Improvement and automation of cleaning processes in the Pharmaceutical Industry

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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 CI Loop also takes into consideration the sustainability of the initiative, aiming for incremental improvements. 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.

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1 Introduction

The cleaning of equipment in between production batches is an essential part of every multi-purpose industry for economic and legislative reasons, even more so in the pharmaceutical industry, where the regulations and implementations of cGMPs (current Good Manufacturing Practices) are more demanding than in other industries.

The Company is a company that 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). 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 equipment. The more time is spent cleaning; the less time is available to produce.

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. It prevents equipment malfunction caused by an accumulation of solid residues. It provides a clean surface for sanitization – 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.

1.1 Scope

It was within the scope of this thesis the mapping of a cleaning process for a specific spray-dryer, SD1 in the Pilot Plant Department, to identify the most time-consuming operations, the most impactful sources of variability and propose tools to promote the continuous improvement of the cleaning process.

To achieve reproducibility between cleaning processes, a significant challenge in The Company, automated cleaning processes are starting to be implemented, and it was within the scope of this thesis to design an optimized sequencing of performing the automated cleaning operations. By reducing the human interaction with the equipment, we reduce the variability between cleaning processes.

2 Literature Review

A literature review was conducted to assess the work that researchers and practitioners have done in related fields that could help discover new methods which may apply to the thesis' work.

2.1 Lean Manufacturing

2.1.1 Historical Context

The Toyota Production System (TPS) – Toyota's manufacturing system – is the precursor of lean manufacturing.

In 1937, Kiichiro Toyoda established The Toyota Motor Corporation. Influenced by the U.S. supermarket system of replenishing products on the shelves just in time as customers purchased them, Kiichiro's would discover the Just-In-Time principle: delivering what the customer wants when it is wanted, and the amount it is wanted [1] and implement it at Toyota.

After World War II and a tour to U.S. Plants, then Toyota's president Eiji Toyoda gave plant manager Taiichi Ohno the task to improve Toyota's manufacturing process productivity to match that of Ford [1]. 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 adopt Ford's manufacturing process to achieve simultaneously flexible, high quality, low cost and with short lead 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 activity, NVA, is much more important than speeding up individual Value-Added operations, VA [2].

In 1988, John F. Krafcik coined the term "lean" in his article *Triumph of the Lean Production System* [3]. The term would be made popular in the two bestselling books *The Machine That Changed the World* [4] and *Lean Thinking* [5].

2.1.2 Lean Wastes

Waste refers to any activity that does not add value to the product. Ohno was the first to identify the seven major types of NVA activity:

1. **Overproduction:** producing items for which there is no order;
2. **Waiting:** involves workers standing around waiting for the next processing step;
3. **Unnecessary transport:** carrying work in progress for long distances;

4. **Over-processing:** taking unneeded steps to process the parts;
5. **Excess inventory:** excess raw material, work in progress or finished goods causing longer lead times;
6. **Unnecessary movement:** any wasted motion the employee has to perform during their work;
7. **Defects:** production of defective parts is waste.

2.1.3 Lean Tools

As exhibited in [6], there is a myriad of tools at disposal to identify, quantify and eliminate waste in a process.

The most relevant to the scope of this thesis are:

- **Gemba Walks:** Japanese for "the place where the work gets done". In manufacturing, Gemba is the factory floor;
- **OEE:** abbreviated from "overall equipment effectiveness", a framework for measuring the efficiency and effectiveness of a process.

$$OEE = Avail. \times Perf. \times Qual.$$

  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;
- **SMED:** abbreviated from "single-minute exchange of die", and deeply discussed in [7], it started with Shigeo Shingo. 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 instructions based on the level of detail of the operation to allow the continuous improvement of the operations.

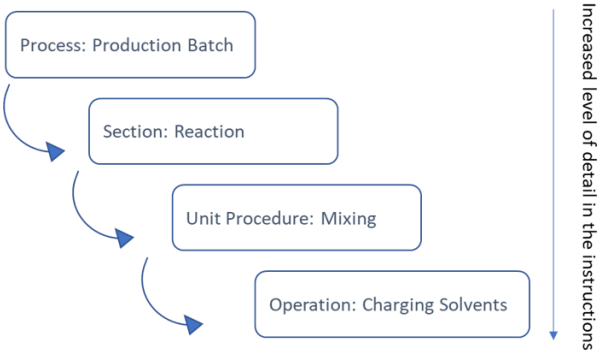

Figure 2.1: Example of application of the Standard Work methodology.

