Implementation of Lean Practices in the Pharmaceutical Industry: Case Study of a Spray-dryer

Joana Grade Pinto

Department of Chemical Engineering, Instituto Superior Técnico, Lisbon, Portugal

Hovione, Loures, Portugal

E-mail: joanagdpinto@gmail.com

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Abstract The purpose of this dissertation was to implement Lean tools, measuring their benefits. The work was carried out at the company Hovione. A piece of equipment was chosen in which these tools have not been introduced and was made an analysis of its initial state. After analyzing the processes, the plan of implementation was defined as: a detailed production analysis of the products P1 and P2, a definition of standard ways of producing them, and the simulation of their production recipes in the SchedulePro software. Once implemented, the final state of the process was assessed. There was a reduction in the variability of some tasks and an increase in the registration associated with the delays that occurred. The KPI defined as "Reduction of the time required for non-added value (NAV) tasks" was measured and a 17% reduction was obtained in the average time spent on these P1 tasks. There was also an 8.4% reduction in the average lead time and an increase of 31.1% in the cycle time. Finally, the goal previously defined as a 15% decrease in time in SD1 NAV, was changed to 7% due to the implementation of standard work on only one product. This objective was not achieved despite a reduction of 2.3% was achieved in the time spent on NAV tasks in SD1.

Keywords: Lean Manufacturing, pharmaceutical industry, standard work, simulation, SchedulePro.

1. Introduction

In 2020, we live in a time of market instability. The same was registered 12 years ago, after the last global economic crisis, where the world market was seriously affected since both consumer demand and industrial production collapsed. However, the last few years have been marked by economic growth and since the end of 2017, the level of production has already exceeded that of 2007 [1]. However, the pandemic caused by Covid-19 caused a worldwide slowdown in economic growth, which can be reflected indirectly in pharmaceutical markets, sensitive to the country's economy [2].

The pharmaceutical industries are then under pressure to increase their competitiveness through R&D, increase manufacturing and value chain efficiency. Gradually, large pharmaceutical organizations have shown their intention to simplify operations and processes and reduce costs, through Lean Management practices that for more than a decade have become the main driver of operational change [3].

The Lean approach is multidimensional and covers a wide variety of management practices in an integrated system. The combination of these practices, when working synergistically, can allow to obtain a simplified system where production is carried out at the client's pace, with little or no waste, and with excellent quality [4].

In this context, the dissertation developed together with Hovione, aims to implement and to measure the impact of applying Lean methodologies and tools, reducing the time spent on non-added value tasks.

Section 2 contains a bibliographic review on Lean practices used. In the section 3 a brief history of the company and the team in which this Master's dissertation was inserted will be presented. In section 4 is described the case study where the analyzed data will be presented and where the initial status of the process will be defined. It is also detailed in section 4 improvement proposals and analysis of the benefits of improvement plans.

2. State of art

The Lean approach was born in the early 19th century when the industrial revolution took place. However, the term Lean was originally coined in 1990 by James P. Womack, Daniel T. Jones, and Daniel Roos. Later, in 1996, the first two, evolved Lean Manufacturing (LM) into philosophy, with the book “Lean Thinking: Banish Waste and Create Wealth in Your Corporation”. In this book they defined the basic principles of Lean, being [5], [6]:

i. Specify Value: can only be defined by the customer;
ii. Identify the Value Chain;
iii. Continuous flow: eliminate waste;
iv. Pull system: generate the product based on the customer's demand;
v. Pursuit of Perfection: constant improvement of the value chain. There is no end to the goal of reducing time, space, cost, and errors.

The principles of Lean Manufacturing are primarily focused on identifying what is considered added and non-added value in the value chain. Added value activities (AV) are those that the customer is willing to pay for. Those considered non-added value (NAV) are divided into two types required or not required. Required NAV tasks can be defined as those that, from the customer's perspective, do not add value, but are necessary for the production of the product - unless there is a radical change in processing (eg: preparation of solutions). These tasks cannot be eliminated, but they can be reduced to optimize the process. The remaining non-added value activities are those that are not necessary for the transformation of raw material into the final product (eg: waiting, transport, etc.). Anything without added value can be defined as waste [7] and therefore can be eliminated. LM focuses on increasing the productivity of operations and creating value by reducing eight types of pure waste: overproduction, waits, excessive inventory, unnecessary movements, transport, overprocessing, defects, unused talent [8].

