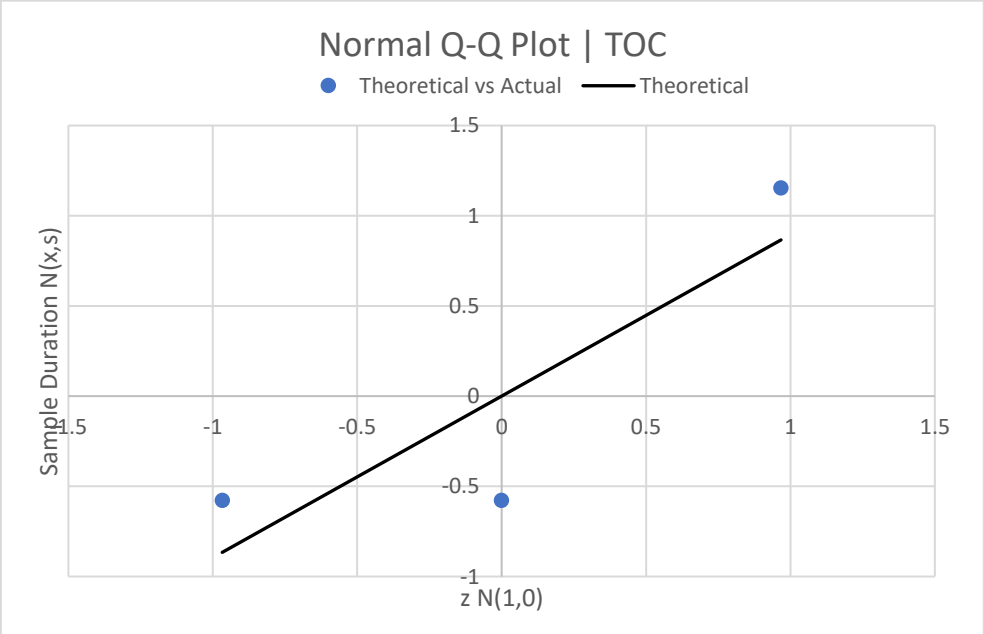

Figure A.1.4: Q-Q Plot for Sample Analysis Duration performed with TOC method.

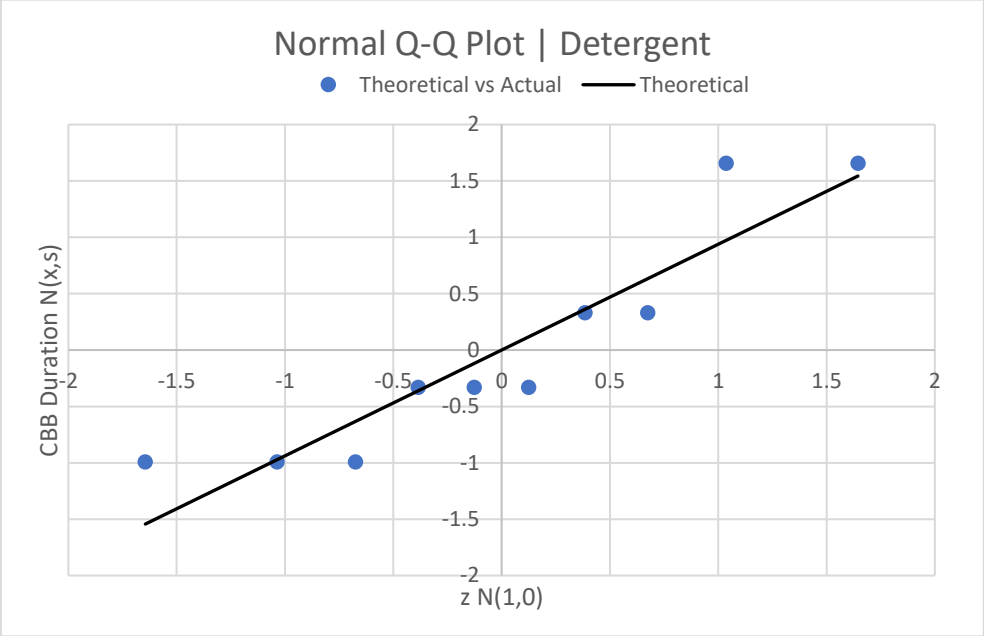

Figure A.1.5: Q-Q Plot for CBB Duration performed with Detergent.