2.1.4 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.

Two types of process maps are presented, the ones most relevant to the scope of this dissertation: Value-Stream Map, VSM, and Cross-Functional Map.

- **Value-stream Map (VSM):** captures all vital flows of work, information and materials in a process and important process metrics to aid in the assessment of the Value-Added, VA, activity and the Non-Value-Added, NVA, activity;
- **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 get transformed into valuable outputs. The Cross-Functional Map is also known as a "Swimlane Map".

2.2 Good Manufacturing Practices

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 to minimize the risks involved in the

pharmaceutical production in any step of the process and distribution.

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

2.3 Cleaning Process

The cleaning process is a product removal process of equipment that takes place in between production batches. Cleaning does not provide any value to the customer but is necessary for multi-purpose installations, so it is considered a necessary waste or a Business-Value-Added activity, BVA.

When it comes to cleaning processes, two methodologies are available: clean-out-of-place (COP) and clean-in-place (CIP).

2.3.1 COP & CIP

Clean-out-of-place, COP, is accomplished by disassembling the equipment to perform manual washing and rinsing. Not useful for large installations.

Clean-in-place, CIP, is performed with the equipment installation setup has it is, where water, detergent solutions or solvents flow through the pipes to clean the equipment.

The core of the cleaning process at The Company is performed in-place.

2.4 Automation

2.4.1 Overview

Automation can be defined as the technology by which a process or procedure is performed without human assistance [8].

An automated system consists of three basic 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;
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. 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. [8].

2.4.2 Batch Recipes

The set of instructions described in the previous section is applied at The Company with a program called DeltaV, developed by a company called Emerson [9].

The DeltaV program is used to create the automated recipe, but it also used to control and operate the process without it. There are three modes in which DeltaV can operate:

1. **Manual-Mode:** the operator will need to open and close all the valves;
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".

All cleaning processes at The Company are currently running on Auto-Mode, and it was within the scope of this dissertation to assess what would be the best sequence of the cleaning operations in the implementation of Batch-Mode.

3 Spray-Drying Cleaning Process and Current Situation

3.1 Spray-Dryer Installation

At any given spray-dryer installation at The Company, the same core equipment is set up within the GMP area: the reactor, the spray-dryer, the cyclone, the bag filter and the HEPA (High-Efficiency Particulate Arrestance) filters which separate the Non-GMP from the GMP area.

3.2 Cleaning Methodology

The cleaning process of the spray-drying installation is performed in between production batches. If the cleaning is performed between batches of the same product, it is called "Cleaning Between Batches", abbreviated CBB. If the cleaning is performed between batches of different products, it is called "Change of Line", abbreviated, COL. The steps comprising the cleaning methodology are:

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.

3.3 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.

3.4 Assessment of the Current Situation

An assessment of the current status of the cleaning process with the readily available data was performed.

The received data is just a sample of the cleaning processes performed from 2017 to 2018; as such, 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 [10]), 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.

Table 3.1: 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 3.2: 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 3.3: 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 %

The cleaning execution with detergent is longer than the one performed with water, which is to be expected. Nevertheless, the cleaning process performed with just water, even being a simpler cleaning, is more variable than the one performed with detergent.

The red written values highlight the misapplication of the t-student method, with a 95% confidence interval. They represent the occasions when the Standard Error is greater the Standard Deviation, which means it is not possible to extrapolate that 95% of the samples of the cleaning processes performed in 2017 and 2018 fall within that Standard Error. The occasions where the 95% confidence interval is not applicable is in the analysis time of the samples, which hints at an overburdening or managing problem by the Quality Control Department.

The available data only informs us of the high lead time and variability of the cleaning process, but it does not hint any possible operational root causes, which makes it impossible to effectively target improvement efforts.

4 Investigation and Improvement of the Cleaning Process

4.1 Gemba Walk – Suggestions Sheet

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.

Table 4.1: Suggestion Sheet's Layout.

Column	Operator Input
1. C. P. Equip.	Problematic Cleaning Procedure
2. C. P. Step	Cleaning Procedure's problematic Step
3. Doubt	The problem in need of clarification
4. Suggestion for Improvement	Suggestion to eliminate the identified problem

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 critical safety measure, are never mentioned.

