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Master of Science in Engineering and Management

Master of Science Thesis

Increasing the OEE of an oral solutions production line by applying lean manufacturing tools

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Abstract

The market for pharmaceutical products has been increasing and will continue to do so in the near future. However, as patents expire, new players such as generic manufacturers get into de market and regulatory bodies limit the price of medicines, tougher competition is becoming a reality in this industry. In this context of rising costs and decreasing margins, the excessively high manufacturing costs may be a source of savings for the pharmaceutical sector.

This thesis discusses the background of lean production particularly as it relates to the pharmaceutical industry and presents an actual application in a production facility of an international CDMO. It firstly assesses the main causes of inefficiencies by means of the well-known OEE and its related sub indicators.

The second part describes lean production techniques used to reduce planned and unplanned stops in an oral solutions production and packaging line. In concrete, the SMED methodology was applied to reduce the duration of 3 different types of CO happening in the same line while discussing the unique characteristics of a pharmaceutical changeover operation. The analysis includes actual modifications to the process as well as long term solutions to further enhance productivity.

Parallelly, unplanned stops were attacked following cause root analysis prioritized by pareto principle. Availability was improved by 7%, which is translated in an OEE improvement of 2.5 points. The increase in production capacity was achieved without addition of facilities, capital investments, or negative impact upon product or process quality.

Acknowledgements

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This work wouldn't be possible without the unmeasurable support received from my family. Special thanks to my father, for inspiring me and teaching me the most important values in life.

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Summary

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Chapter 1- Introduction

1.1. Thesis' Scope

This project documents the efforts to improve productivity in an oral solution production and packaging line by monitoring the OEE evolution over time. Although it only focuses on one line, results obtained can be easily extrapolated to the rest of the production plant.

The assessment is mainly focused on reducing set up times, since they were identified as the greatest of the 6 big losses happening in the line aforementioned. Nevertheless, unplanned stops were also addressed by applying cause root analysis.

Four different types of changeover can be distinguished, from which, only the biggest 3 in terms of downtime were assessed. 4 interdependent projects were designed to reduce both planned and unplanned stops. The document presents the selected methodology and discuss the implementation phase and results obtained in each one of them.

Finally, the report also suggests long term alternatives to further reduce set up times by capital investments and process modifications.

1.2. Acronyms

SMED Single Minute Exchange of Dies

CO Changeover

VA Value added

NVA Non-Value added

OEE Overall Equipment Efficiency

KPI Key Process Indicator

LM Lean Manufacturing

GMP Good Manufacturing Practices

APIs Active Pharmaceutical Ingredients

TOC Total Organic Carbon

CRO Contract Research Organizations

OTIF On-Time and In-Full (delivery)

PMDA Pharmaceutical and Medical Devices Agency

FDA Food and Drug Administration

EMA European Medicines Agency

NPV Net Present Value

IRR Internal Rate of Return

1.3. Pharmaceutical Industry Overview

This section's purpose is to provide the reader with the background knowledge needed in order to understand the environment in which the company was inserted. It is neither an essential part of this thesis nor a mandatory section that must be read if the scope of the reader is just to go directly to the point. However, since the company is an open system included in a bigger one, the author considered helpful to provide a short description of the latter. In other words, the pharmaceutical sector has some peculiar features that should be in the reader's mind while she goes through the subsequent chapters.

1.3.1. Structure of the Pharmaceutical Sector

The pharmaceutical industry comprehends all the identities that are involved in the production and distribution of medications. Thus, its objective is to provide drugs that prevent or treat diseases. Basically, it includes the same main elements of any industry *raw materials manufacturers, finished goods manufacturers, R&D companies, marketing companies and, of course, consumers. However, because of its intrinsic nature, it is far more regulated and capital-intensive than other industries. This is due to the fact that, unlike other sectors, this industry directly affects the health of the final customers (deviations could have tremendous impact in the life of the patients) and therefore a wide number of international regulatory bodies (like FDA, WHO, or MHRA, for instance) monitor things like drug safety, patents, quality, and pricing.

It is more capital intensive than other industries partly because of the R&D activities that must be undertaken in order to develop a new product. In fact, it is the industrial sector that spends more money in R&D activities as a percentage of net sales according to a 2016 study by the industrial R&D investment scoreboard. In addition, the necessity to comply with

severe regulations in terms of equipment validations and to produce in controlled atmospheres require larger investments in facilities and technology than other sectors.

The industry comprises different subfields pertaining to the development, production, and marketing of medications (figure 1.1). These more or less interdependent subfields consist of:

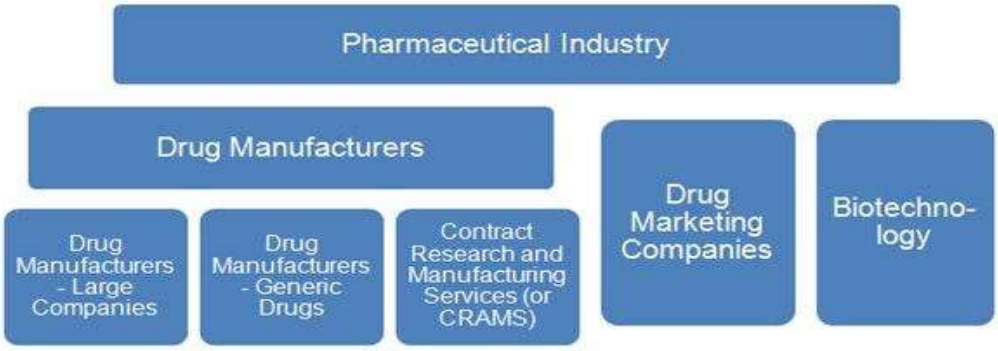

Figure 1.1-illustration of the different subfields of the pharmaceutical industry (Courtesy of Market Realist https://marketrealist.com/2015/01/easier-way-understand-pharma-industry)

1. **Drug manufacturing**

    1.1. **Drug makers**: Basically, here are included API and formulations manufacturers, which can make the following types of drugs:

        1.1.1. **APIs:** The raw materials used to manufacture drugs. Usually these are made by large setups because of the special environmental conditions required

        1.1.2. **Generic drugs:** Companies sell these off-patented, cost-effective drugs at low prices using no specific brand name in order to serve the public.

        1.1.3. **Patented drugs**: Either from in-house research or licenses from other firms, companies can manufacture patented drugs, which provide high profit margins because of market exclusivity.

    1.2. **CRAMS:** Companies that provide these contract services conduct research and manufacture drugs under licenses from other companies.

2. **Drug marketing:** Their goal is to help increase the market reach of drugs. Sometimes, manufacturing companies are not able to sell their product in a specific region because of the lack of a license or a marketing network to promote. This is where drug marketing companies come in to facilitate sales.
3. **Biotechnology and R&D:** Pharmaceutical companies are either dependent on their in-house R&D centres, or they rely on biotechnology companies to provide them with licenses to manufacture patented products.

In addition, there are other entities which indirectly participate in the production and commercialization of medications, such as:

- **Drug regulators:** Entities that regulate the development, approval, manufacturing and marketing of drugs such as the FDA, EMA or PMDA, for instance.
- **Drug distributors and wholesalers:** Entities that purchase inventory and sell manufacturer's pharmaceutical products.
- **Drug information, prescribers and retailers**: May be anything from well-qualified specialists in hospitals down to unlicensed "quacks". Retail outlets may be operated by qualified pharmacists, pharmacy assistants or technologists, or untrained drug sellers.

1.3.2. Global Figures

The previous section illustrated the organization, division and interaction of the different subfields pertaining the pharmaceutical industry. This section instead puts the reader in touch with the numbers that characterize and describe the sector, so she can build up an idea about the current state of pharma worldwide.

As can be seen in figure 1.2, the pharmaceutical market has been growing uninterruptedly for more than 20 years. In fact, in 2014 it reached the 1 trillion USD dollars

milestone and it is expected to grow at an annual rate of 4.9% to $1.3 trillion by 2020, according to the International Trade Administration. North America is responsible for the largest portion of these revenues, due to the leading role of the U.S. pharmaceutical industry. However, as in many other industries, the Chinese pharmaceutical sector has shown the highest growth rates over previous years. While other industries also present a positive growth rate over the past years, the reasons underlying the growth in pharma market are quite case-specific. In other words, the rise in sales in developing countries such as China, India or Brazil is not the only reason why this sector keeps expanding. The past and the future (expected) growth of the pharmaceutical industry can be explained by the aging population, changing lifestyles, and increased income and chronic diseases, among other factors[1]. Even more, for non-generic pharmaceutical goods, demand can be considered to be quite inelastic, since in most cases customers are forced to buy a specific product depending on their diagnosis and treatment. Therefore, the pharmaceutical market is expected to keep growing during the following years since the lifestyle of modern society demands constantly new drugs to cope with the diseases of the future.

- [1] Aging population: the average human life span has increased substantially over the last few decades. However more infections and diseases have come along with this longevity growth. This has led to the increased research on aging populations.
- Changing lifestyles: hectic daily schedules have led to unhealthy eating habits, a lack of exercise, less sleep and other problematic lifestyle choices. This has resulted in high obesity rates, poor digestion, hallucinations, breathing difficulties and other physical problems
- Increased income and chronic diseases: the middle class has been growing in both emerging and developed markets. People in these markets have more disposable income and expect better healthcare solutions.

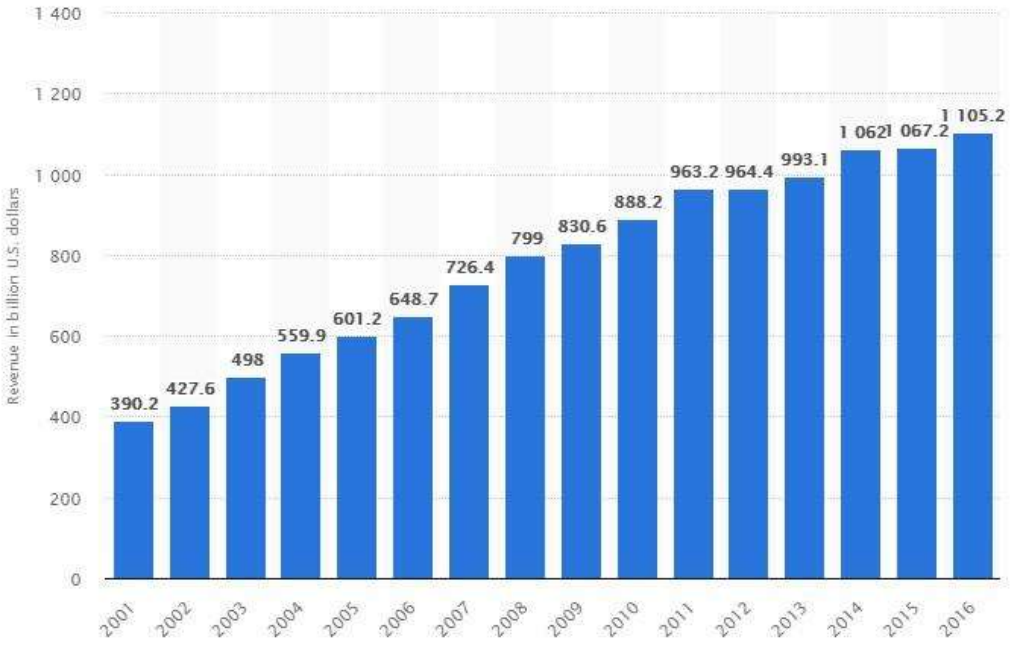

Figure 1.2-Revenue of the worldwide pharmaceutical market from 2001 to 2016 (in billion U.S. dollars)

Pharmaceutical companies have some of the highest profit margins in the world. The average net profit margin for drug companies, including pharmaceuticals and biotech, was about 12.5 percent to 14 percent, according to a January 2018 study by New York University's Stern School of Business. However, they can vary widely, from less than zero to more than 40 percent, depending on the size of the company and whether it's a powerhouse like Pfizer[2] or Novartis[3] or a start-up still in the research and development phase.

Gross margins are also above-the-average for the pharmaceutical industry, being as high as 98.8% in some cases (see Appendix 1). This distinction has earned the industry criticism from both politicians and consumers, who often complain about the high prices of

[2] An American pharmaceutical corporation headquartered in New York City. the company develops and produces medicines and vaccines for a wide range of medical disciplines, including immunology, oncology, cardiology, endocrinology, and neurology. It is one of the world's largest pharmaceutical companies.

[3] Novartis International AG is a Swiss multinational pharmaceutical company based in Basel, Switzerland. It is one of the largest pharmaceutical companies by both market capitalization and sales.

prescription drugs, since the higher the gross margin, the more power a company has to raise prices.

The overall average spending on R&D by industrial firms engaged in developing new products is a mere 1.3% of sales revenues. Instead, pharmaceutical companies spend, on average, about 17% of revenues on research and development, making the pharmaceutical industry one of the biggest spenders in this area as well as the high technology sector with the highest added-value per person employed, significantly higher than the average value for high-tech and manufacturing industries. According to the 2016 EU Industrial R&D Investment Scoreboard the pharmaceutical and biotechnology sector amounts to 19.1% of total business R&D expenditure worldwide. However, lately many companies have focused developing biological drugs and outsourcing their R&D activities to contract research organizations with the ultimate goal of reducing operational costs and improving competitive positioning due to the loss of patent exclusivity that allowed competition with generic pharmaceutical manufacturers (Green & O'Rourke, October 2006).

Finally, it is particularly important for the sake of this thesis to highlight that manufacturing costs are a substantial part of pharma total cost (Abboud & Hensley, 2003). In fact, the cost of goods sold is found between 25 and 50 % for manufacturers of pharmaceutical products (Basu, Girish, Saket, Pradeep, & John, 2017). Figure 1.3 shows the cost structure for different types of pharma organizations. As can be seen, manufacturing costs are the main contributor to final price, even for brand-name companies and especially true for contract manufacturers.

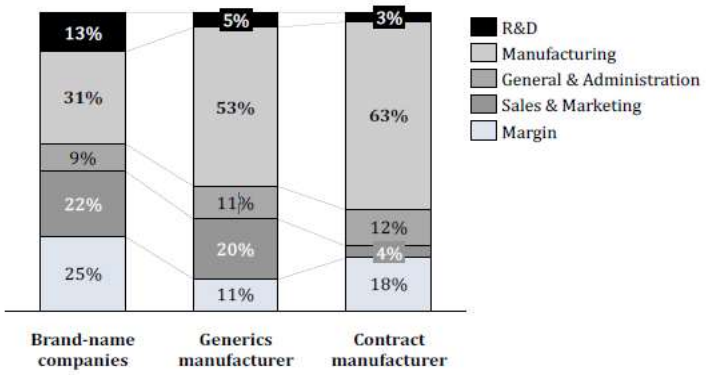

Figure 1.3- final price contributors for different types of pharmaceutical manufactures

In conclusion, the pharmaceutical industry is a growing sector driven by demographic factors, so future growth is expected not only in the short- term but also in the long run. Manufacturing costs represent a substantial part of final price for most generic products and R&D spending is significantly higher than that of other sectors, since innovation is considered a key competitive factor. However, the expiration of patents, among other issues, has offset one of the main features in this industry: the entry barriers. Because of this, generic manufacturers are now raising their market share and tougher competition will be a natural consequence. Is in this context of rising costs of commercialization, shorter effective exclusivity periods, and diminishing returns on R&D investment where the excessively high manufacturing costs may be a source of savings for the pharmaceutical industry (Suresh & Basu, 2006). In fact, may authors argue that continuous improvements of manufacturing practices for pharmaceutical companies will gain importance as simply focusing on R&D will most likely not pay off in the future (Kickuth, Gebauer, & Friedli, January 2009) (Bene, July 2016). This is the reason why the following section is specifically devoted to analysing the relationship between the pharmaceutical industry and the lean manufacturing philosophy.