Standard Work

Standard work (SW) is a Lean tool that allows processes to be performed consistently, at the right time, and in a repeatable way, aiming to eliminate variability and increase production yield [9]. This method consists of identifying, documenting, disseminating, and implementing best practices at work [10].

With SW, everyone in the team is playing at the same tempo at the same time. Concurrently, SW keeps variability out of the process and enables engineers, managers, supervisors and operators to work together by following the same operating procedure [9]. In the long term, this approach can have benefits such as greater safety, better quality, greater productivity, cost reduction, and increased team morale - these being the pillars of operational excellence [11].

As Taiichi Ohno said: "There is no improvement without standardization". On the other hand, it is necessary to have SW to perceive and reap the benefits of an improvement. Therefore, it is necessary to have a standardization before and after an improvement project being alternating processes [11].

Kaizen

Kai (change) and zen (for the better) are words of Japanese origin that together form the word Kaizen. This word represents the concept of continuous improvement in the standard way of working [12]. This tool, used to achieve Lean, includes the implementation of improvements as well as the measurement of results and subsequent adjustment[13]. The PDCA method consists of a logical four-step sequence for continuous improvement, problem-solving, and change and learning management. The PDCA method is described by four phases [14]:

1. Plan: Setting goals; Method of execution;
2. Do: Training of those involved; Effective execution of the plan; Record of changes;
3. Check: Comparison of the execution with the plan; Check objectives initially proposed.
4. Action: Take corrective action: If the results have been achieved, they must be standardized, ensuring continuity; if not, a corrective action study must be carried out, and the PDCA method should be resumed. After the standardization and the stability of the process, the PDCA method should be used again to control the results and boost a new improvement.

3. Company

Hovione was founded in Portugal in 1959 by Ivan and Diane Villax with two more Hungarians, Nicholas de Horthy and Andrew Onody. With 60 plus years of experience, Hovione is a contract development and manufacturing company dedicated to helping pharmaceutical customers bring new and off-patent drugs to market. Based in four countries, Portugal, the United States of America, Irland, and Macau, Hovione has more than 1300 m^3 of production capacity.

The journey through continuous improvement in Hovione started at the Sete Casas site in 2007. Currently, the Operational Excellence team (OPEX) has as main tasks the implementation and follow-up of continuous improvement tools, make sure that the PDCA cycles are done, controlling the results obtained as well as propound actions for the problems encountered.

The OPEX team's mission is to build an organization focused on efficiency, increasing profitability by reducing costs. Due to having an essential role, “Operational Excellence” is considered as one of the three pillars in Hovione’s culture, along with “Quality” and “Security”.

4. Case Study

The project of this dissertation aims to assess whether the implementation of Lean methodologies can lead to improvements in the process or not. More precisely if the introduction of SW can improve the time spent in non-added value tasks.

To assess the impact of SW on time spent on non-added value tasks was chosen a piece of equipment on which it was not yet implemented. As Hovione is the leader in spray drying, many of its processes are based on the operation of this equipment and, therefore, a spray dryer (SD) whose SW has not yet been applied was chosen as the focus of analysis.

For the correct definition of the project, it was chosen to follow Kaizen’s PDCA method to trace the steps that this project should go through. Following this, the plan was divided by:

Plan (Problem identification; Process analysis; Action plan): sections 4.1 and 4.2 - analysis of the basic situation of SD1 and implementation plan;

Do (Educate and Train; Execute the plan - Keeping record): section 4.3- implementation;

Check (Check the effects of Execution vs Plan): section 4.4- evaluation of benefits;

Act (Act Correctly / Standardize; Conclusion): chapter 5- conclusion and future work.