If we observe the raw data regarding the CBBs performed with water, we will find 3 sample points, all of the duration one day. As such, there is no distribution of the sample points whatsoever, and normality testing is pointless.

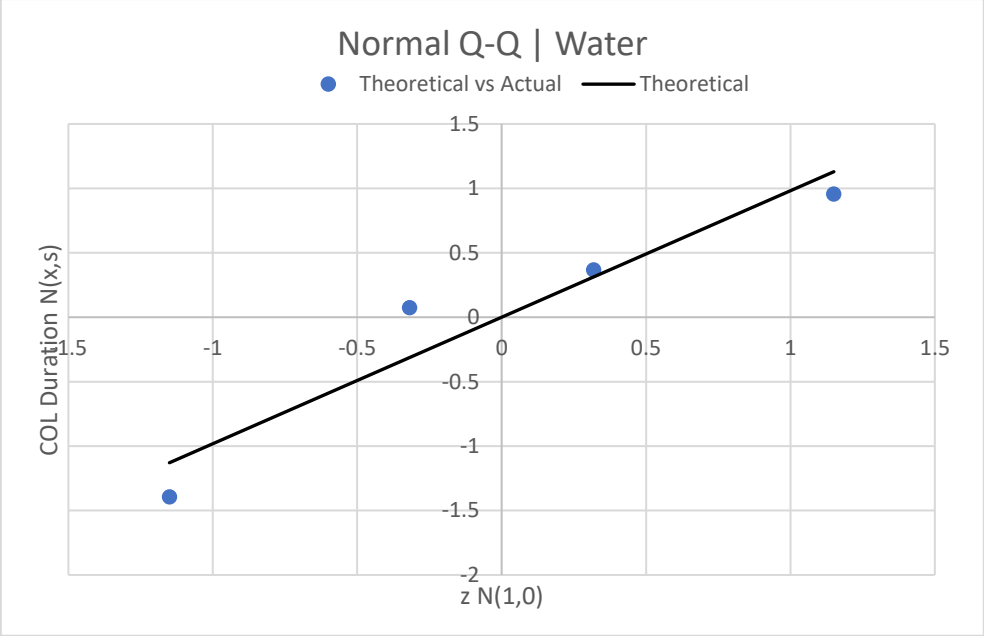

Figure A.1.6: Q-Q Plot for COL Duration performed with Detergent.