1.3.3. Pharma and Lean

It is no news that the pharmaceutical industry has always been way behind other industries when it comes to lean production. If the trend of inventory turns improvement[4] is selected as a proxy for lean improvements, this industry has always ranked at the bottom. Schonberger (Schonberger, Best Practices in Lean Six Sigma Process Improvement – A Deeper Look, 2008) argues that it has been so probably due to the lack of a "burning platform" for change. In other words, when profit margins are high, little attention is given to competitive edge elements such as speed and cost. In contrast, pharma has always been characterized for focus on R&D rather than operations.

During the last decade, however, things began to change. In particular, both government and society began putting pressure to reduce prices, improve quality and provide better traceability across the whole supply chain. In addition, the expiration of patents caused price to be a competitive factor as new players entered to the market. It that were not enough, more packaging configurations were introduced to facilitate marketing campaigns to target smaller groups. This brought a wider product mix and, consequently, more frequent changeovers between runs[5].

During this time, the little attention that operations did get was focused on compliance rather than process improvement (Spector & West, 2006). In fact, excessive inventories were the logical outcome when the lack of operational efficiency was coupled with overproduction.

[4] Although there is no universally accepted measure of a company's "leanness," inventory turns are a reliable indicator. The trend of inventory turns over time indicates how well a company is progressing in terms of becoming leaner and improving its processes. Lower levels of inventory directly correlate to improvement in the competitive edge factors of speed, quality and cost. That's why the companies that have successfully implemented lean have focused intently on reducing inventory, sometimes characterizing inventory as "evil." (Spector, The Impact of Inventory Turns on Speed, Quality, and Costs, 2009)

[5] As the frequency of changeovers increases, the related downtime has become a major concern as it influences line capacity and per package cost. .

An analysis performed in 2010 (Spector, 2010) utilizing data from the top pharmaceutical companies by revenue on the trend of inventory turns indicated that the average inventory turns remained essentially flat over both the previous five- and 10-year periods.

The literature shows some efforts to enhance operational efficiency through lean tools that have had mediocre or worse than expected results. Among the wide array of factors associated with these implementation difficulties, the following three are the most cited ones:

- Lack of Senior Management Commitment: This is a prerequisite that virtually every business improvement initiative sus as Six Sigma, Agile Manufacturing or WCM states as vital. Historical data from companies suggest that the most successful improvement initiatives are driven by top management, e.g., Jack Welch at GE[6], and are driven top-down on a company-wide basis, across departments, functions and geographic borders. However, in the pharma industry, lean initiatives have been typically promoted by low management and applied in an isolated manner, i.e., in one manufacturing facility or solely in manufacturing operations, rather than as a concerted effort across an entire company. It seems that lean is not seen as a strategic capability by pharma executives and, thus, there are not actively engaged in driving change - a prerequisite for success.
- "Operations only" focus*:* While successful application of lean across the supply chain are usually evidenced by reduced inventory in all instances of the supply chain, Schonberger (Schonberger,2016) carried out a study in which he divided total inventory into its components: purchased/raw material (RM), work-in-process (WIP) and finished goods (FG). In this study, improvement showed up only in the WIP percentage, i.e., internal

[6] John Francis Welch Jr. was chairman and CEO of General Electric between 1981 and 2001. During his tenure at GE, the company's value rose 4,000%. Welch worked to eradicate perceived inefficiency by trimming inventories and dismantling the bureaucracy.

manufacturing related processes, which is evidence of lean initiatives solely focused in manufacturing operations.

- Cost reduction focus: The benefits of lean applications are associated with strategical, financial and operational capabilities of the company such as speed, quality and tailored products. However, lean case studies are usually evaluated in terms of cost reduction, with other benefits like responsiveness and quality remaining in a secondary mention. While this is true across all business cases form any industry, since labour cost are always the easiest to quantify in a reasonable objective manner, pharma executives don't seem to even consider additional benefits when evaluating results.

To sum up, there is a lot to be gained by companies in the pharma industry through the implementation of lean. A pharma company that focuses on lean as a strategic tool will clearly have advantages over its competitors and can capture additional market share. Nevertheless, up to now there have been scarce successful implementation-cases due to the reasons described above, and some authors believe that it will continue to be so unless some vigorous competition takes place (Eilat, 2018) (Snee, 2007).

Chapter 2- The Company

This thesis has been developed while working in a global contract development and manufacturing organization (CDMO) that falls into the category of "Drug Manufacturer" described in the previous section. Production for this company takes place at different sites in Europe, where two operating divisions manufacture drug delivery devices and APIs and finished dose, respectively. The site at the focus of this lean production application is a multi-purpose production facility for bulk and packaging of injectable and oral liquid dosage forms as well as the packaging of oral solid forms, located in Italy.

The facility houses several production lines, which are physically divided in two different production sections: Liquids and solids. The former is composed of seven production lines that only perform the packaging operation for blisters of tablets and capsules, and the latter comprises 5 production lines that both bulk and package diverse products, divided as follows:

- One production line exclusively for drops[7]
- One production line exclusively for oral solutions[8]
- Two production lines for ampoules[9]
- One production line for vials[10]

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[7] *Oral drops are liquid preparations for oral use that are intended to be administered in small volumes with the aid of a suitable measuring device.*

[8] *Oral solutions are clear Liquid preparations for oral use containing one or more active ingredients dissolved in a suitable vehicle.*

[9] *A hermetically sealed container, usually made of glass, containing a sterile medicinal solution, or powder to be madeup in solution, to be used for subcutaneous, intramuscular, or intravenous injection.*

[10] *A small bottle or receptacle for holding liquids, including medicines*.

Table 2.1 summarizes the annual plant capacity, the used capacity and the average price per unit of output for each type of product normalized for 3 shifts per day and 5 days per week.

	Capacity	Average price (weighted) [€]	Used capacity [units]	Used capacity [€]	Used capacity [%]
Drops (bottles)	10,000,000	0.49	9,500,000	4,655,000	95%
Oral Solutions(bottles)	10,000,000	1.13	5,500,000	6,215,000	55%
Blisters	140,000,000	0.11	95,000,000	10,450,000	68%
Vials(vial)	2,000,000	1.10	275,000	302,500	14%
Ampoules(ampoule)	25,000,000	0.18	11,000,000	1,980,000	44%

Table 2.1- Annual plant capacity, used capacity and average price for different products

As can be seen, the oral liquid forms present a much more interesting average price than the oral solid forms (especially true for oral solutions and vials). Also, the table shows how the drops, blisters and oral solutions are the most saturated lines in terms of capacity (95%, 66.87% and 55% respectively).

Keeping in mind that blisters are produced using 7 production lines, the oral solutions line comes up as the most critical and profitable one, generating 26.33% of the company's net sales. In addition, during the time this thesis was being written, the oral solutions line was the only production line with overdue orders, with a 3-month OTIF[11] average of 63%.

[11] A measurement of logistics or delivery performance within a supply chain. Usually expressed as a percentage, it measures whether the supply chain was able to deliver the expected product in the quantity ordered by the customer at the place agreed by the customer and at the time expected by the customer.

Several authors recommend to start the application of lean tools in a pilot area (Shingo, 1983) (Kim, Arizne, & Bannerjee, 1995) (Upton, 1995), and only after achieving pre-established SMART goals, to move on with the remaining sectors in one or more waves depending on the particular application case. In order to maximize the project's output, the pilot area should be chosen according to the following criteria:

- Employees familiar with the equipment (operators, maintenance personnel, quality assurance, and supervisors) are engaged and motivated
- The equipment is a constraint/bottleneck – thus improvements will bring immediate benefits
- Changeovers are usually long and unstructured
- Process step results can be obtained in a short period of time

It comes up naturally that for the scope of this thesis the oral solutions line was the perfect candidate to start with, since any improvement made would have an immediate impact in terms of strategic KPIs such as OEE, OTIF or MTBF, for instance; and that is the reason why the analysis hereafter is focused exclusively in this particular production line.

2.1. The Oral Solutions Line

2.1.1. Production Process

This section briefly describes the production process that the oral solutions line carries out. If the reader wants an even better description, she can always consult Appendices 2, 3 and 4 for additional information.

The production process starts in the mixing tank, where the solution is prepared by filling it with the raw ingredients (dosed in the exact quantity needed) and then performing a mixing cycle. This operation can take from 2 to 4 hours, depending on the batch size and the type of solution that is being prepared. Once the solution is ready, half of it is poured (passing through a filter) to the storage tank. The latter one will feed the filler's tank, with a second filtering operation being performed between them.

In the primary packaging section, an operator constantly feeds a spinning buffer with empty bottles which in turn supplies the air blowing machine[12]. The machine consists of 24 independent blowing devices that rotate around a horizontal axis to clean and remove impurities that could be present inside the bottle.

Once the bottle is cleaned, it follows its way through a belt conveyor to the filler machine[13], which pours the solution inside the bottles progressively with an array of syringes (The number of syringes varies depending on the volume of solution to be deposited). Once

[12] The air blower, as part of the bottle preparation process, before filling, delivers pressurized air to the internal and external parts of the bottle to remove any foreign material that may have settled in it.

[13] The filling machine is a primary packaging machine that fills empty bottles with the oral solution by means of an array of syringes.

the bottle is full, the capper machine[14] adds the cap. 2 cameras control the process and instantly discard non-conforming bottles.

The product arrives to the secondary-tertiary packaging room by means of a belt conveyor, where the labeler machine[15] attaches the label to the bottle, with all the variable information stamped in real time. A rotating buffer connects the exit of the labeler with the case packer machine[16], where the secondary packaging takes place. Here the bottle, the leaflet and the oral liquid measuring device (either a spoon or a syringe) are inserted into the case.

The next machine in the line is the Data Matrix Station, which performs an optional step that prints variable unique data on the case. Its use depends on the particular production order and, if it is not needed, it can be by-passed.

Finally, the tertiary packaging, where several cases are aggregated in a single carton, is performed by the cartoning machine[17]. After that, an operator attaches an identification label to each box and allocates them on a pallet. Once the latter one is completed, it is moved to the finished product SAS where supply chain staff stores it until it is delivered.

Concerning the personnel, figure 2.1 shows the portion of the company's organization chart that is involved with the management and operation of the oral solutions production

[14] The capping machine is an automatic device that is used to cap bottles

[15] Labeling machines are machines that dispense, apply or print-and-apply labels to various items, products, containers, or packages (bottles in this case).

[16] The case packer is a machine that performs three distinct operations: case erecting, case packing/filling and case sealing. In addition to the bottle, the machine also fills the case with a measuring device such as a spoon or a syringe and a leaflet

17 A cartoning machine or cartoner, is a packaging machine that forms cartons: erect, close, folded, side seamed and sealed cartons

line. Of course, the head of the liquid department and the team leader have also to manage the other production lines that are inside the liquid department.

Under this hierarchical structure, each member had predefined tasks to perform in order to produce oral solutions. The weighing operator basically had to prepare and dose the raw materials needed for each bulk, while the preparer's task was to pour these ingredients inside the tanks as well as to perform the mixing and cleaning cycles. The maintenance operator performed corrective maintenance interventions most of the time, as can be expected from an organizational chart in which instead of a central maintenance department, maintenance personnel is directly subordinated to production managers. Finally, the production line was run by three line-operators, one in the primary packaging sector and two in the secondary-tertiary packaging sector.

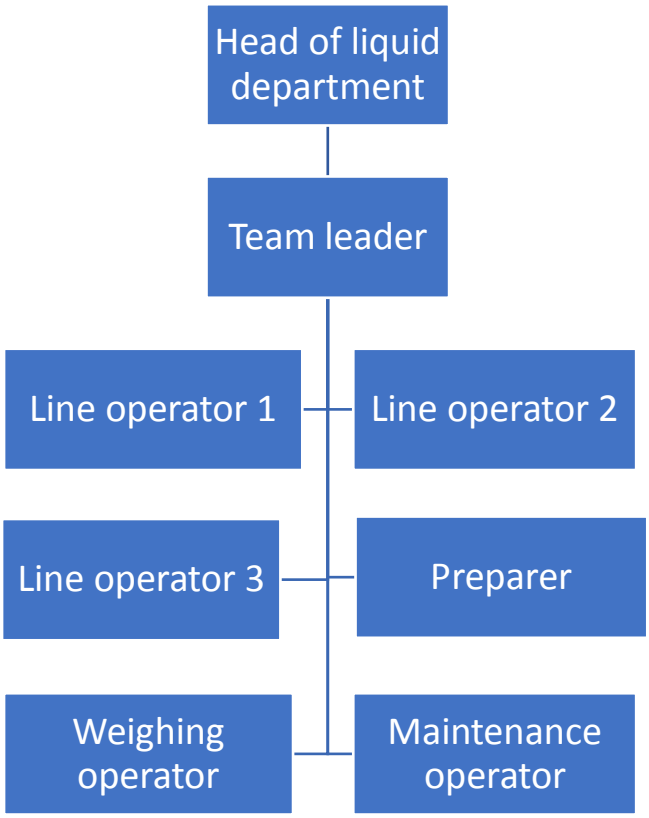


Figure 2.1-organizational chart in charge of the oral solutions production line

2.1.2. Production Mix

The oral solutions line can produce different types of products. A generic product is defined by 4 attributes, namely:

- **Solution:** The line is enabled to produce 2 different types of solutions, which are used to fill the bottles. From hereafter they will be called “solution X” and “solution Z”.
- **Format:** The line can produce several product sizes. In particular, it is able to deliver 6 different final volumes using 4 different bottle dimensions. Table 2.2 summarizes this information.
- **Country:** The production plant sells oral solutions to a variety of customers, each one of whom serves several countries. Therefore, each client request specifies the secondary packaging materials (such as cases, leaflets, type and format of variable data present on labels and cases, etc.) that must be used for that production order.
- **Batch:** GMP requires printed information in secondary packaging materials such as labels or cases. (Chotai & Patel, 2011) Among this information, batch number, manufacturing date and expiration date must be present. Thus, a product that matches format, solution and country specifications but contains mistaken information pertaining the batch is a non-conforming one.

	Actual filled volumes [ml]	Bottle dimensions [mm]	folding carton dimensions[mm]
Bottles	60 70	diameter=47.0 height=84.4	61x52x110
	75 100	diameter=47.0 height=110.4	61x52x125
	150	diameter=54.3 height=128.0	70x58x139.5
	200	diameter=55.0 height=148.0	70x58x160

Table 2.2- Filled volumes, bottle dimensions and folding carton dimensions that the line was able to deliver

Each time one or more of these attributes must change, a CO operation must be performed. Naturally, the activities that have to be carried out during a set up depend on the specific attribute that has to change. After analysing the possible scenarios, the following types of CO were identified:

- **Type A Changeover**: This is the changeover that has to be performed when the attribute "Country" has to change. Hence, materials used for product "A" should be removed from the line and materials for product "B" should be brought to the line. In addition, leaflet dimensions may change and the format in which the variable data is stamped can differ from one country to another. This type CO does not require any activity to be performed in the primary packaging section.
- **Type B Changeover**: This CO is performed whenever a new batch of the same type of solution has to be prepared. The tanks must be cleaned, a new batch has to be prepared and poured, and filters must be changed. Also, the filler machine's tank must be washed, as well as the syringes and the hoses. In the secondary-tertiary section, stamps containing batch information must be changed.

- **Type C changeover**: A CO performed whenever the size of the bottles to be filled changes. Activities include interchanging formatted pieces in virtually every machine as well as small adjustments.
- **Type D Changeover**: This type of CO is performed when the type of solution has to change. The activities are practically the same as in the Type B changeover, but TOC[18] water thresholds must be satisfied in 4 different measuring points before production can begin.

These COs can occur either individually or at the same time (except type B and type D changeovers which are mutually exclusive). With the intention to provide an example, table 2.3 illustrates a hypothetical simplified production schedule for 2 weeks. As can be noticed, the first CO to be performed is a type A one, since between rows 1 and 2 the only attribute that changes is "Country" from "Argentina" to "Sweden". Analogously, between rows 6 and 7 there are 3 attributes that must change (Country, Format and Solution); hence 3 different types of changeovers must be performed before production can start.