4.1. Baseline of SD1

To measure the impact that Lean methodologies can have on the time spent on the processes, there is a need to measure the baseline of the machine. Therefore, was made a data collection regarding the occupation of the equipment - assigning the name hereinafter SD1. The occupation of SD1 in the year 2019 and the impact of tasks performed on it or delays is shown in Figure 1. This occupation includes the duration of delays and tasks associated with all the equipment and services related to SD1.

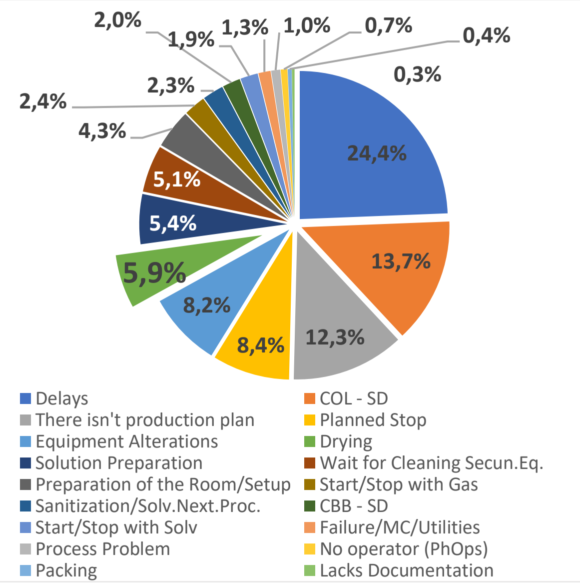

Figure 1 - Types of activities carried out in the SD1 as a percentage of the total time available for analysis (343.5 days), referring to the year 2019 (COL- Change of Line; CBB- Cleaning Between Batches, MC - maintenance).

Drying is considered the only activity for which the customer is willing to pay and is, therefore, the only one with added value. In Figure 1 we can see that this task corresponds to only 5.9% of the occupation, being the other 94,1%, NAV tasks. The NAV non-required – pure waste that could be all eliminated - occupies 45.2% of the available time. The tasks needed for production, but with potential for optimization, (NAV required) consume 49.0% of the time. This shows that the occupation of SD1 is not optimized and that there is a lot of potential for improvement.

4.2. Implementation plan

Knowing the advantages of associating this equipment with SW, was traced a plan to do so. In the timeframe of the internship, two of four productsd are being produced, P1 and P2, which are the focus of the study. The implementation will essentially consist on:

1. Gather information about the production of the products - procedures, comments, times, and sequence of execution;
2. Draw the common order of execution;
3. Simulate the production recipes of the products using the SchedulePro software;
4. Identify the critical path and the bottleneck, to study the biggest problems;
5. Study of delays and the biggest failures;
6. Analyze potential improvements;
7. Define the goal and KPI;
8. Training of technicians on SW;
9. Discussion with technicians and operators of the best practices and make adjustments;
10. Implementation on the production line.

Therefore the focus of the implementation is on the detailed analysis of the products and on the implementation in the simulation software.

SchedulePro is a software developed by Intelligen for planning production processes. This tool uses an intuitive recipe-oriented representation of a manufacturing process and handles resources such as equipment, work areas, labor, materials, utilities, and inventory capacity [15]. To work around delays due to equipment failures or other unexpected events that often lead to planning conflicts with future activities, SchedulePro is supported by two satellite applications: SchedulePro Tracker and SchedulePro Web Viewer. These work in a server, using a database for data storage. Both, allow updates in real-time, which could modify planned activities to represent deviations from the original planning, as well as present these changes in the production line, in real-time [15].

The SchedulePro Tracker is an application used on the production line that allows an authorized employee to update the planned activities. The SchedulePro Web Viewer is an application based on a web server that allows operators, technicians, and other users to view, through a browser, the planning, both initially planned and updated in the SchedulePro Tracker.

4.3. Implementation

4.3.1. Data collection

The first step is to collect information about the products under study. The measurement of the initial state of production of these products began, with the collection of data from the production sheets (BPR - Batch Production Record) of all eleven batches produced in 2019. With this information, it was possible to trace the frequent order of production, as well as the average and median time of each step of the process. For better visualization of these procedures, block diagrams were developed using the Microsoft Visio tool, to represent them in a more intuitive and organized way. This diagram, contains the equipment that is being used, the order in which the procedures take place, the step related to the one in the BPR, and the average production time. These diagrams were made to be presented at the first meeting with operators and production technicians, before the simulation, to identify the best practices. This practice is recurrent at Hovione, but due to the situation of the Covid-19 pandemic, this was not possible.