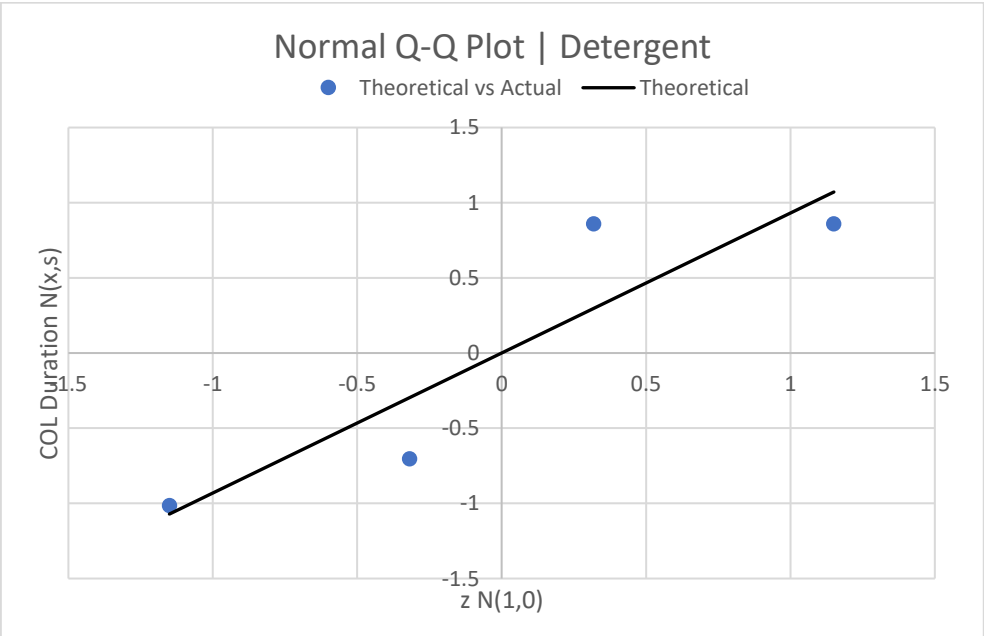

Figure A.1.7: Q-Q Plot for COL Duration performed with Water.

Appendix A.2 – Graphs for Mean and Standard Error of the Cleaning Times

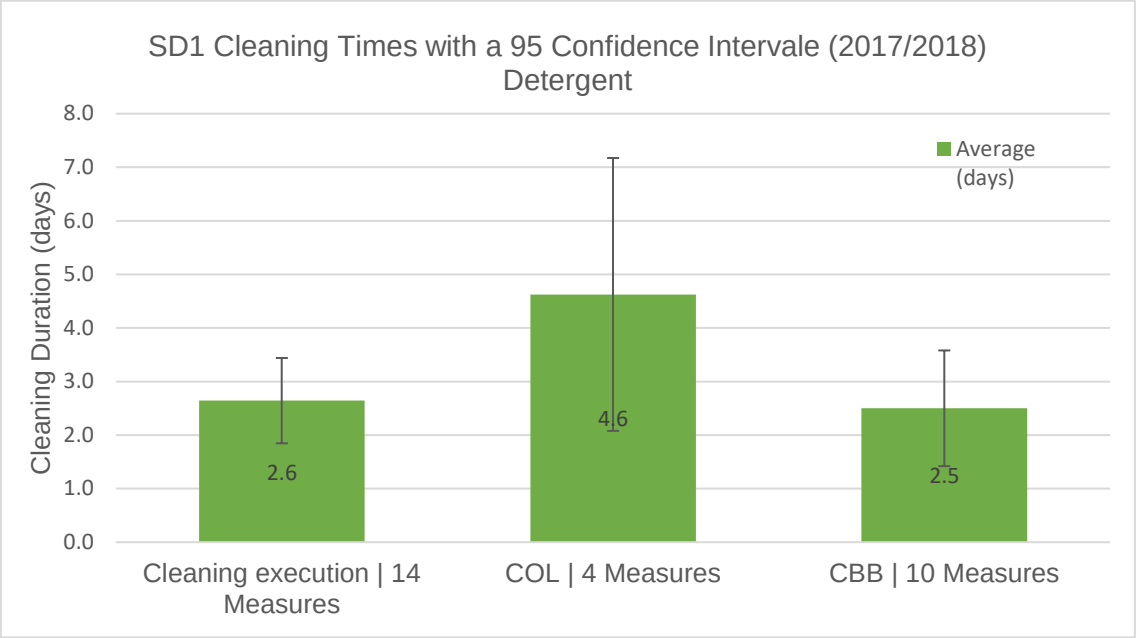

Figure A.2.1: Average cleaning times for cleaning performed with Detergent with Error Bars.