Row	Programed week	Solution	Country	Format [ml]	Ordered Quantity	Equivalent in litres
1	36	X	Argentina	75	5,000	375
2	36	X	Sweden	75	20,000	1,500
3	36	Z	Spain	60	20,000	1,200
4	36	Z	Thailand	60	5,000	300
5	36	Z	South Africa	60	5,000	300
6	36	Z	Chile	60	80,000	4,800
7	37	X	Canada	200	15,000	3,000

Table 2.3- Simplified example of production schedule

[18] Total organic carbon (TOC) is the amount of carbon found in an organic compound and is often used as a non-specific indicator of water quality or cleanliness of pharmaceutical manufacturing equipment.

The company did not contemplate batch changes in the long-term planning horizon. Instead, they were considered while the production orders were being prepared (production scheduling), generally 2/3 days prior to produce. Thus, the exact moment when a type B CO had to be performed could not be known by just reading the master production plan.

2.1.3. The Impact of GMP

The production process may seem relatively simple so far but, since it produces medicines, it is regulated by the GMP. Hence, it must comply with a wide number of international standards in order to guarantee the quality that the consumer expects. Since it is not the purpose of this thesis to assess and discuss these regulations, this section instead will explain in practical terms how these norms impact the oral solutions line.

First of all, a distinction between primary (also known as consumer or retail packaging), secondary (grouped or display packaging) and tertiary packaging must be made. The former is defined as the packaging in direct contact with the product itself. Its main purpose is to protect and/or preserve, contain and inform the consumer. Secondary packaging is used for protecting and collating individual units during storage and it serves as a branding display tool. Finally, tertiary packaging facilitates the protection, handling and transportation of a series of sales units or secondary packaging in order to group everything into unit loads during transit. This type of packaging is rarely seen by the consumer.

The GMP explicitly states that should primary and secondary packaging had to be performed, both of them have not to be carried out in the same room. Because of this requirement, the oral solutions production line is chiefly divided in two sections, where the first performs the primary packaging and the latter deals with both secondary and tertiary packaging.

Secondly, GMP also imposes strict measures in order to avoid cross contamination for both products and raw materials. These requirements have a strong impact on changeovers, videlicet:

- The production line must be empty from all the raw materials used to produce "product A" before an external controller (Quality control personnel in this case) confirms that the changeover can continue and, only after her approval, materials for "product B" can be brought to the production line.
- Concerning the bulk of oral solutions, a cleaning process must be carried out in both tanks each time a new bulk has to be made.
- After cleaning the tanks where the solutions are prepared and stored, water samples must be taken from them and, only if the TOC is below a predefined threshold, the changeover process can continue. Otherwise, washing cycles and TOC measurements must be iterated until the carbon levels are acceptable. This procedure is performed once every 4 batches of the same solution and whenever a Type D changeover has to be made.
- When the production must change from solution X to solution Z, in addition to the tanks, TOC water measurements must be also taken from the filler machine's tank and at the output of the syringes.
- Cleaning operations must constantly be performed on machines and workspace in general whenever a CO is performed.
- Extensive batch production records must be compiled during production as well as when the production run is finished, and a CO has to take place. (Chotai & Patel, 2011)
- As can be seen in appendix 2, GMP requires different input and output flows for raw materials, personnel and finished products. Consequently, the workshop is made up by several rooms with different relative air pressure with the aim of preventing cross contamination.

Summarizing, COs in the pharmaceutical environment must comply with strict measurements in order to avoid product contamination. Cleaning operations must be performed more often than in other production contexts and physical analysis will certify that the surfaces are clean enough. Finally, batch production records are also to be considered, since they are extensive and must be compiled before other actions can take place (World Health Organization WHO Technical Report Series, No. 957, 2010).

Chapter 3- Problem Statement

As a company that operates in the environment described in chapter 1, the company shows all the symptoms expected from a contract manufacturer operating with relatively little attention given to production efficiency.

From a qualitative point of view, the direction was not concerned about continuous improvement until 2017, when they decided to create a Project Management and OPEX department. Unfortunately, it was much of the former and little of the latter. In one year, practically no kaizen improvements were made; partly because of the limited senior management commitment and also because of the lack of cross-functional department collaboration. Also, it was noticed that excessive attention was given to short-term benefits such as cost reduction, with nought consideration of the long-term benefits that some proposals would have had in terms of flexibility and competitiveness.

In response to low productivity and excess of overdue orders, the company decided to produce also during weekends, creating a new agreement with the workers union. Although this decision helped to cope with the delivery issues, productivity was even lower during weekends (figure 3.1) mainly because of the low morale, scarce motivation and the fact that inexpert workers were assigned to the line during this period. Even more, the internal survey showed that blue collar workers were displeased and unmotivated with management decisions.

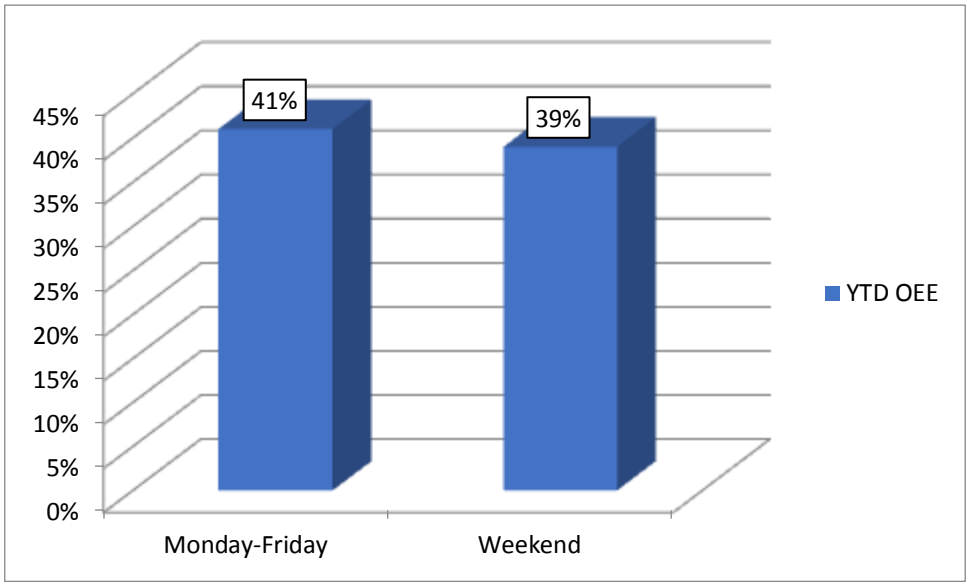


Figure 3.1-Productivity comparison in different days of the week

Maintenance was another issue, since the absence of a maintenance department and, consequently, the fact that maintenance operators were directly subordinated to production managers, naturally provoked excessive focus on corrective maintenance. Although the company did plan preventive maintenance interventions on the most critical machines, there were no signs of TPM practices such as the measurement of indicators like MTTR or MTBF, the existence of a machine ledger, FMECA analysis or autonomous maintenance applications. Moreover, no cause-root analysis, Ishikawa diagrams, 5W2H or similar tools were used after corrective interventions.

Although the company did certify the ISO-9001 standards, some of the fundamental principles that the latter one requires were not actually applied inside the company. Among them, there were neither signs of “continuous improvement” driven actions, nor “employees’ participation” whenever decisions had to be taken.

Production performance was evaluated by the level at which the production department was able to stick to the master production plan, leaving the line's productivity in a second place. Although it is not the scope of this thesis to redesign the performance measuring system, the latter one did not link appropriately long-term goals with basic sub-indicators derived from everyday activities (Kaplan & Norton, 1996).

Numbers also were in accordance with literature. In figure 3.2 shows how the revenues and EBITDA have been increasing over the last 4 years. The mean EBITDA margin for this period approximately 15.11%, which can be considered fair good compared with other pharma CDMO (figure 3.3) .

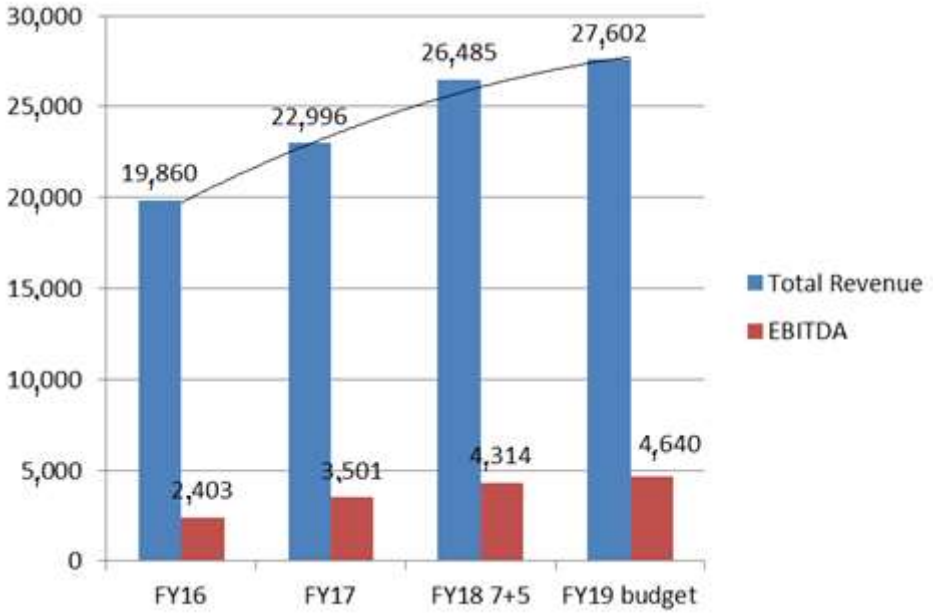
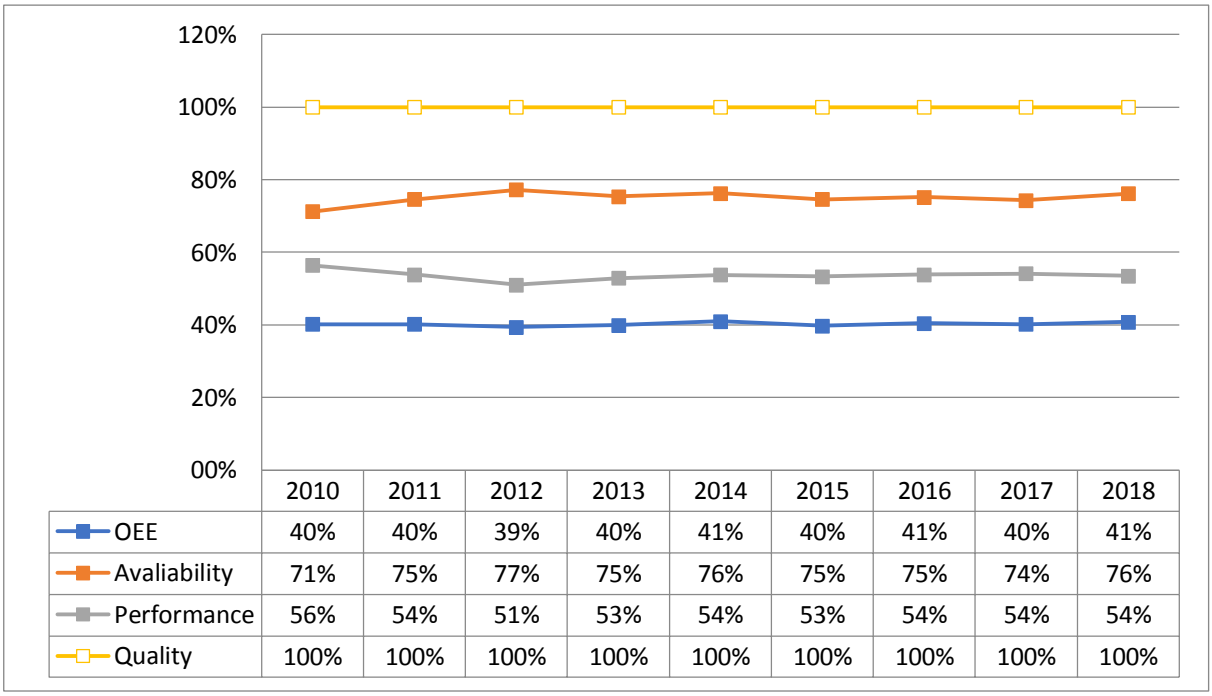


Figure 3.2-Company's revenue and EBITDA for the last four years

Company	HQ	Ownership	Revenue (US$m, 2016)	EBITDA margin (2016)
Recipharm		Public	519	16.2%
AMRI		Public	571	10.1%
Patheon		Public	1,867	19.2%
Aenova		Private (PE)	814	12.0%
Catalent		Public	1,848	20.3%
Amatsigroup		Private (PE)	~32	15.6%
WuXi PharmaTech		Private	780	17.0%
Strides Shasun		Public	476	16.5%
Piramal		Public	1,016	29.8%
Siegfried		Public	707	12.5%

Figure 3.3- Pharma CDMO top consolidators

Concerning production efficiency, the wide-spread accepted metric that best describes equipment performance is OEE. (Williamson, 2006). Figure 3.4 shows the latter one for the oral solutions production line, over a 9 years period. As can be seen, the mean annual values do not present any upward trend, which again shows the lack of improvement actions towards productivity. The graph also shows the respective values for quality, performance and availability, the 3 sub indicators from which the overall equipment effectiveness is made up of.



	2010	2011	2012	2013	2014	2015	2016	2017	2018
OEE	40%	40%	39%	40%	41%	40%	41%	40%	41%
Avaliability	71%	75%	77%	75%	76%	75%	75%	74%	76%
Performance	56%	54%	51%	53%	54%	53%	54%	54%	54%
Quality	100%	100%	100%	100%	100%	100%	100%	100%	100%

Figure 3.4- OEE decomposition year by year, calculated for the oral solutions production line

Some comments should be made concerning quality, which in OEE metrics is similar to "first pass yield", in that it defines good parts as parts that successfully pass through the manufacturing process the first time without needing any rework. Hence, it should include scraps as well as parts that need rework. The oral solutions line's quality indicator did not include the former nor the latter, as the Gemba walks confirmed. In fact, if that had been the case, only the exact quantity of raw materials would have been required on each production order. Of course, reality was different, since the company allocated 1.03 times the net material requirements when performing the MRP.

Scraps were produced practically in all the production steps, were PLC systems discarded automatically products that did not meet the product specifications. Some of them were reprocessed and others were discarded. Therefore, based on the definition stated above, the real quality measurement should be far below 100%.

Since the OEE can be defined as the relation between the actual yield obtained and the theoretical maximum output for a particular process, the way in which the company measures quality should not impact on the final value. In fact, since the OEE is a derived indicator that fulfils the property of compensation (it is expressed in a rational scale (Stevens, 1951)), variations in quality would be compensated with variations in performance, and the final derived indicator's value should not change (Franceschini, Galetto, & Maisano, 2007). Figure 3.5 shows how the derived indicator OEE should be calculated.