4.3.2. Initial simulation and analysis

After drawing the schematic diagram for a better perception of the process, the recipie for these products was simulated in SchedulePro. With the simulation of a campaign containing two lots of each one of the products.

Having outlined the information about the production process steps, it becomes intuitive to define the bottleneck and the critical path of each product. Being the bottleneck the resource/work area that defines the limitation of the production system, and the critical path the longest chain in the process, each time lost in both, represents a loss in the process as a whole [11],[12]. Hereupon, the definition of these concepts in the process is important because it facilitates the identification of the most important and crucial tasks. Note that at Hovione, the term bottleneck is associated with the busiest equipment.

The R01 is the *bottleneck* equipment, as it is the busiest and thus creates the production step. Crossing this information with the knowledge of the critical path, it is possible to define which are the critical procedures of the processes and focus the study on those that can generate the biggest problems and improvements.

4.3.3. Improvements to be introduced

In the new planning of P1, as there are more operators available, it is possible to plan production so that the first post-drying occurs simultaneously with drying in SD1. The drying of SD1 also could be done in two phases, so it is possible to transfer the product for post drying, at the end of the first one. Due to this shift, the lead time decreased from 5500 minutes (91h40) to

4600 minutes (76h40), decreasing approximately 17% (900min). In addition to this improvement, it is also expected that, as a result of the application of SW, the variability of the bottleneck will reduce, as described by Lu and Yang [9]. It was assumed that there will be a reduction in the duration of the bottleneck tasks from the value of the 75th quartile (Q3) to the value of the 50th quartile (Q2). Once the statistical calculations of this decrease have been made, a reduction of 142.25 minutes is obtained. A total deduction of 1042.25 minutes is expected.

In the production of P2 was identified a wait in the bottleneck. Also, in the baseline state, to make the SD1 available, before the post-drying phase the next batch is started. With a greater number of operators, it's possible to rearrange the planning to start the post-drying phase at the same time that the start of a new batch occurs. By eliminating waits in the bottleneck and rearranging the production, a deduction of 2400 minutes from the initial planned lead time (4545 minutes) is done. Adding to this, as in P1, the reduction in variability is expected to cause 525 minutes. In total, a reduction of 2925 minutes is expected in the batch execution time.

Table 1-Summary of the expected improvements P1 and P2.

		Added value Duration (h)	Non-added value Duration (h)		Total Duration (h)
			Required	Non-required	
P1	2019	290	880	922	2092
	2020	290	688,9 (-22%)	857,5 (-10%)	1559,4 (-25,5%)
P2	2019	118	939	402,8	1786
	2020	118	402,8 (-~40%)	656,1 (-10%)	1176,9 (-35%)

To understand the dimensions of the proposed changes, a comparison was made with the year 2019. Imagining that in the year of the new implementations (2020) there would be the same number of batches produced and that all would contain the new modifications, we would obtain the improvements presented in Table 1. Note that this also included a 10% reduction in the time spent on non-required NAV tasks, since, by gaining more control in the process, it is expected that there will be an improvement in waste.

4.3.4. Expectations, KPI and end goal

The optimization of the occupation of SD1 is done by improving the production system of products P1 and P2, therefore It is interesting to measure how the improvements will act in the global occupation of SD1. From the values shown in Table 1, it can be seen that there is a reduction in the time spent on the production of the product P1 by 25.5% and product P2 by 35%. These changes would cause a reduction in the duration of the NAV tasks of SD1 of about 15% (14.71%).

After analyzing the process and before creating a final proposal for the production line, it is important to clearly define the objective and the KPI. The goal of the project is to "*Maximize profit by reducing the time spent on non-value-added tasks*". The KPI, which will be used to measure the efficiency of the implementation, was defined as "*Decrease of the time needed for non-added value tasks*", with the target of a 15% reduction in the time in NAV of SD1, due to the exposed in the previous paragraph.