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.

4.2 Analysis of the Cleaning Procedures

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 the cleaning operations are exhibited in Table 4.2.

Table 4.2: Cleaning Operations identified with the Standard Work Methodology.

No.	Cleaning Operation Description
1	HEPA's Integrity Tests
2	CIP Tank Fill w/ Industrial Water
3	Setup SD1 - CIP Assembly
4	Setup R1 - CIP Assembly
5	Flush 1 SD1
6	Flush 1 R1
7	CIP Tank Refill w/ Industrial Water
8	CIP Tank Detergent Mixing (If Applicable)
9	Flush 2 R1
10	Flush 2 SD1
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
16	Flush 3A SD1
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
21	Flush 3B SD1
22	Drying R1
23	VI R1
24	Drying Setup SD1
25	Drying SD1
26	VI SD1
27	Product Removal Sampling + Analysis R1
28	Product Removal Sampling + Analysis SD1
29	Solvent Removal Sampling + Analysis R1
30	Solvent Removal Sampling + Analysis SD1
31	Drying R1
32	VI R1
33	Drying SD1
34	VI SD1

It is important to mention at this instant that there were no more records or historical data readily available 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 amounts 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.

The data regarding the last four Cleaning Procedures was used. After which, the meantime, the standard deviation, and the coefficient of variation (or relative standard deviation) of the measured cleaning operations were calculated. 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 4.3: 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

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 since the operator does not have to be operating the control system.

4.3 Swimlane Map – Register Sheet

The Cleaning Procedures did not facilitate the quantification of the cleaning operations. Since proper quantification of the cleaning operations is crucial because it makes it possible to target continuous improvement efforts effectively, a Register Sheet was created to be filled by the operators during the cleaning process.

With the data collected with the Register Sheet, a collection of Excel Templates was left prepared to allow an automatic treatment of the data identifying 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.

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 4.4: Continuous Improvement Loop.

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

The Register Sheet and the Suggestions Sheet are never meant to be used simultaneously, and at the third cleaning process, no use of any tool is demanded to prevent the operator's overburdening.

5 Auto-Mode vs Batch-Mode

A study to determine the best automated execution sequence, the Master Batch Recipe, was performed. The aim of the study is to maximize the parallelization between the operations that are fully automatable and the operations that have to be

performed manually by the two operators assigned to the cleaning process.