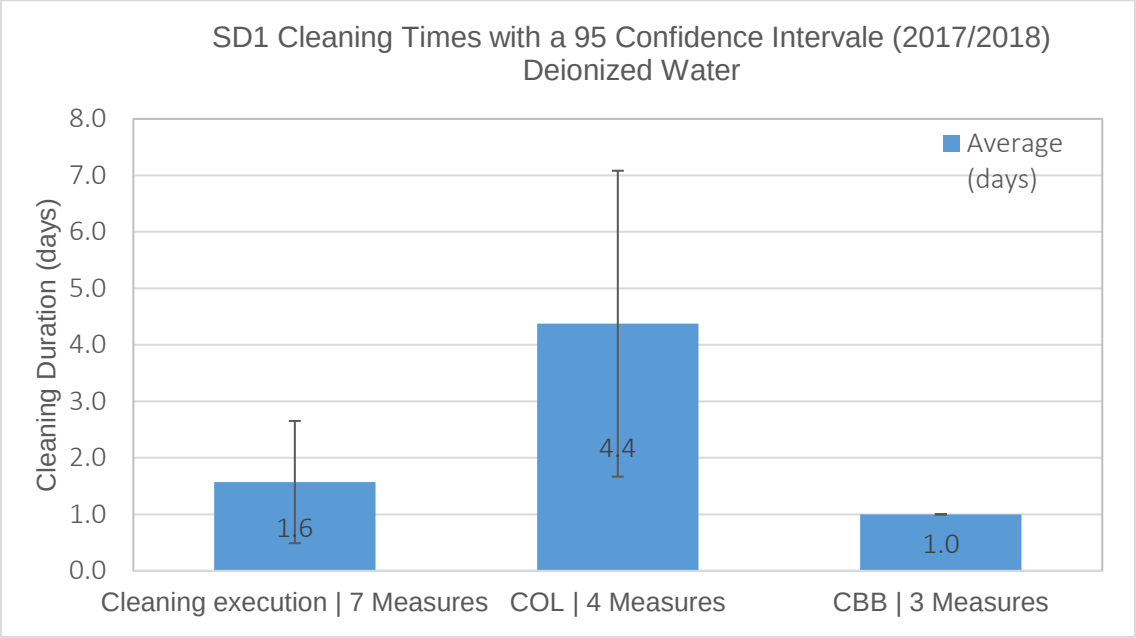

Figure A.2.2: Average cleaning times for cleaning performed with Deionized Water with Error Bars.

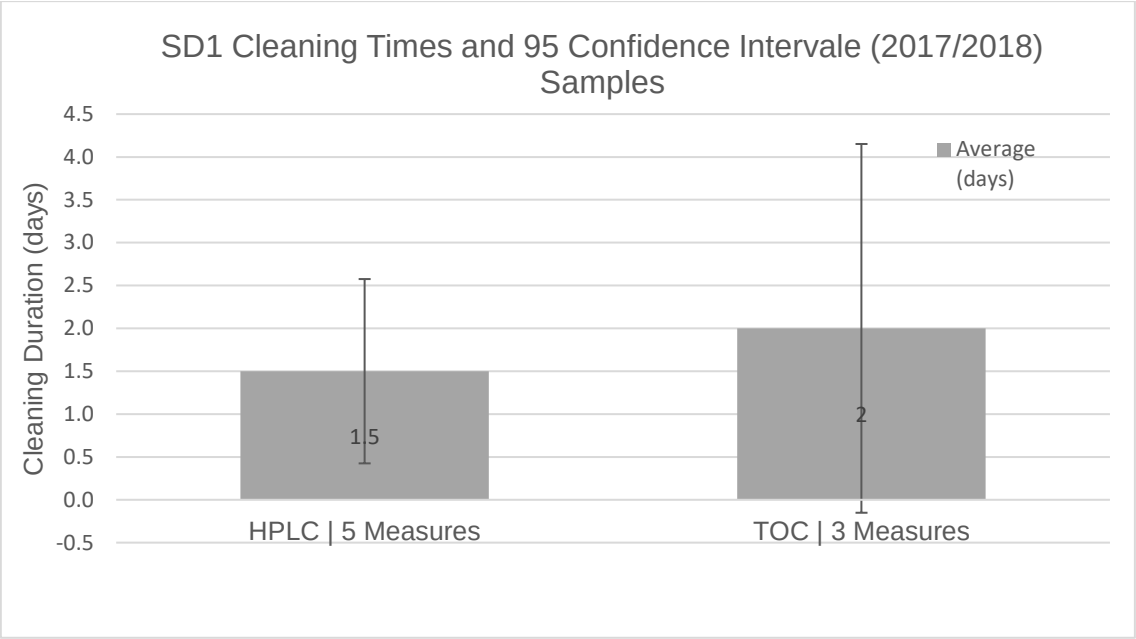

Figure A.2.3: Average Sample Analysis Times performed with HPLC and TOC methods with Error Bars.