4.3.5. Implementation of the simulation in the production area

For the success of online implementation, it is important to train technicians and operators on SW and the SchedulePro software. The technicians' instruction aims to present the concepts that will be used such as lead time, cycle time, critical path, bottleneck; the meaning and advantages of introducing SW; and tools used in SW - such as continuous improvement meetings or nomenclatures used. The purpose of this training is to have a well-defined objective, conformity between the understanding of the concepts, and still tries to break any skepticism that may be associated with the introduction of this methodology.

It will also be necessary to hold a meeting, to present the simulation and discuss best practices. In this, ideally, one or more members of the OPEX team, one or more technicians responsible for the machine, and one or more operators are present. These meetings aim to analyze the planning to see if it is optimized and if it represents what happens on the production line.

Due to logistical problems, the theory described in this section only ran for product P1. Even so, the simulations performed for P2 will later be used by the OPEX team, but will not be analyzed in this dissertation since they did not fall within the time horizon of the internship.

As a result of the P1 meeting, some adjustments and improvements in the simulation were made to portray better the reality, some tasks were added, some were clustered, and others were removed from the critical path. During the internship period, five batches were produced in which the first two were carried out before the training and the improvement meeting, which may have generated some errors in registration. Adding to this, the meetings only took place with the members of the OPEX team and the technicians, as a consequence of the pandemic situation that ensued, production operators were not present due to their small number.

After these changes, the new planning was carried out according to the expected day and hours of production. The planned recipe was exported to the servers that allow the interaction with the software-SchedulePro Tracker and WebViewer. Figure 2 shows the image reproduced on the screen in the control room of the production line. This view allows you to view the expected and current status.

4.4. Analysis of Benefits

The improvement of a process is continuous and results from cycles of implementation and analysis of results. Thus, after the implementation of the SW, it is important to identify the advantages and the systematic problems, to create new procedures to achieve the best possible results. It is, therefore, in the Check phase of the Kaizen PDCA method.

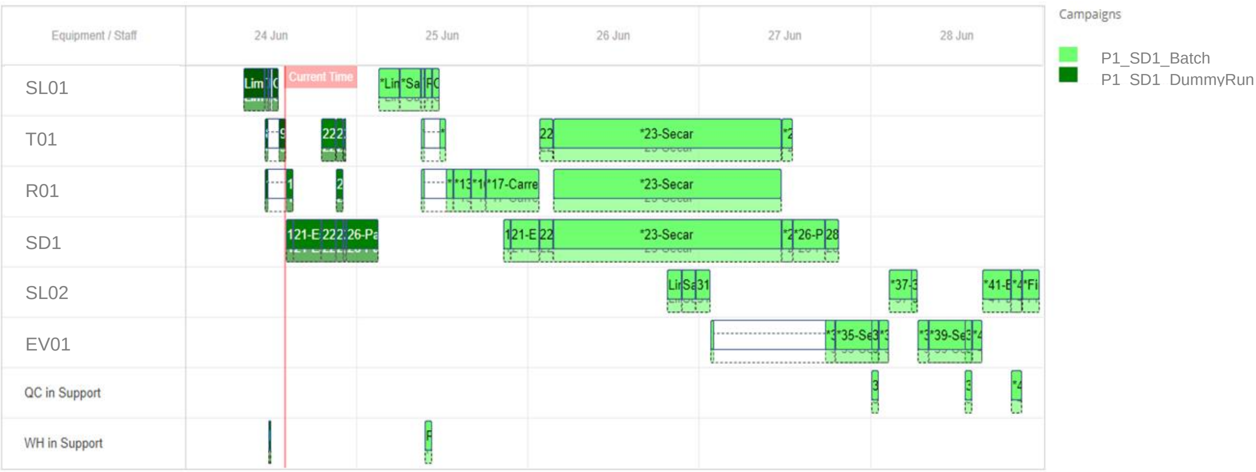

Figure 2- SchedulePro Web Viewer of the P1 recipe after the improvements done with the technicians. Dark green can be seen the dummy run and light green can be seen in production of the batch. Shaded boxes indicate where the tasks were initially planned, and opaque boxes show tasks in updated planning (with delays or longer durations, among others).