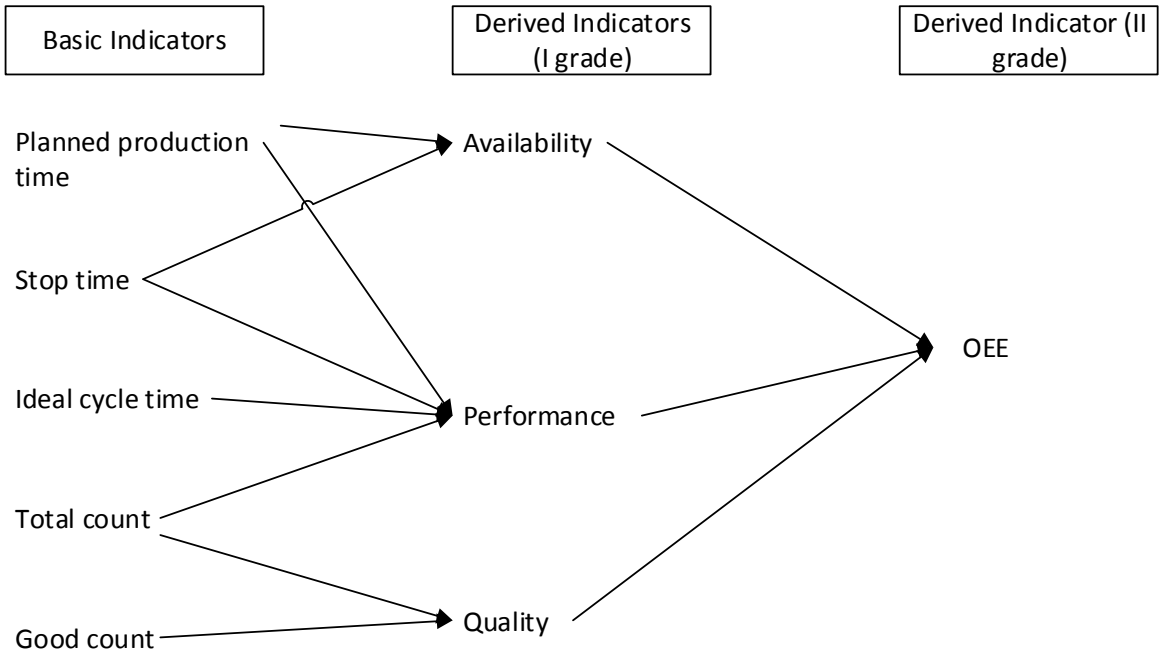


Figure 3.5- Basic and derived indicators for OEE calculation

Figure 3.6 shows a graphical representation of the OEE decomposition, given in time values. Remembering that OEE is defined as:

$$OEE = Availability\ x\ Performance\ x\ Quality$$

And keeping in mind that these sub indicators can be calculated as follows:

$$Availability = \frac{Available\ Production\ Time}{Running\ Time} = \frac{D}{C}$$

$$Performance = \frac{Net\ Operating\ Time}{Running\ Time} = \frac{E}{D}$$

$$Quality = \frac{Productive\ Time}{Net\ Operating\ Time} = \frac{F}{E}$$

The OEE indicator can be rewritten as:

$$OEE = Availability\ x\ Performance\ x\ Quality = \frac{D}{C}\ x\ \frac{E}{D}\ x\ \frac{F}{E} = \frac{D}{C}\ x\ \left(\frac{\cancel{E}\ x\ F}{\cancel{E}\ x\ D}\right) = \frac{D}{C}\ x\ \frac{F}{D}$$

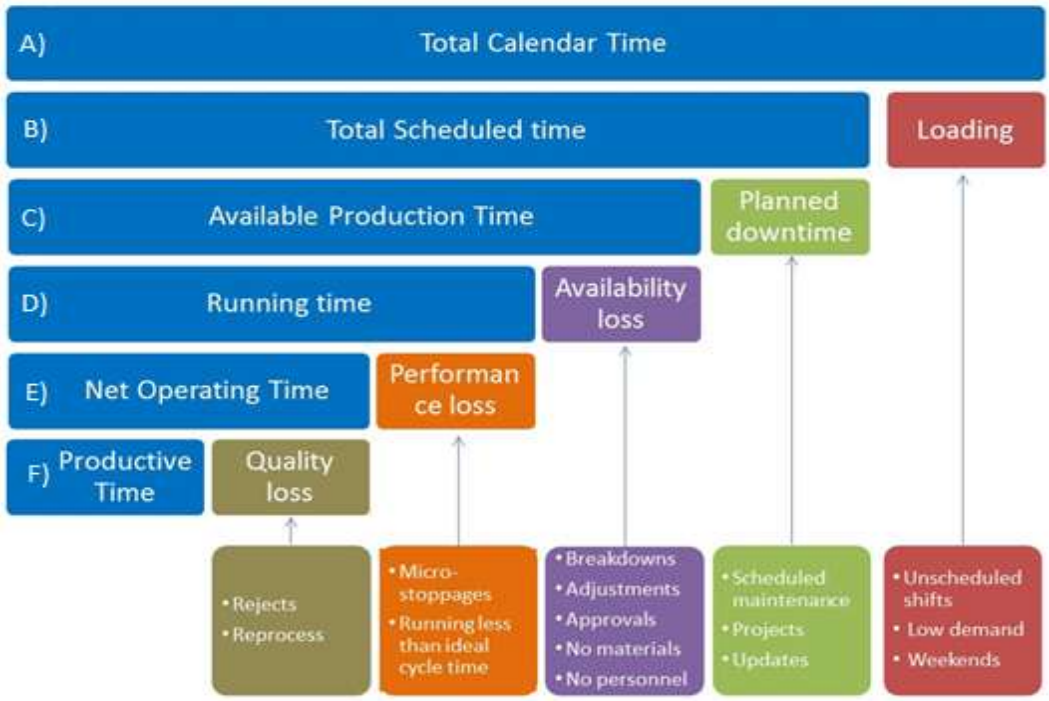


Figure 3.6-graphical decomposition of OEE factors based on time

The $\frac{F}{D}$ Factor includes both quality and performance losses and could be seen as a compound indicator for both. The performance indicator, as it was calculated by the company, follows this reasoning. However, availability losses included only a part of the total downtime

due to changeovers[19]. This caused availability to be overestimated, allocating part of the changeover time in "performance" losses. Although higher resolution would provide more accurate data from which decisions could be taken, the precision of an indicator should be the one that allows the users to perform evaluations, make comparisons and take decisions in a feasible way (Franceschini, Galetto, & Maisano, 2007).

Figure 3.7 shows a more accurate decomposition of OEE for the last 6 months, where the availability losses were recalculated, taking the information from the logbook and applying the correct definition of changeover time (performance and quality were kept under the voice of "performance").

Based on these data, it was decided to start assessing the availability issues, since they were causing the greatest inefficiencies. Also, availability losses are the easiest to attack, since the causes can be seen immediately, the impact can be easily measured, and the analysis does not require a deep knowledge of the working principles of the machines.

[19] Whenever performing a CO, the activities performed were written down in a logbook that included diverse" categories" were to allocate the time spent. These categories included "cleaning", "clearing" and the "changeover time". The company only considered the "changeover time" when calculating the OEE. However, as it is explained in chapter 4, changeover time should be measured as the time between production of the last good part (at full speed) and production of the first good part (at full speed). Therefore, it should include all the time spent preparing the line, no matter in which "category" the activity falls into.

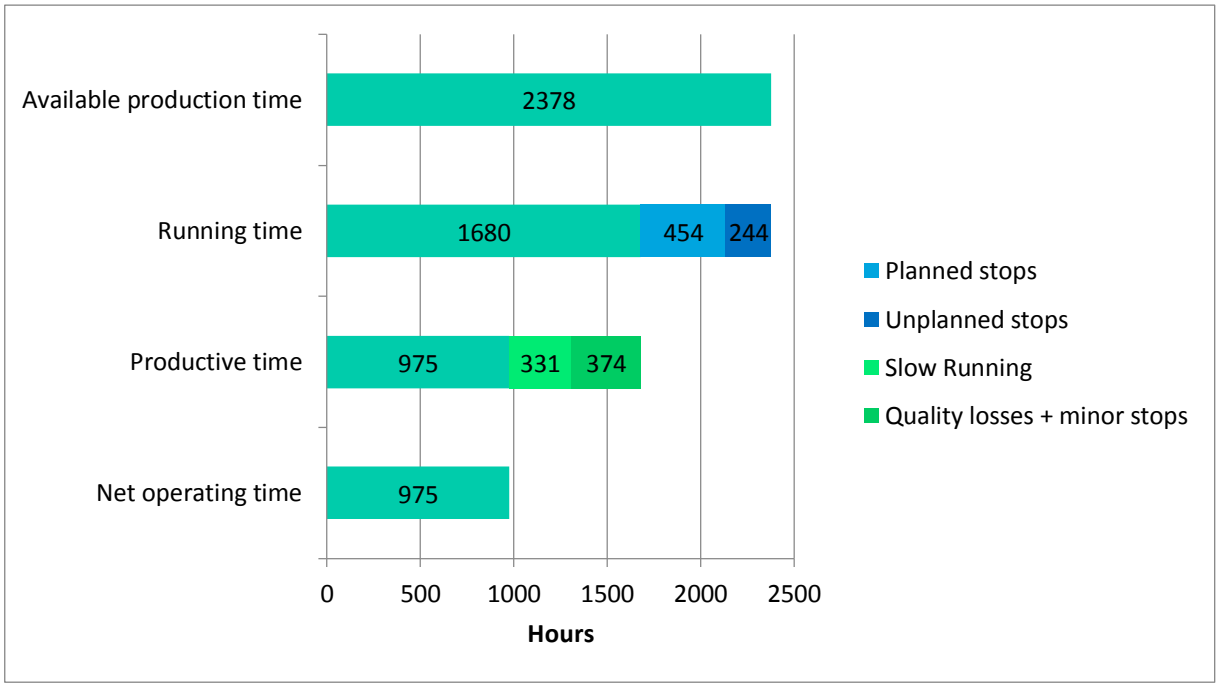


Figure 3.7- OEE estimation- corrected by correct CO definition

Availability can be further subdivided in planned and unplanned stops, with the former representing time lost due to changeovers and adjustments, and the latter showing downtime due to equipment failure.

Fig 3.8 shows the availability losses breakdown measured in a 5-month time frame. As can be seen, the major contributor to availability losses was the planned stops, with 65% of the total downtime. Figure 3.8 also shows the different types of COs performed and their percentual contribution to the total. For instance, 17% of the availability losses were due to Type A CO, which is quite counter-intuitive, since most of the managers thought type C CO was the most time consuming.

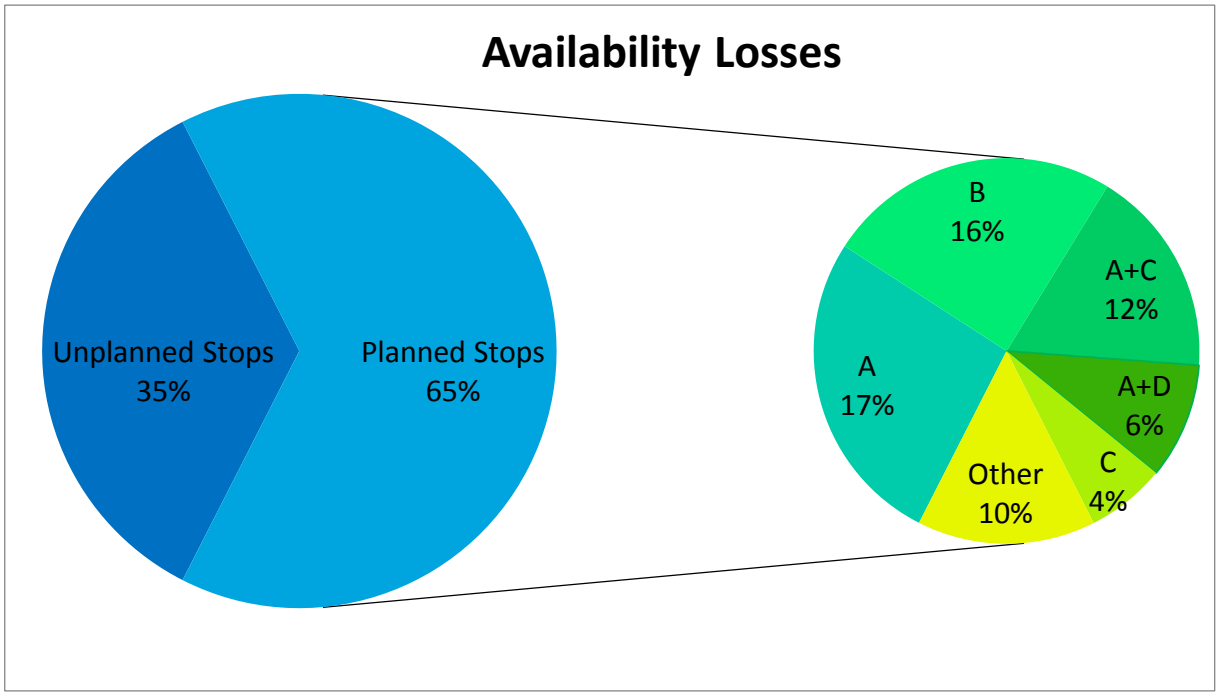


Figure 3.8- Availability losses breakdown

With the purpose of enhancing the line's productivity, 4 interdependent projects were designed with the aim of reducing the major inefficiencies found during the analysis phase:

- **Project 1**: Reducing type A changeover time
- **Project 2**: Reducing type B changeover time
- **Project 3:** Reducing type C changeover time
- **Project 4**: Reducing unplanned stops

The following chapter will discuss each one of the projects presented above in terms of activities performed and results obtained.

To summarize, the company's situation was in a with the general pharmaceutical landscape described in chapter 1. With rising revenues year by year, no attention was given to

production efficiency. Management was not in possession of lean manufacturing knowledge, since productivity was not interpreted as a key competitive factor. Maintenance practices were way behind the world class practises, mainly because of the organizational structure. Concerning the oral solutions production line, the miscalculation of performance indicators such as availability, performance and quality prevented the management to identify the underlying issues that were causing the low productivity. A deeper analysis identified availability as the biggest inefficiency-driver, with planned stops dominating the picture with 65% of the total stop time. The following chapter will discuss the 4 projects dedicated to enhancing the line's availability.

Chapter 4- Solving the Problem

4.1. Methodology

In order to maximize the success likelihood, a revision work concerning literature on SMED methodology was performed. Such work allows to identify key parameters that should be taken into account when implementing improvement tools, since previous studies provide invaluable knowledge extracted from past applications. The revision is based mainly upon key topics such as project planning, team composition and training.

Concerning project planning, the projects were divided into four main phases: strategic, preparatory, implementation and control; following the guidelines proposed by Guzman and Kostantinos (Guzman & Konstantinos, 2013). According to the authors, such division allows to focus on the most important aspects during each phase, ensuring that every element is considered in detail without losing the big picture. In fact, the quality of project planning is a great predictor of success likelihood and, therefore, it should receive the right attention. Resources constraints or task's duration longer that needed (a phenomenon known as Parkinson 's Law[20]) (Parkinson, 2002) are among the drawbacks that can be avoided using this methodology.

The four stages model was in fact best proposed by McIntosh et al. (McIntosh, Culley, Mileham, & Owen, 2001) in his overall methodology for changeover improvements. However, Guzman and Kostantinos (Guzman & Konstantinos, 2013) argue that control should be a separate phase, since while implementation is aimed at introducing changes to achieve results, control's scope is to check that those results are sustained and to evaluate if they successfully fulfil team expectation.

[20] Parkinson's law is the adage that "work expands so as to fill the time available for its completion". It is sometimes applied to the growth of bureaucracy in an organization. This law is likely derived from ideal gas law, whereby a gas expands to fit the volume allotted.

Strategic phase

During this stage, general guidelines are considered on a macro level to frame the project in terms of the amount of resources that will be committed with and the kind of results expected (McIntosh, Culley, Mileham, & Owen, 2001). To start with, several authors mention senior management commitment as the strongest driver in order to achieve good results (Shingo, 1983) (Snee, 2007) (Ohno, 1988). Keeping in mind that, as it was commented in chapter 1, one of the main reasons improvement projects fail in the pharma realm is because of the lack of direction support, it is not surprising to say that senior management support was almost unexisting. Therefore, the goal of the project was to achieve measurable improvements with as minimum investment as possible, in order to show the management that lean tools can be successfully applied in pharma Concerning project duration, a six-month time frame was set for, in which at least a 5% improvement on the OEE mean value should be achieved.