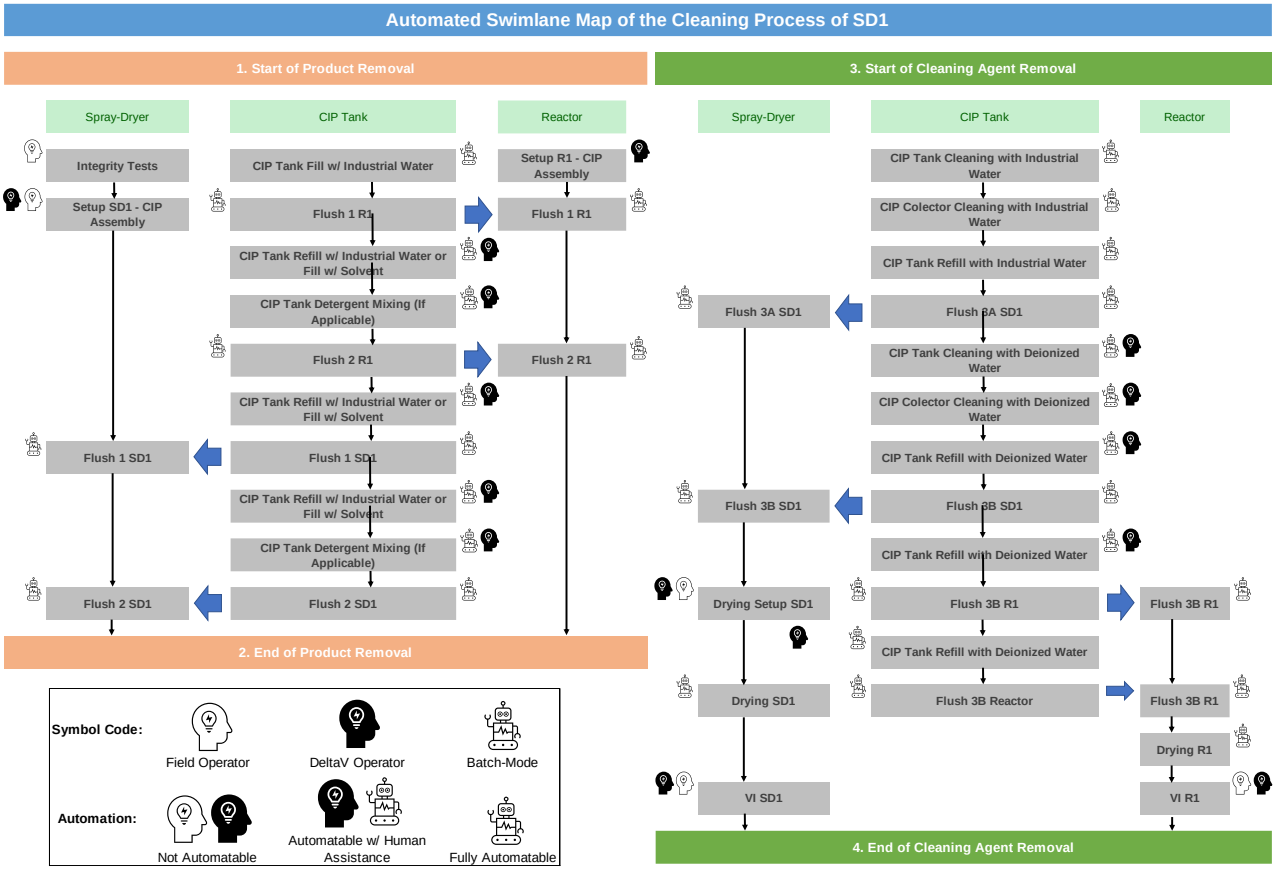

Figure 5.1: Best execution sequencing for the automated Master Batch Recipe of the cleaning process.

The Master Batch Recipe exhibited was designed considering only one CIP Tank is available and lead to a reduction in the lead time of 21%. If two CIP Tanks and in-line mixing technology are considered the CIP Tank Refill and Detergent Mixing operations can be eliminated, leading to a lead time reduction of 36%.

Table 5.1: Lead Time Reduction with Automated Cleaning Operations.

Mode	Lead Time, h	Reduction, %
Auto	33.5	-
Batch w/ 1 CIP Tank	26.5	21
Batch w/ 2 CIP Tanks	21.5	36

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.

6 Conclusions

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

The Standard Work Methodology was used, and an investigation of the Cleaning Procedures was carried out to determine the Top 3 Time-Consuming Operations and the Top 3 Sources of Variability.

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 was automatically linked with Visio's Cross-Functional Map to allow a 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. In the CI Loop, the two tools are never meant to be used at the same time to prevent the overburdening of both the operators and the process engineers. In the end, a Gemba Walk should be done to evaluate the cleaning operations where they are performed: in the shopfloor.

The potentiality of having batch mode implemented in the cleaning process control system was investigated 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.

Bibliography

[1] J. Liker, *The Toyota Way − 14 Management Principles From The World's Greatest Manufacturer*. McGraw-Hill, 2004.

[2] T. Fujimoto, *The evolution of a manufacturing system at Toyota*. Oxford University Press, 1999.

[3] J. F. Krafcik, "Triumph of the lean production system," *Massachusetts Inst. Technol. Cambridge, MA*, 1988.

[4] J. P. Womack, D. T. Jones, and D. Roos, *The machine that changed the world: The story of lean production − Toyota's secret weapon in the global car wars that is now revolutionizing world industry*. Simon and Schuster, 2007.

[5] J. P. Womack and D. T. Jones, *Lean thinking − banish waste and create wealth in your corporation*. Free Press, 1996.

[6] M. George, J. Maxey, D. Rowlands, and M. Upton, "Lean six sigma pocket toolbook," 2004.

[7] A. P. Dillon and S. Shingo, *A revolution in manufacturing: the SMED system*. CRC Press, 1985.

[8] M. Groover, *Fundamentals of modern manufacturing: materials processes, and systems*. 2007.

[9] "DeltaV by Emerson." https://www.emerson.com/en-us/automation/deltav.

[10] D. Altman, D. Machin, T. Bryant, and M. Gardner, "Statistics with confidence: confidence intervals and statistical guidelines," 2013.