The produced batches were analyzed separately, as changes were done in the meeting with the technicians. The planned versus lead time obtained is in Table 2.

Table 2 - The lead time of the produced batches.

	Lead Time Before meeting	Lead time After meeting
Planned	78h30	77h00
Real	**1. 167h30** **2. 148h05**	**3. 160h30** **4. 143h22** **5. 114h30**

The lead time of the batches was greater than the planned, Despite this, there was a reduction in lead time from batch to batch, which represents an improvement.

It's also important to study the variability of the bottleneck tasks. Since the R01 is the bottleneck equipment (section 4.3.2.), the tasks performed on it are those that limit the production pace and, therefore, must be optimized. Thus, after the implementation of the SW, to analyze the variability, the durations of the R01 tasks were collected from the BPR sheets. By observing Figure 3 it is possible to speculate a possible reduction in the variability of the load tasks, except for 17. The term speculation is used since only five points are studied, so it is not possible to ensure continuity of values, but still so it is possible to visualize a trend. Added to this it is clear that the tasks of stabilization, loading of hypromellose and drying increased their variability. This happened due to problems with the dissolution of hypromellose, with the humidity and tempeture of the room, due to cyclone clogging and due unavailability of the post-dryer.

The KPI chosen was "*Reducing the time needed for non-added value tasks*", which allows understanding the waste that occurred in the batches under study. To better understanding the behavior of the batch, other indicators such as average lead time and average cycle time were measured. These values were measured globally to understand if there were real benefits from this application, being these in Table 3.

Comparing what happened before and after the application of the SW, an improvement is observed in the KPI and lead time parameters, but a worsening in the cycle time. The average time spent on NAV tasks decreased by about 23 hours, which led to a total reduction of 17%. Besides the difference with the planned value (Table 2), it was achieved a reduction of 15 hours in the average batch duration, which represents an 8.4% decrease in the time spent on production. Regarding the cycle time, the values increased by 31.1%. However, these cycle time values are a reflection of five batches before and three batches after implementation, so are, therefore, unreliable.

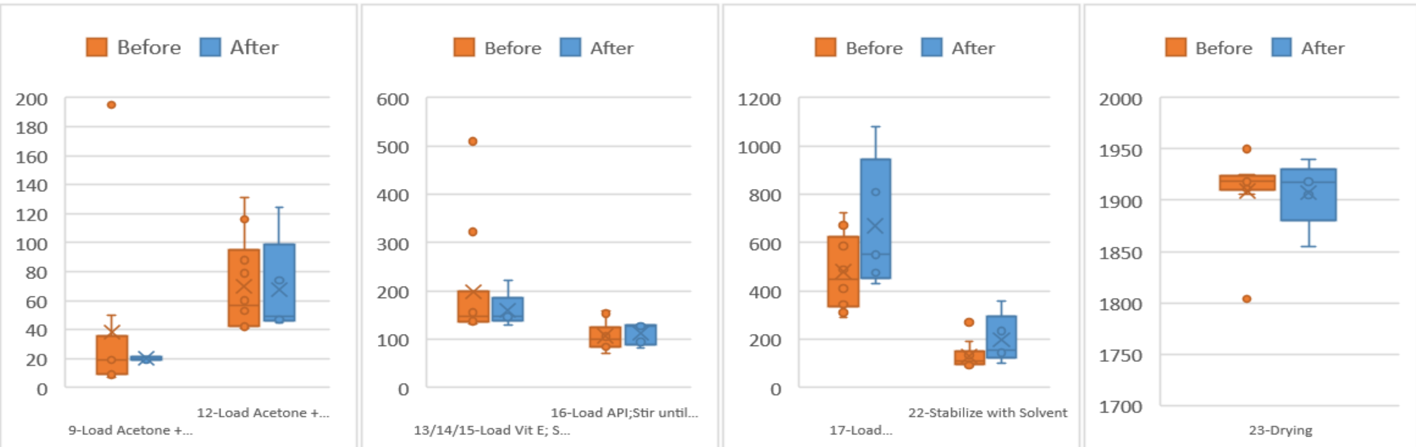

Figure 3- Study of the variability of bottleneck tasks before and the implementation of SW. (9- Load Acetone + Purified water; 12-Load Acetone + Purified water; Adjust Temperature + Stir 13/14/15-Load Vit E; Stir until dissolution; Attach labels; Confirm Weights; 16-Load API; Stir until dissolution; 17-Load Hypromellose; Stir until dissolution)