Another key element that should receive attention during this phase is project planning. In particular, clear and measurable targets should be carefully set to drive actions towards a desired outcome, all the relevant tasks should be precisely scheduled and resources should be consequently assigned. Finally, milestones and deadlines help to keep the project on track and should also be included(Krajewski, Ritzman, & Malhotra, 2010). With the purpose of showing an example concerning how the project planning was made, the reader can consult appendix 5, where she can find a Gantt chart, in which the main tasks are defined with their respective assigned duration.

Last but certainly not least, the kind of improvement that is preferred should be considered. it Emphasis could be on low-cost organizational improvements or design improvements (McIntosh, Culley, Mileham, & Owen, 2001). Such a decision depends on the level of improvement required and the budget available for the project. High expectations

might be managed with focussing on both pathways. Because of the little senior management commitment, the emphasis was set mainly on low-cost organizational improvements, with the possibility to evaluate technical improvements provided a sound financial analysis and always constrained to the direction's approval.

Preparatory phase

This phase switches attention from project planning and strategic decisions to team composition and preparation. In fact, the selection of project team members should never be an arbitrary decision, as it can be determinant with regards to the success likelihood. Even the perfect strategy can fail if it is not executed correctly, and execution is highly dependent on the technical skills of the people involved as well as their capacity to motivate and drive the members to a desired outcome. Cross functional teams are the preferred choice, as they allow to evaluate the situation from different perspectives (Krajewski, Ritzman, & Malhotra, 2010). In particular, it should include people from operations, logistics, quality and engineering, preferably form different hierarchical levels. The authors also mention technical competence, curiosity and dedication as the desired characteristics of the composing members.

In a manufacturing changeover analysis, the team should include people from the shop floor, maintenance, logistics, engineering department, lean department and senior management. With regards team members, Krajewski et al. (Krajewski, Ritzman, & Malhotra, 2010) mention technical competence, sensitivity and dedication as the most important characteristics that members should possess in any project team. These skills are necessary but do not guarantee teamwork success. McIntosh et al. (McIntosh, Culley, Mileham, & Owen, 2001) include attitude, awareness, resources availability and team director among the key elements needed for teamwork success on achieving the goals predefined.

Following the recommendations of these scholars, the project team was constructed with all the in-house stakeholders, namely:

- 1 Team leader
- 3 Line operators
- 1 Maintenance operator
- 1 Quality control operator
- 1 OPEX specialist
- The Head of the liquid department.

Due to the lack of cross functional collaboration and team working culture, personnel from logistics and senior management were not included in the team. Remembering that there is a consensus in the literature that direction commitment is a key factor to success, it is possible to state that the improvement potential of the project was not very high and that is the reason why a mere 5% increase in the mean OEE value was set as the target.

The next key element to consider is training. Goubergen et al. (Goubergen & Landeghem, 202) cite training as one of the most suitable methods to guaranty motivation and discipline. Concretely, those who would be in charge of performing the standards resulting from the study should possess knowledge regarding the entire SMED methodology and theoretical drivers that explain the importance of shorter set ups. This opportunity could be conveniently used to spread a continuous improvement philosophy, in order to multiply the amount of people that is able to see and identify waste (Imai, 1986).

Following this reasoning, the 3 projects included training session during which the tools needed to correctly apply the methodology were explained. During these meetings,

SMED principles, 5W2H, cause root analysis and Ishikawa diagrams were introduced in order to provide the team with the theoretical knowledge.

Finally, within the preparatory phase, it is vital to ease and facilitate communication between the different actors by means of a predefined system. It is important to assess how the information will flow from improvement team to the rest of the company. In particular, since the company was producing using a 3 shifts production scheme, the communication of problems, initiatives and the like was quite difficult with the night shift (6AM-2PM). In response to this issue, a panel was located in the shop floor, to be updated frequently with the conclusions obtained from each implementation step.

Implementation phase

During this phase the actual application of the SMED methodology should happen. Shingo (Shingo, 1983) identified 4 different stages within the entire methodology (Figure 4.1). Each one of them should be scheduled to force progress to occur in the desired manner.

Figure 4.1- Graphical representation of the four steps proposed by the SMED methodology

Control phase

As it was commented before, control was designed as a separate phase since focus switches from action to checking and verifying. Its purpose is to monitor key performance indicators, where the changeover time is logically raked in first position. An increase in availability should be a natural consequence and, therefore, should receive special attention. Finally, OEE mean value should increase as well, since it is the indicator that would ultimately show if the project was successful or not. Furthermore, according to continuous improvement philosophy, subsequent SMED implementations can be scheduled in order to capitalize the experience gained over adjacent production lines.

4.2. Literature Review

4.2.1. Lean Manufacturing

Lean production is a term that was first used in "The Machine That Changed the World" by Daniel Roos and James P. Womack (Womack, Jones, & Roos, 1991), to describe a new production philosophy that was being applied by Japanese car manufacturers during the 70s and 80s. It can be explained through the concept of productivity. This latter one can be understood as a ratio between output and inputs per period. Thus, in a manufacturing system, productivity has to do with the amount of product(output) generated and the resources activated to obtain it (to unify different measuring units such as kwh, cubic meters or labour, it is common practice to merge them into a monetary value) over a period.

Logically, anything more than the theoretical quantity of inputs needed would increase the denominator and, therefore, decrease overall productivity. Here is where lean comes. Its ultimate goal is to increase productivity or, in other words, do more with less. Ohno (Ohno, 1988), the father of lean philosophy, defines "waste" as 'anything other than the minimum amount of equipment, materials, parts, space and time that are essential to add value to the product". Additional benefits include customer responsiveness, better quality and a highly motivated workforce.

Organizations that have succeeded in the implementation of lean manufacturing methods usually present a substantial cost and quality advantage over those still practicing traditional mass production methods (Fleischer and Liker, 1997). While there are uncountable ways to measure improvement such as inventory, cycle times, set up times, lead times, etc. the final benefits can should always be evident in terms of productivity.

From an operative perspective, lean offers a very complete toolbox, including well-known elements such as poka yoke, kan ban, 5S, SMED. These tools basically apply the scientific method to analyse and improve production efficiency, usually by reducing non-value-added activities in different areas of business.

Summing up, although there is not an universal consensus about the definition of lean manufacturing, it could be explained as a philosophy that applies the scientific method to eliminate waste in every business area with the final goal of increasing productivity and flexibility.

4.2.2. SMED

Multiple benefits can be gained by applying rapid setups, starting from improved quality on an operational level, increased equipment utilization on a tactical level and customer responsiveness on a strategical one (Leschke & Elliott, 2009). Shingo (1985), one of the key figures in the introduction of rapid setups at Toyota, developed the SMED theory, which could be defined as a technique for simplifying and improving operational activities to complete a setup operation in less than ten minutes.

Shingo created a first distinction regarding the setup activities, which he divided into internal and external ones, with the former being the ones that can be performed only when the machine is shut down, and the latter being those that can be conducted during the normal operation of machine, while it is still running. These internal and external set-up activities involve different operations, such as preparation, after-process adjustment, checking of materials, mounting and removing tools, settings and calibrations, measurements, trial runs, adjustments, etc.

SMED methodology is formed by four single stages:

- A preliminary stage where the internal and external set-up conditions are not distinguished
- The first stage, where the separation between internal and external activities takes place
- The second stage, where the aim is to convert internal activities into external ones
- The third stage, which focuses on streamlining the internal set-up operations that cannot be converted into external.

The application of Shingo's methodology usually results into two main benefits: increasing manufacturing capacity and improving the equipment flexibility (Coimbra, 2009). That allows to work with smaller batch sizes, creating a smooth flow of materials by eliminating non-productive time. Both benefits can be translated in increased productivity. Recalling the Economic Order Quantity (EOQ) model, the preferred lot size is the one that minimizes total annual cycle-inventory holding and ordering costs (Coimbra, 2009). Knowing that the latter one is mainly affected by set up times, a lot size reduction can be expected by shortening set up activities (Figure 4.2)

Figure 4.2- Economic Order Quantity and SMED effect on reducing ordering cost due to changeover time reduction (Guzman & Konstantinos, 2013)

Although SMED is a well-known methodology and with uncountable examples of successful applications, a number of companies have failed when it comes to implementation. Some studies have been published analysing the possible causes of failing initiatives, with McIntosh et al. (McIntosh, Reik, Culley, Mileham, & Owen, 2006) being the most respected exponent. In their work, it is stated that one possible reason might be the strictly application of the methodology. In fact, it seems like the four stages pathway might not be the most efficient way to reduce set-up times in all situations. Indicatively, some companies focus mainly on transferring changeover internal tasks to external, missing the importance of minimizing or streamlining internal and external activities by means of design improvements. This problem can be linked to the fact that Shingo mainly focuses on organizational-led improvements and not enough on equipment design improvements (McIntosh, Reik, Culley, Mileham, & Owen, 2006). The former are those improvements focussed on changing the way the people work. In contrast, the latter tries to physically modify manufacturing equipment or production processes.

Fig. 4.3 presents the reduction on changeover time that in theory could be achieved depending on the different focus that can be adopted during the SMED implementation. If focus is only on methodology, results can be acceptable with little investment. In contrast, by combining design modifications and methodology improvements, the outcomes can be significative greater with a moderate investment. The design of a new system is out of scope when implementing SMED programmes, although results can be excellent.

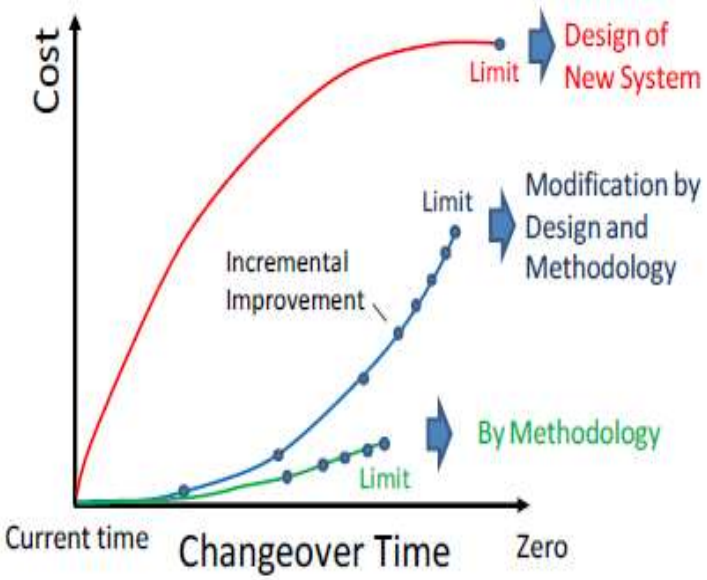


Figure 4.3- Limits and costs for changeover improvements strategies (Cakmakci, 2009)

One shortcoming of SMED method lies with the fact that it analyses set-ups performed by one operator involving one single machine, when, in practice, there is a need of implementation in manufacturing lines formed by multiple machines and controlled by multiple operators (Sherali, Goubergen, & Landenghem, 2008). When a changeover is being run in a manufacturing cell, the SMED methodology is not specific about how the set-up time should be measured.

To summarize, the run-up and run-down periods, the appropriate team to be involved on the initiative, the definition of achievable targets, the type of industry and machine where SMED is going to be implemented, the focus of the initiatives (organizational or hardware improvements) all of them are issues than should be considered in every changeover improvement initiative.

4.3. Reducing Planned Stops

As discussed in chapter 2, a product was defined by 4 attributes, namely solution, format, batch and country and, logically, a CO should be performed each time one of them must change.

Counter-intuitively, the easiest CO in terms of activities to be performed, parts to be changed and adjustments to be made (type A CO) was also the highest single contributor to the total CO downtime (figure 4.4); followed by the type B changeover. Type C CO alone represented 7% of total downtime (32% if Type C changeovers performed simultaneously with other types of CO are also considered).

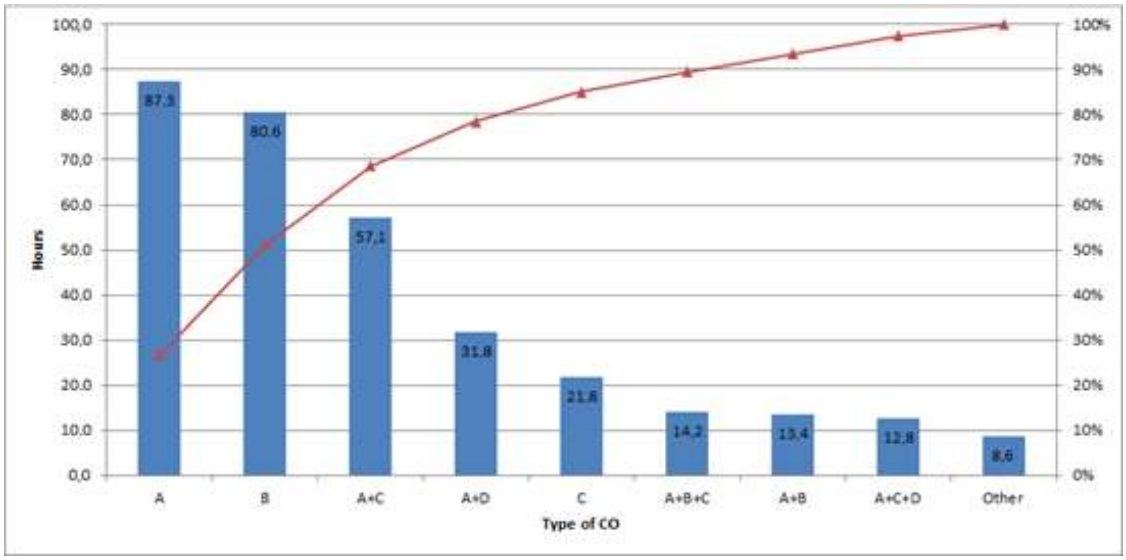


Figure 4.4- Planned stops breakdown by type of setup

On the other hand, type D COs were seldom performed, the procedure to be followed was similar to that of type B COs but more time consuming since TOC water thresholds should be satisfied in 4 points before production can start[21] .

[21] The measuring points were water samples had to be taken were the mixer tank, the storage tank, the filler's tank and at the outlet of the syringes

Following the Pareto principle, it was decided to set aside the type D CO and to focus exclusively on type A, B and C. Each one of them was assessed on a separate improvement subproject but these latter ones were carried out in an overlapped way. Therefore, in spite of the fact that they are discussed in different subsections, some improvement activities were chosen taking into account the compounded impact that they would have on the three projects combined. Notes can be found wherever the author considered necessary to explain this kind of interrelated decisions that affected more than one project.

For each one of the projects defined above, specific goals were defined after observing the activities performed during the COs. Analogously, the project planning phase stated how the different activities were going to be organized, setting deadlines. During this phase it was decided that emphasis should be on low-cost organizational improvements rather that design improvements, since the direction was not willing to make significant investments.

Guzman and Konstantinos (Guzman & Konstantinos, 2013) proposed to calculate the monetary value of CO saved time as:

$$(Annual\ Savings) = 12\ x\ (N°\ of\ COs\ per\ month)x\ (Time\ saved\ per\ CO)x$$
$$x\ (Labour\ costs)\ x\ (Number\ of\ operations)$$

However, as the company's ultimate objective is to sell products, any minute saved should be used to produce in order to maximize the output for a given input of resources (keeping in mind that for this particular production line, customer demand is greater than the current production capacity). Therefore, it was considered more convenient to calculate the cost savings based on the following formula:

Cost per Changeover=Line Speed x Contribution x Average Changeover Time

Contribution is defined as price minus variable costs. Since the time frame where a CO takes place is usually not longer that one production shift (8 hours), labour was assumed as a fixed cost. Therefore, contribution is calculated as price minus cost of materials, since any reduction in CO time will cause a monetary gain of the same value. All the other costs incurred for oral solutions production (employee wages, depreciation, consumables, etc.) are sunk costs and will be accrued no matter if the line is producing or not. Since the line produces a wide variety of products (89 in total, remembering that every product is defined by Country, Format and Solution), the calculations are based on average values, weighted by the proportion of total produced volumes (Table 4.1).