*Table 3- Analysis of time spent on NAV tasks (KPI), lead time, and cycle time before and after standard work (SW). *In Hovione cycle time is related to the time between the start of two consecutive batches. Due to the lack of information before implementation, the calculations were made assuming the start at the preparation of room SL01.*

	KPI	Average Lead time	Average Cycle time*
Before SW	131h18	160h18	71h28 ± 04h55
After SW	108h19	146h47	93h40 ± 23h32
Result	-17,0%	-8,4%	+31,1%

Since the goal is "*Maximize profit by reducing the time spent on non-added value tasks*", it is also interesting to analyze the KPI applied to the SD1 NAV time. Initially, the target was a reduction of 15% concerning the year analyzed. As it was only possible to implement SW in one analyzed product, it was decided to calculate what value would be expected in this case. It was obtained as a goal of a decrease of about 7.0% (6.81%). The achievement made on the five batches after implementation was also measured, and was done an extrapolation to the same number of batches as last year. The mentioned parameters values are showed in Table 4.

Table 4- Reduction of time spent on NAV tasks in SD1 - Objective, objective only with P1 and achieved.

	Reduction of time spent on NAV tasks in SD1
Goal	15,0%
Goal with only P1	7,0%
Attained	2,3%

Table 4 shows that it was possible to achieve, in the period under analysis, a reduction of 2.3% over the value obtained in the year 2019. This reduction of 2.3% in the time spent on NAV tasks is less than the objective of 7,0% but still positive. It should be noted that the application of this methodology in the process is at an early stage, so one only begins to see the effects of gaining control of the system - the increase in registrations, the improvement in execution times, and the decrease in the variability of some tasks. It is possible to understand what is disturbing the flow of the process and so to find solutions to these disturbances to increase their efficiency.

Conclusions and future work

The present dissertation aimed to evaluate the impact of the implementation of Lean tools, namely SW, in the reduction of the time spent on non-added value tasks on SD1, a spray-dryer at the company Hovione. An analysis of the initial state was carried out and, later, the evaluation of the benefits of the application of Lean. The processes were analyzed in detail, and it was proposed to define standard forms of work to produce them and to simulate the production recipes using the SchedulePro software.

After the implementation and the production, the final state of the process was measured. It was possible to observe a reduction in the variability of some critical tasks - loads of TPGS and API - and also an increase in the number of records of delays that occurred, which will allow control over the process. A 17% reduction in the average time spent on P1 NAV tasks (KPI) and an 8.4% reduction in the average lead time was obtained. However, cycle time increased by 31.1% which may be related to the fact that the comparison was made with only five batches before and three after implementation.

Finally, the defined objective of 7% due to the implementation of standard work on only one product, was not achieved. There was only a 2.3% reduction in the time spent on NAV tasks in SD1, probably because this is a very early stage in the process where only three batches were produced after the instruction of those involved.

To facilitate the continuation of the work carried out in this dissertation, some proposals could be done. It's proposed to implement SW on the other products produced on the machine to identify the biggest delays and increase control and knowledge about SD1. It is proposed to introduce other Lean tools such as Gemba Walk, space organization techniques (5S) and SMED methodology. The Gemba Walk is a walk performed by managers, on the factory floor where production takes place, and will help to identify the biggest physical barriers that cause friction to production and to identify the biggest complaints from operators. The SMED and 5S tools will allow the reduction of waste caused by excessive setup time and excessive movements. Finally, to facilitate the visualization of results is proposed the introduction of efficiency measures such as OEE. This proposals could not be implemented due to the limitations imposed by the Covid-19 pandemic and also lack of time.

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