	Contribution [€/unit]	Line capacity [units/min]	Contribution per minute [€/min]	% of total produced volume	Weighted Contribution Margin [€/unit]	Weighted contribution per minute [€/unit]
60ML	0.53	70	37.73	3%	0.018	1.30
70ML	0.55	70	38.52	1%	0.05	0.38
75ML	0.60	66	39.98	68%	0.41	27.32
100ML	0.40	60	24.31	2%	0.01	0.60
150ML	0.96	54	52.06	3%	0.02	1.47
200ML	0.99	48	47.77	22%	0.217	10.45
				1	0.69	41.55

Table 4.1- Calculation of the average margin contribution per minute of the oral solution production line

However, proposing the number stated above as the monetary value for each minute gained in setup improvements would be incautious, since the line capacity is a theoretical one and would assume that the extra available time would be used to produce at top speed and 100% quality. Logically, this assumption is both optimistic and unrealistic. A more conservative, and probably sincerer, value is obtained by multiplying the obtained result by

the performance indicator (remembering that, as discussed in chapter 3, such indicator included both quality and performance yields). Therefore, the average cost per changeover is calculated as:

Cost per Changeover = Average CO time x Contribution factor

Where "Contributor factor" is calculated as the contribution times the line speed, corrected by performance and quality yields and weighted by the average produced volumes.

4.3.1. Type A Changeover

During the preparatory phase, data was collected from the logbook and in situ measurements were made in order to create the baseline. Figure 4.5 presents all the Type A CO since the beginning of the year until right before the implementation phase begun.

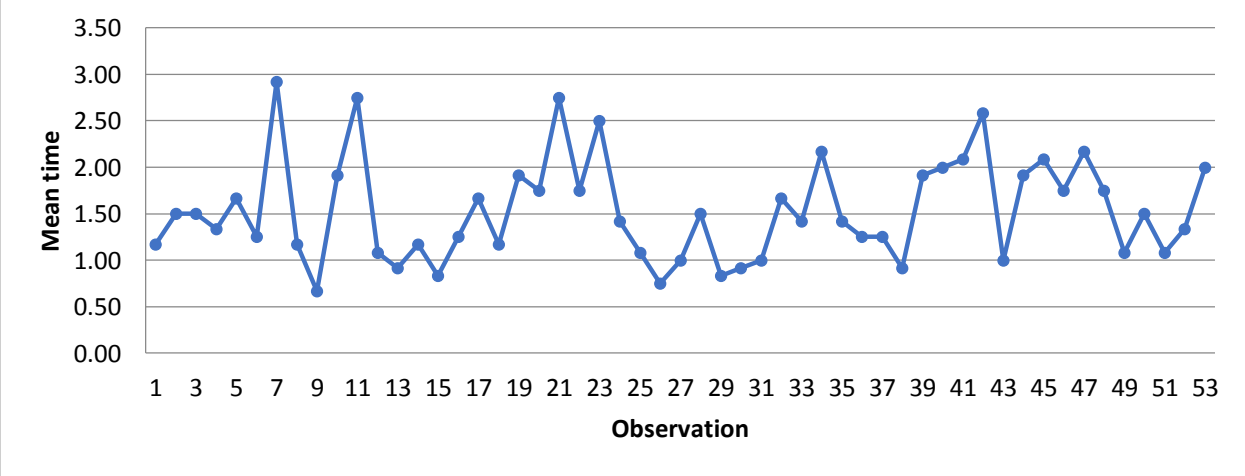


Figure 4.5-Evolution of type A COs duration since the start of the FY2019 until the start of the project

As can be seen, the main issue was the excessive variance that the historical data possessed. In concrete, the data set presented a mean value of 1.54hs and a standard deviation of 0.544hs, which particularly surprised the staff, since they there used to measure the set-up time in a different way (see chapter 3). Among the factors that caused these deviations, the team identified the following:

- **Not all Type A changeovers are equal**. Leaflet dimensions may vary depending on the country, some clients require serialisation[22] while others do not, some orders require syringes as measuring devices, others require spoons, the layout and format of printed variable data is not necessarily equal for all production orders, etc.
- **Material waiting time**. As can be seen in appendix 2, space is limited in the oral solutions production plant. Therefore, material for "product B" is brought to the line only after the remaining material (material not used) for "product A" has been removed. It was noticed also that the material was not requested in anticipation, often generating waiting periods of more than 10 minutes.
- **Quality control waiting time**. Each time a CO takes place, external personnel (form the quality department in this case) must ensure that all the materials from the previous production run have been removed before other activities can take place (line clearance[23]). This proceeding is also valid for the other 11 production lines. Since there are only two quality control operators working during each shift, it may happen that the quality control personnel are busy with other production lines and, therefore, some waiting time can be expected.
- **COs were usually longer during weekends**, since they were performed by inexpert personnel.
- **Different teams performed the activities in diverse sequences,** since there was not a formal standard for type A CO.

[22] Serialization is the assigning of a unique serial number to each saleable unit of each prescription product, which is linked to information about the product's origin, batch number and expiration date. The units can then be tracked through its entire supply chain — from production to retail distribution to the final dispensation to the patient.

[23] Typically, line clearance is done prior to a production run to prevent any error and cross-contamination. It is required that a production facility (line) and its associated working area are completely clear of all materials, waste, products, samples, documents, etc. used in the previous production run before the introduction of materials, product samples, documents, etc. needed for the commencement of the next production run.

These issues were analysed by the team and, subsequently, diverse ways to reduce variability to more acceptable levels were discussed. After debating the applicability of each proposal, the following ideas were implemented:

- The oral solutions production line had been identified as the most critical line. Thus, it should have the highest priority when it comes to quality controls. Therefore, the team leader must request the QC inspection 10 minutes before finishing the production run and the latter one should arrive on time, minimizing waiting time.
- Materials should also be requested before finishing production in order to have them ready to be brought to the line as soon as the line clearance and the quality control have taken place.
- After passing through a thorough analysis, the team identified the best way to perform a type A CO, which became the standard to follow in order to minimize variance.

With all the teams working under the same standard, it was possible to correctly inventory the different operations (with their corresponding duration) that formed part of the type A CO process. The analysis of video-recordings allowed to construct appendix 6, which inventories the activities performed and shows their respective duration.

During the implementation stage, a number of workshops took place in order to implement the SMED methodology, based in McIntosh et al. (McIntosh, Culley, Mileham, & Owen, 2001) overall methodology for changeover improvements and Shingo's SMED methodology (Shingo, 1983). The overall methodology can be found in the methodology section. The rest of this section is devoted to highlight the activities performed and the results obtained.

Stage 1: Classify activities into External, Internal or to be eliminated.

The question "*can this element, as currently performed or with minimal change, be completed while the equipment is running?*" was asked for each one of the operations listed in appendix 6. Depending on the answer, the activities were categorized as external, internal or, in case it did not add any value to the CO process, to be eliminated.

As can be seen, the majority of operations were internal ones, showing that the teams already performed a good sequence of operations even though they did not have the formal knowledge of SMED methodologies. Therefore, the team concluded that the time reduction achievable with steps 1 and 2 was very limited and trying to implement these small improvements in form of SOPs was a waste of time and resources (the bureaucratic process that a procedure had to undertake inside the company in order to be approved was thorough and slow).

Stage 2: Separate External work and Internal Work. Eliminate activities that are not necessary.

During this step, the team attempted to reassign the activities to the different operators that were in charge of the CO. Expected time reductions were in the order of 8%, showing that, as it had been predicted in step 1, the marginal gain did not worth the standardization of the new type A CO process. However, following the PDCA model, the standard's applicability was checked in the workshop to corroborate that the CO could effectively be done in less time applying the conclusions obtained from step 1.

Stage 3: Convert Internal work into External work.

According to Shingo (Shingo, 1983), this stage involves two significant activities to be performed by the improvement team: the detailed analysis of internal operations to detect wrong assumptions, and the research of different ways to convert these activities into external work.

The question to answer was "*If there was a way to make this element external, what would it be? How could we do it?*". Keeping in mind that during the planning phase it was decided that focus would be on low-cost organizational improvements rather that design improvements, the only improvement action with a moderate investment and ease to apply was to externalize the characters change on the mechanical stamps.

If there were another set of stamps for both the labeler and the case-packager, the operations involving the change of characters on these devices could be done before shutting down the machine, reducing substantially the CO total time (these operations represented 20.15% of all the operations to be performed).

In order to prepare the extra set of stamps, one line-operator should get away from the line and perform the operation inside the office, thus avoiding cross contamination of data. The line cannot be managed by only one operator in the secondary-tertiary packaging section and, consequently, the weighting operator must occupy this position (since it is the only one whose activities can be delayed by 30 min without compromising the outcomes). Therefore, the equivalent of 0.5 hours of weighting operator cost should be considered when assessing this proposal.

The extra stamps (with their respective set of characters) had a cost of 874€, which was not negligible. With an average of 12 type A COs per month, performed 11 months a

year and assuming a 3 years analysis horizon (which are conservative hypothesis), table 4.2 shows a simulation analysis, varying both the minutes gained per CO and the "performance*quality" factor. As can be seen, even in the worst-case scenario, the company would save more than 8 k€ per year.

		Performance*Quality												
		40%	45%	50%	55%	60%	65%	70%	75%	80%	85%	90%	95%	100%
Minutes saved per changeover	4	26327	29618	32908	36199	39490	42781	46072	49363	52653	55944	59235	62526	65817
	5	32908	37022	41135	45249	49363	53476	57590	61703	65817	69930	74044	78157	82271
	6	39490	44426	49363	54299	59235	64171	69108	74044	78980	83916	88853	93789	98725
	7	46072	51831	57590	63349	69108	74866	80625	86384	92143	97902	103661	109420	115179
	8	52653	59235	65817	72398	78980	85562	92143	98725	105307	111888	118470	125052	131633
	9	59235	66639	74044	81448	88853	96257	103661	111066	118470	125874	133279	140683	148088
	10	65817	74044	82271	90498	98725	106952	115179	123406	131633	139860	148088	156315	164542
	11	72398	81448	90498	99548	108598	117647	126697	135747	144797	153846	162896	171946	180996
	12	78980	88853	98725	108598	118470	128343	138215	148088	157960	167833	177705	187578	197450
	13	85562	96257	106952	117647	128343	139038	149733	160428	171123	181819	192514	203209	213904
	14	92143	103661	115179	126697	138215	149733	161251	172769	184287	195805	207323	218840	230358
	15	98725	111066	123406	135747	148088	160428	172769	185109	197450	209791	222131	234472	246813
	16	105307	118470	131633	144797	157960	171123	184287	197450	210613	223777	236940	250103	263267
	17	111888	125874	139860	153846	167833	181819	195805	209791	223777	237763	251749	265735	279721

Table 4.2- Simulation analysis evaluating the savings due to the extra set of stamps. Numbers refer to savings over 3 years and are expressed in euro [€]

It is worth to point out also that, even though there is not quantitative data to support the statement, a good proportion of type A CO duration variability can be linked to stamp issues. During the analysis phase, it was noticed that it was not uncommon for line operators to misassemble the stamp the first time, which was noticed only when the team leader controlled the data, and thus enlarging the changeover's duration. Among the factors that could predispose the operator to mistakes, the following ones can be identified:

- Performing the change of characters during the CO (as an internal task) provoked excessive pressure to hurry up in order to cope with the imposed durations
- The operation was performed while standing up next to the line
- The labeler's stamp has a working temperature of approximately 80°C, which caused the operation to be particularly dangerous and uncomfortable.

- The operation required especially good vision, which was a problem for some people since luminosity levels in the workshop were not appropriate for that particular task
- Externalizing the changing of characters permits to perform the activity inside the office, whilst seated down, with appropriate luminosity and calmer, so a reduction in variability was also expected.

Stage 4: Streamline and reduce internal work

Finally, during the last stage of the implementation phase, the questions to ask for each internal operation were: "*How can this element be completed in less time? How can we simplify this element?*".

Although some modifications in the batch documentation where suggested, the quality assurance office was not willing to change its actual procedures and, therefore, the only actions actually carried out were simplification of adjustments activities in both the labeler and the leaflet bender:

- **Adjustments on the GUK[24] intake**: manual adjustments were done in a very rudimentary way, without having graduated scales or similar aids. The device also had 2 screws which should be loosen up and readjusted each time the leaflet dimensions had to change. Information provided by the company showed that there were only 5 possible leaflet dimensions to be worked with in the oral solutions production line. Consequently, the machine was modified, replacing

[24] The GUK was the machine in charge of folding the leaflets. it consisted of a adjustable intake from one side and a barcode reader in the other side. Both had to be readjusted whenever the leaflet dimensions changed

screws with clamping levers, as well as introducing colour-tags to be matched with depending on the leaflet dimensions.

- **Adjustments on the labeling machine**: Also, during this operation small manual adjustments were made whenever the label height or length changed. In order to streamline these operations, position indicators were installed, so the correct position could be imposed the first time, without needing dexterous workers.

During the control phase, the emphasis was imposed on the changeover time. Figure 4.6 shows the evolution of the type A CO duration during the implementation and control phases. Additionally, economic figures were derived using the formula presented in the methodology section. Annual savings were calculated to be in the order of 83.45 k€.

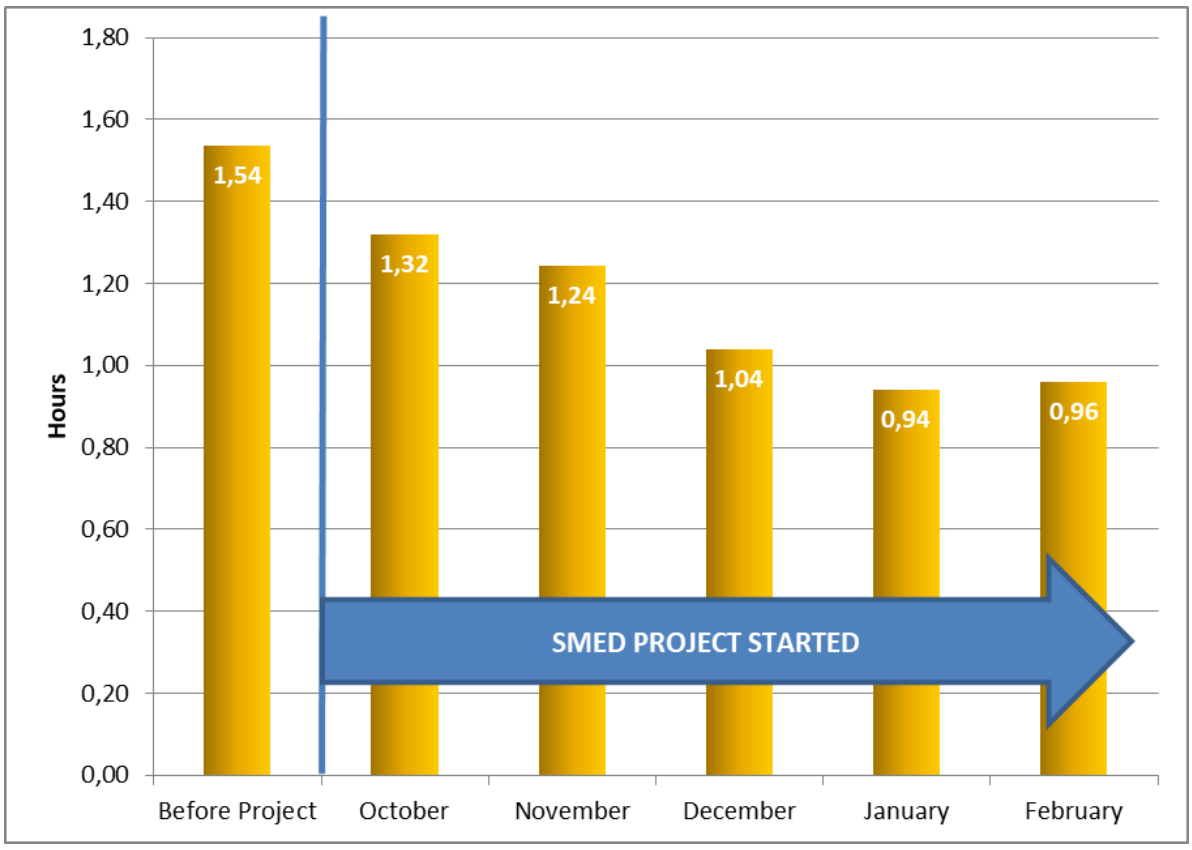


Figure 4.6-Evolution of Type A Changeover average time

4.3.2. Type B Changeover

Type B CO was assessed following a preparatory phase similar to that of type A CO, excepting for the standardization part, since these kinds of CO presented a reasonable acceptable variance (figure 4.7). Going into the details, it was noticed that the batch change time reduction was more complex and nuanced than it was thought at the beginning. Concretely, the operations could only be carried out in a certain order, since this changeover was more technically-constrained than type A CO.

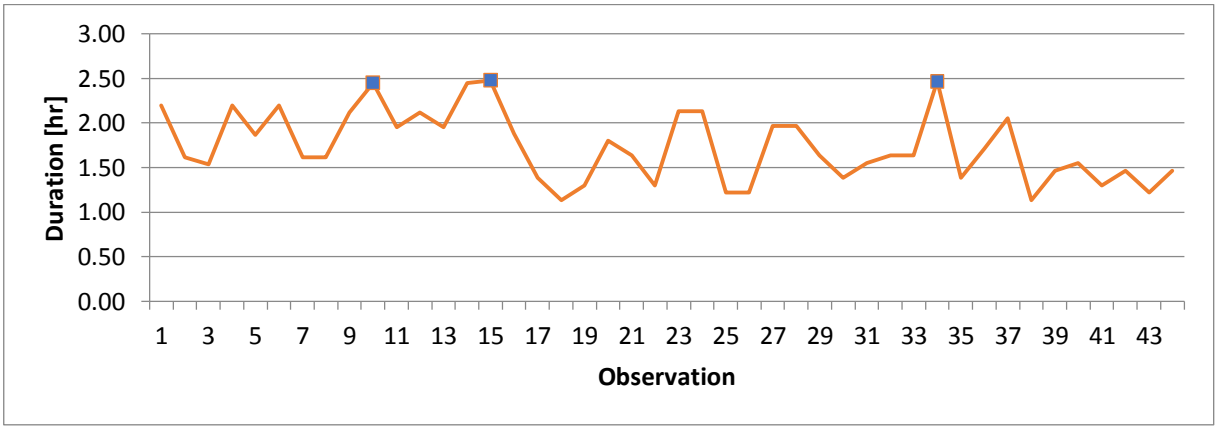


Figure 4.7- Type B CO control chart. The blue dots represent the instances in which TOC water samples were not satisfied the first time and thus longer washing cycles were needed

Conveniently, the operations to be performed in the secondary-tertiary packaging section were almost the same as in the type A CO (actually, the procedure was even simpler since there was no need to change the materials used for packaging-cases, syringes, labels, etc.- and, thus, a significant amount of activities did not have to performed). It is because of this reason that these operations were leaved out of scope in the analysis hereafter.

The washing cycle on the storage tank had a fixed duration of 1 hour, followed by 30 minutes needed to pour the solution from the mixing tank into the storage tank. The washing can start only when the storage tank is empty from solution (that is, when all the remaining solution from the previous batch is inside the filler's tank).

This means the washing cycle on the storage tank can start while the line is still producing. The filler's tank had a capacity of 100 l., which means the overlapped time depended on the format that was being produced. Table 4.3 shows the different filled volumes, the production speed and the theoretical time it would take to consume all the solution inside the filler's tank. Logically, the values are weighted by the proportion of units produced by the line in order to provide a representative proxy for the time consumed. The mean weighted value of 17.65 min was used in order to make the necessary calculations.

Format	Line speed [units/minute]	Time needed to manufacture 100 l of solution [min]	% of total produced volumes	Weighted contribution[min]
60 ML	70	23.80	3%	0.71
70 ML	70	20.40	1%	0.20
75 ML	66	20.20	68%	13.73
100 ML	60	16.66	2%	0.33
150 ML	54	12.34	3%	0.37
200 ML	48	10.41	22%	2.29
				17.65

Table 4.3- Theoretical time needed to manufacture 100 l of solution for each format. The green cell shows the weighted average value.

Summing up, 1.5 hours are necessary to wash the storage tank and to pour the solution inside it. Not all of this time falls inside the changeover time, since the washing cycle can start, on average, 17.65 minutes before.

While gathering data, it was noticed that the operations needed to perform the type B CO (both internal and external) required less time than the duration of the washing cycle, even when performed by only one operator (that is, without parallelization of activities). Nevertheless, the methodology was implemented in order to show how much time could be saved by implementing alternative washing cycles of lower duration. Additionally, although improving efficiency in this type of CO without reducing the time of the washing cycle would not have an impact in terms of time available to produce, it would certainly reduce the amount

of man hours needed to perform the change and, thus, free up resources that could be used for other tasks.

Appendix 7 shows the activities performed during a type B CO, together with their respective durations. During this type of CO, only one line-operator remained in the primary packaging section, carrying out the activities presented in the table. The other two operators were assigned to the secondary-tertiary packaging section, performing activities like those of type A CO.

Steps 1 and 2 were applied following the procedure described in the methodology section, giving limited results. Among the activities that could be externalized, the team identified the following:

- Bring a cauldron filled with osmotic water next to the line
- Prepare the necessary tools to be used during the type B internal operations

As can be seen, no appreciable time could be gained by externalizing these activities, confronting again the general recommendations of Shingo (Shingo, 1983) and showing that, at least in this particular industry, operations needed to perform COs are already acceptably divided into internal and external ones. Contrastingly, step 3, where internal activities should be transformed into external ones, brought some innovative ideas:

A. Buying an extra filler's tank. In that way, the set of operations needed to wash it and reassemble it could be externalized.
B. Buying another set of hoses and syringes. Following the same reasoning, the used syringes could be replaced with clean ones during the CO and be washed in other moment. Although it was leaved out of scope, this proposal would have a significative positive impact in type D COs and the type B COs where TOC water

samples must be satisfied. After all, it is in these situations where the washing cycles for syringes turn into a long operation with unacceptable variance.

C. Convert the storage tank into another mixing tank. In that way, with a moderate investment, all the operations related to the storage tank (which did not add any value to the final product since it was just a storage operation) could be deleted. The drawback is that the additional mixing tank would have a capacity of 2000 l (Instead of 4000 l). This suggestion will be referred to as "project B" from hereafter.

D. Replace the storage tank with a new mixing tank. Since the storage tank does not add any value (it basically works as a buffer, allowing the personnel to start producing a new solution while the line is still working), it would have more sense to have two mixer tanks. In that case, there would be neither washing cycle nor pouring to be performed during the type B CO. With a higher investment (since a new tank would have to be bought) this solution would provide results similar to the previous one, except that having two tanks of the same dimensions would require less solution preparations and the time slot available to wash a tank and prepare a solution would be enough to withstand extra washing cycles in the case water TOC measurements were not satisfied the first time. This suggestion will be referred to as "Project A" from hereafter.

Given the two major improvement proposals (C and D) it was decided to analyse the financial feasibility of both them using the payback period and NPV. Although academics recommend more complex methods such as NPV or IRR as the best way to analyse the economic impact of different alternatives, companies usually prefer the use of simpler metrics such as the payback period or the benefit/cost ratio, since these latter ones rely upon less assumptions. The following values were used in order to make the proper calculations:

- There was a mean value of 15 type B Cos per month and, due to the fact that the company is closed during holidays, 11 months per year were scheduled to produce.
- The theoretical value of 41.55€ per minute was used in order to calculate the monetary value of savings.
- A "Performance*Quality" indicator of 0.7 was used to adjust the theoretical savings in order to give more realistic results.
- With any of these proposals, an estimated value of 60 minutes of time reduction per CO was used, since with anyone of them, the washing cycle would become an external operation. This would leave an approximate value of 0.877 hours to perform the remaining internal operations needed for the CO.
- The main difference concerning the projects' output is that, while working with two 4000lt tanks, it is virtually impossible to be delayed due to TOC issues. On the other hand, using one 2000 l mixing tank would mean having 6 hours to wash the other mixing tank and to prepare the solution. Working under these conditions means that if TOC thresholds are not satisfied the first time, the type B CO would inevitably extend its duration.

With these input data, table 4.4 shows the payback period analysis for both proposals, where project B is preferred since it pays the initial investment in less than one year and, therefore, it is considered safer. This case happens when the proportion of type B COs that do not satisfy the TOC water measurements over the total type B Cos performed is set at 0.1 or 10%. In order to show a more general landscape, figure 4.8 shows a simulation analysis were the proportion mentioned above changes. As can be seen, the break point is found at 0.39, which is almost impossible to happen (the company's historical mean value is 0.0712). This gives enough confidence to affirm that, from a payback period perspective, project B is preferred.

	Project A	Project B
Cost of the project(k€)	320	215
Expected annual returns(k€)	287.947	267.446
Payback period (years)	1.11	0.80

Table 4.4- Payback period analysis for Project A and Project B

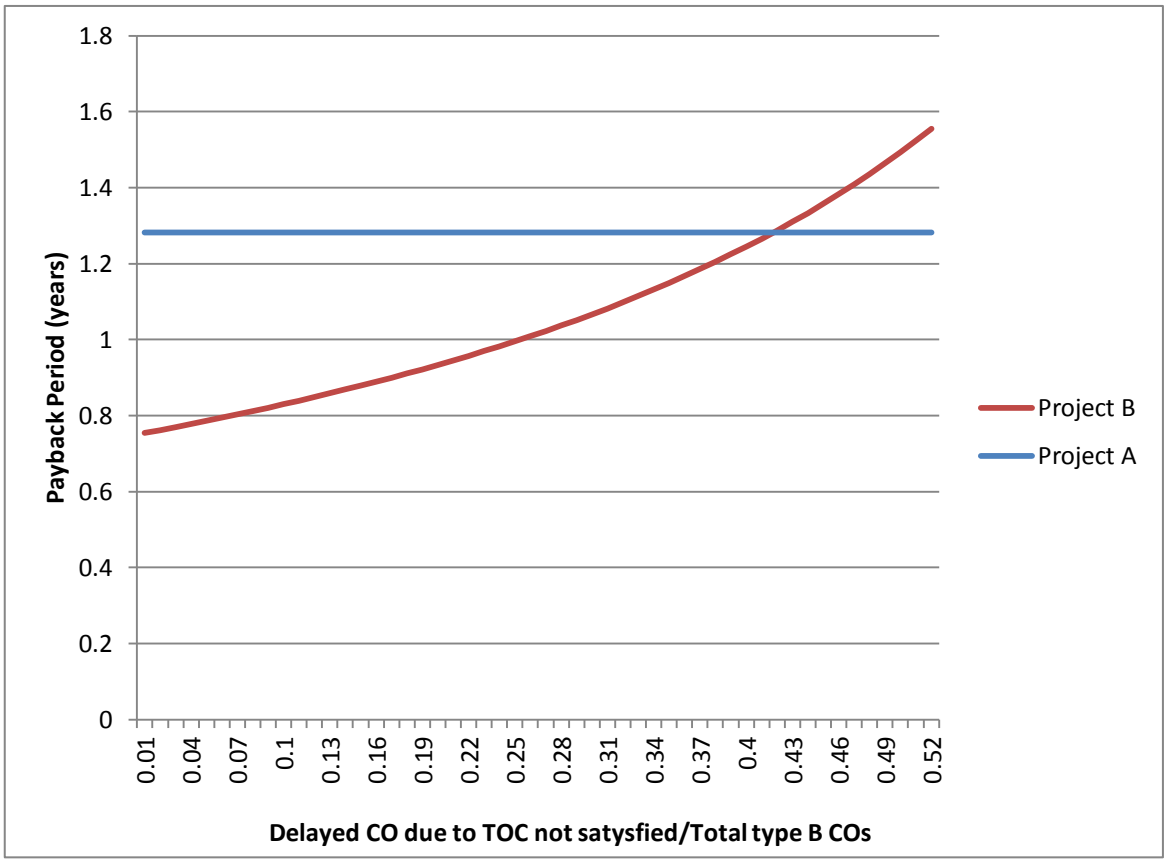


Figure 4.8-Project A and Project B payback period comparison when varying the proportion of TOC water measurements not satisfied the first time

The next financial indicator requires also an analysis horizon to evaluate the proposals and a corresponding interest rate to reflect the time value of money. The company's project manager suggested a 5-year time frame in which the project should be analysed, since there are no plans for changing the current process for the next couple of years but also a longer horizon would imply greater uncertainty. Concerning the discount rate, the company did not provide the author with an internal figure used for that purpose and, therefore, he decided to use the return on investment as a proxy[25].

With the input data stated above, table 4.5 can be constructed. As can be seen, even considering the time value of money project B is preferred. Nevertheless, possible alternative scenarios were also considered in the analysis and the conclusions extracted are present in Appendix 8, where two tables show the NPV when varying both the discount rate and the proportion of type B CO that do not satisfy TOC water measurements the first time. Table 4.6 compares the two projects in terms of NPV and presents the one that maximizes it for each scenario.

	Project A		Project B	
	Outflows	Inflows	Outflows	Inflows
Year 0	-320000		-215000	
Year 1		287947.97		267446.1
Year 2		287947.97		267446.1
Year 3		287947.97		267446.1
Year 4		287947.97		267446.1
Year 5		287947.97		267446.1
NPV	885,428.40 €		900,739.09 €	

Table 4.5- NPV analysis for project A and Project B

[25] The company was a publicly traded company in the London stock exchange while this thesis was being written. By that time, the company's ROI was 4.93%.

		TOC not satisfied							
		0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1
Discount rate	0.015	Project B	Project B	Project B	Project B	Project B	Project A	Project A	Project A
	0.02	Project B	Project B	Project B	Project B	Project B	Project A	Project A	Project A
	0.025	Project B	Project B	Project B	Project B	Project B	Project A	Project A	Project A
	0.03	Project B	Project B	Project B	Project B	Project B	Project A	Project A	Project A
	0.035	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0.04	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0.045	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0.05	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0.055	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0.06	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0,065	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0.07	Project B	Project B	Project B	Project B	Project B	Project B	Project A	Project A
	0.075	Project B	Project B	Project B	Project B	Project B	Project B	Project B	Project A
	0.08	Project B	Project B	Project B	Project B	Project B	Project B	Project B	Project A
	0.085	Project B	Project B	Project B	Project B	Project B	Project B	Project B	Project A
	0.09	Project B	Project B	Project B	Project B	Project B	Project B	Project B	Project A
	0.095	Project B	Project B	Project B	Project B	Project B	Project B	Project B	Project A

Table 4.6- Best project in terms of NPV when varying the discount rate and the proportion of TOC water measurements not satisfied the first time

As can be seen, when interest rate is taken into account and the project's output is evaluated over a time horizon, project A starts to be more attractive. Remembering that the historical proportion of TOC water measurements not satisfied the first time is 0.0712, the table suggests that no clear alternative can be selected with enough confidence. Project A would imply a more robust system that nullifies the probability of delays due to longer-than-planned washing cycles. Project B, on the other hand, requires a lower initial investment, pays it back sooner in all the reasonable expected scenarios and shows a greater NPV in scenarios with a low discount rate and low proportion of TOC measurements not satisfied. The final decision of course depends on the strategic tents of the direction, the market features and the core competences that the company wants to develop over the next years.

Also, during this time, step 3 was also being applied in the project for reducing type A CO duration, where the idea of converting the stamps change into an external operation had been already commented and studied. Logically, this proposal has also an impact in this

project, since every time a batch change was to be performed, the expiration date and manufacturing date, as well as the batch name had to be updated. With this proposal, it has even more sense to have two operators in the primary packaging section and one in the secondary-tertiary packaging section whenever performing a type B CO.

Step 4 is aimed to streamline the internal operations that cannot be converted into external ones. Here, some technical modifications were suggested in order to ease manual operations. Normal screws were replaced with handle screws whenever possible and remaining bolts and nuts were standardized in order to minimize the number of tools that were to be used.

While discussing step 4, one person commented that the washing system was changed several years ago but the duration of the washing cycle was not modified. In other words, a better system was installed but the time to wash the tanks remained the same. Water samples were taken during a washing cycle to check if the time could be reduced. The data suggested that 40 minutes were enough to correctly wash the tanks during a normal type B CO.

Before adopting a new process, the company must validate it in order to certify that it does not affect the final quality of the product itself. The bureaucratic procedure comprehended about two weeks but, since the company was already validating several processes concerning a new production line that was being installed, it was estimated to be about a month. Therefore, the author was not able to see the new washing cycle time applied.

Because of this, the author has taken the liberty of estimating savings based upon the successful application of a shorter washing cycle (table 4.7). Estimations include the savings due to time available to produce as well as the cost reduction in osmosed water and energy

consumption. Even though these numbers may seem insignificant, if one considers that there are (on average) 15 type B CO per month and the fact that each extra minute available to produce means up to €41.55 in revenue, the implementation of a shorter washing cycle can save as much as €138,827 annually with virtually no investment (the only associated costs would be those ones associated with the validation of the new process).

	60 min. washing cycle	40 min. washing cycle	Savings
Cost of osmosed water[€]	23.645	15.76333333	7.881666667
Cost of energy [€]	7.432	4.954666667	2.477333333
Time spent [min]	60	40	20

Table 4.7-Savings achievable per CO with a shorter washing cycle

4.3.3. Type C Changeover

This type of CO was particularly interesting since, although seldom performed, would give the company a tremendous impact in terms of flexibility and demand-response. Also, after a type C CO, the workers usually had to keep making small adjustments and interventions for the next 2 or 3 shifts before the line returned to its normal performance.

As can be seen in figure 4.9, type C CO represented 7% of total planned stops. However, if all COs including format changes are taken into account, this number rises up to 32%.

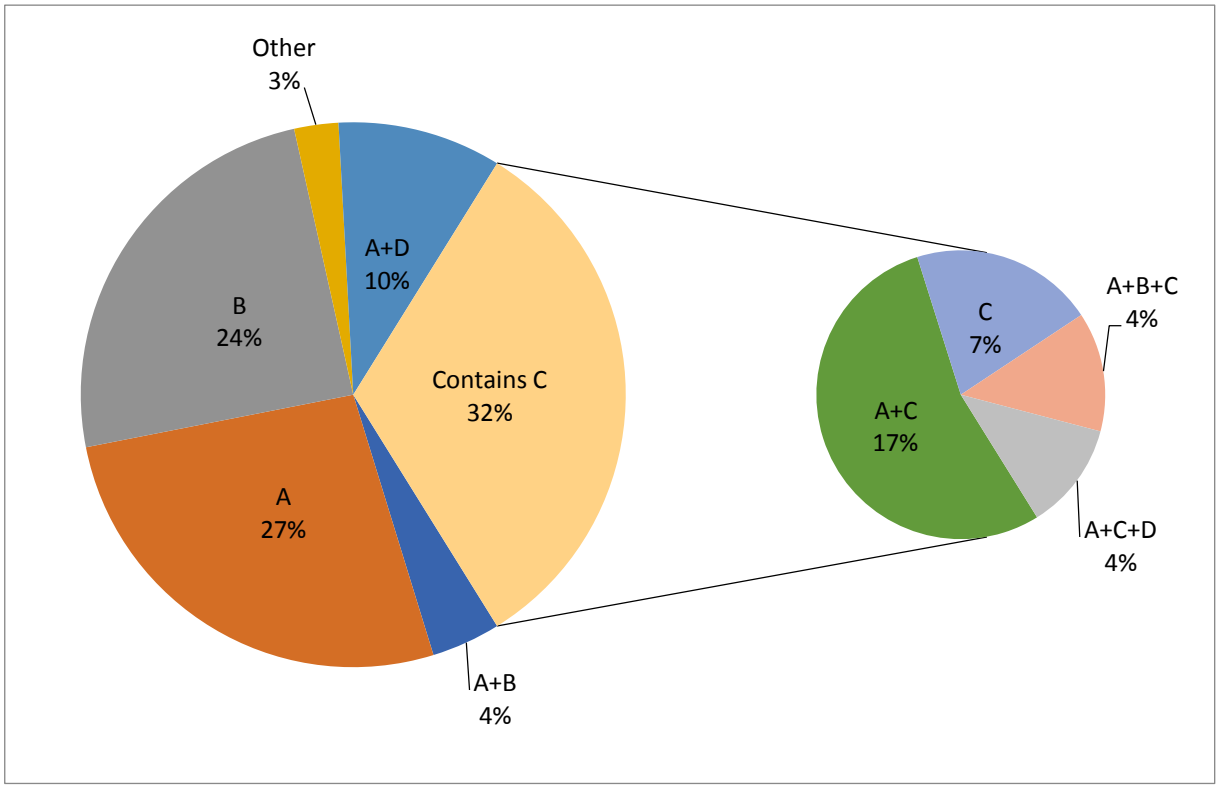


Figure 4.9-Pie Chart showing the planned stops breakdown.

The machines that form part of the line suffered several modifications over the years, but the format changes were never addressed as a problem. Therefore, there were incomplete procedures (and even unexisting procedures for some machines) and the majority of existing documents contained mistaken or out-of-date information. Some tools were not present in the

workshop, which forced the workers to bring their own ones. Also, some operations (such as the change of the blowing wheel in the blowing machine) were not ergonomic at all, which goes against any improvement methodology that as a first step always ensures safety (such as TPM or WCM pillars).

Another impediment was the fact that, according to Italian law, workers in the pharmaceutical sphere can be assigned different levels. Depending on these latter ones, the worker will be authorized to perform certain type of activities but not others. Since not all the workers were allowed to perform all the operations that were part of the type C CO, the parallelization of operations (Shingo, 1983) was particularly difficult because of both technical competences and bureaucratic rigidity.

Because of the lack of standard settings, changeovers were performed following an extensive and tedious sequence of adjustments without scales, measuring devices and indicators of position. Basically, the correct position was found following a "trial and error" approach. Consequently, the duration was highly dependent on the particular group of persons that were performing the CO. As Shingo states, adjustments must be replaced by settings as much as possible (Shingo, 1983).

Most of the time, only one operator would perform the CO in a sequential way, having the other two doing ancillary things like adjusting bolts, seeking documentation, cleaning, etc. This of course has a negative impact in terms of productivity, since having 3 workers performing the set up did not mean a direct reduction in type C CO duration of the same factor.

Despite all these drawbacks that should be solved before assessing any improvement initiative, the methodology was applied since the available time span to bring results was limited. During the preparatory phase, a baseline was created, in which 2 different kinds of

type C CO can be identified: a partial type C CO and a complete type C CO, with the former being the one in which only the height of the bottle was different but the diameter remained the same (thus the CO did not involve the whole spectrum of activities). The latter, on the other hand, involved a wider range of activities, since both diameter and height of bottles changed (Table 4.8).

		To					
		60	70	75	100	150	200
From	60			Partial	Partial	Total	Total
	70			Partial	Partial	Total	Total
	75	Partial	Partial			Total	Total
	100	Partial	Partial	Partial		Total	Total
	150	Total	Total	Total	Total		Partial
	200	Total	Total	Total	Total	Partial	

Table 4.8-Type of change that need to be performed when moving from one format (left column) to another (upper row)

The graph in figure 4.10 shows the mean value for the two type C COs (partial and total). As can be seen, nearly one work shift was used to prepare the line for production whenever a complete format change had to be performed. However, when videotaping the changeovers, it was noticed that the effective time in which the personnel was "adding value" to the changeover (changing tools, adjusting positions, etc.) was less than 4 hours, as can be seen in figure 4.11. That means that in theory, with the existing methods, machines and tools, a type C changeover could theoretically be performed in 3.2 hrs by one single operator (and a third of that value with 3 operators). The rest of the time was wasted by one or more of the following reasons:

- Waiting for maintenance personnel
- Looking for pieces

- Looking for tools
- Waiting for help (when performing some particular operations that had to be performed by two operators at the same time)
- Waiting for QC operators
- Missing tools
- etc.

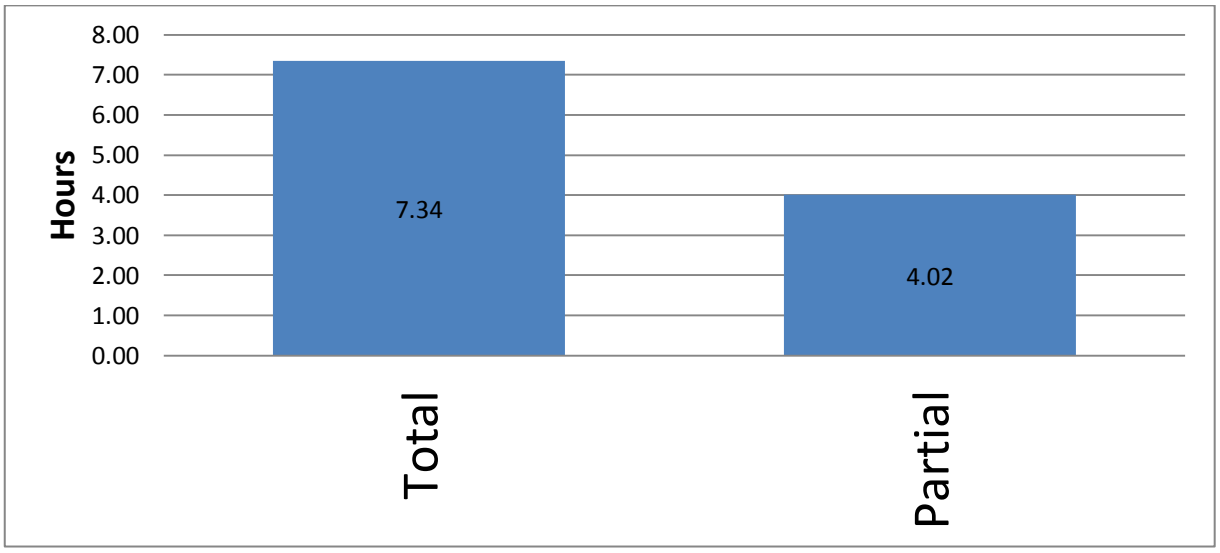


Figure 4.10- Mean time to perform a type C changeover (both partial and total ones)

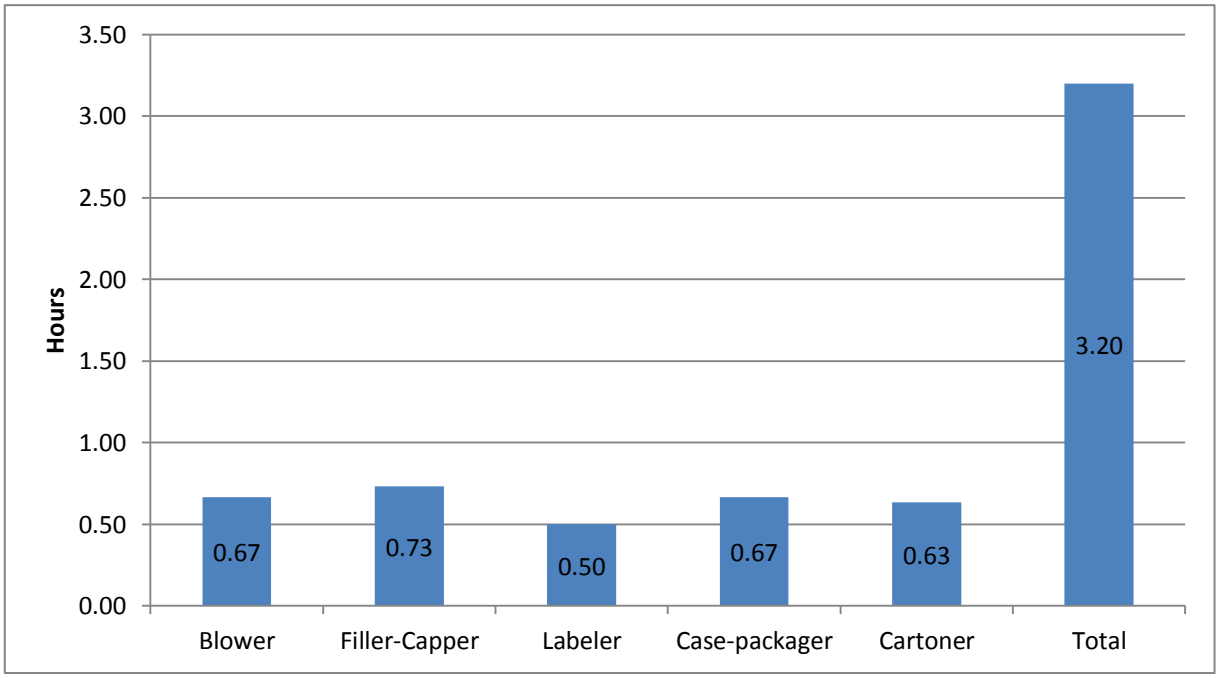


Figure 4.11-Time where operators were actually "adding value" during type C changeovers

In order to bring the most out of the methodology, it was crucial to start assessing the problem with a polyvalent team, familiar with the changeover and capable to perform it in a parallel way. Appendix 9 shows a competence matrix in which each operator has been assigned a changeover level for each machine composing the line. The team with the higher base level (team 1) was chosen for the project since parallelization of activities was easier.

After the preparatory phase, the implementation phase was applied as it was explained in the methodology section. The main conclusions taken from each step are presented in the following paragraphs.

Stage 1: Classify activities into External, Internal or to be eliminated.

The team identified diverse operations to be performed externally (such as preparing the tools and the pieces to be changed) .Appendix 10 shows an example of the checklists that were created in order to assure that the parts to be mounted were ready-to-use, eliminating the

possibility to have last-minute surprises such as a missing bolt or a worn out profile. Only with this step, the expected time reduction was about 19.2%.

Stage 2: Separate External work and Internal Work. Eliminate activities that are not necessary

This step was aimed to effectively apply the conclusions extracted from step 1. A time reduction of 17.4% was achieved by externalizing external operations and minimizing the probability of having last-minute corrections to be made.

Stage 3: Convert Internal work into External work.

While applying this step, it was noticed that it would be impossible to externalize activities without technical modifications in the machines. This troublesome situation constrained the team, since packaging machines are quite complex in terms of computerization and operations. Shingo (Shingo, 1983) provides a wide spectrum of examples concerning technical modifications made mostly on dies and washing-machines assembly lines. However, these kinds of improvements were possible partly because of the relative simplicity of control systems and automations. In addition, the company did not possess the technical capabilities needed to analyse and design complex solutions aimed at externalizing operations. It is because of these reasons that the team decided to analyse the oldest and simplest machine of the line: the blowing machine.

The blowing machine counted with two different blowing wheels, one for the smaller bottle diameter (47 mm, corresponding to 60, 70, 75 and 100 ml) and one for the bigger one (55 mm, for both 150 and 200 ml). The previous method used to take more than 1 hour for total format changes (and half of that time for partial ones), which consisted in putting apart the current wheel, mounting the new one, adjusting one by one the 24 blowing devices using a

bottle (that is, without a predefined position) and relocating the bottle support as well as the bottles intake (red and blue parts in fig 4.12, respectively). In addition, the blowing wheel corresponding to the format not being produced at the moment was kept in the locker of appendix 4, which made the operation hazardous since the space to manoeuvre was reduced and the part weighted more than 100kg.

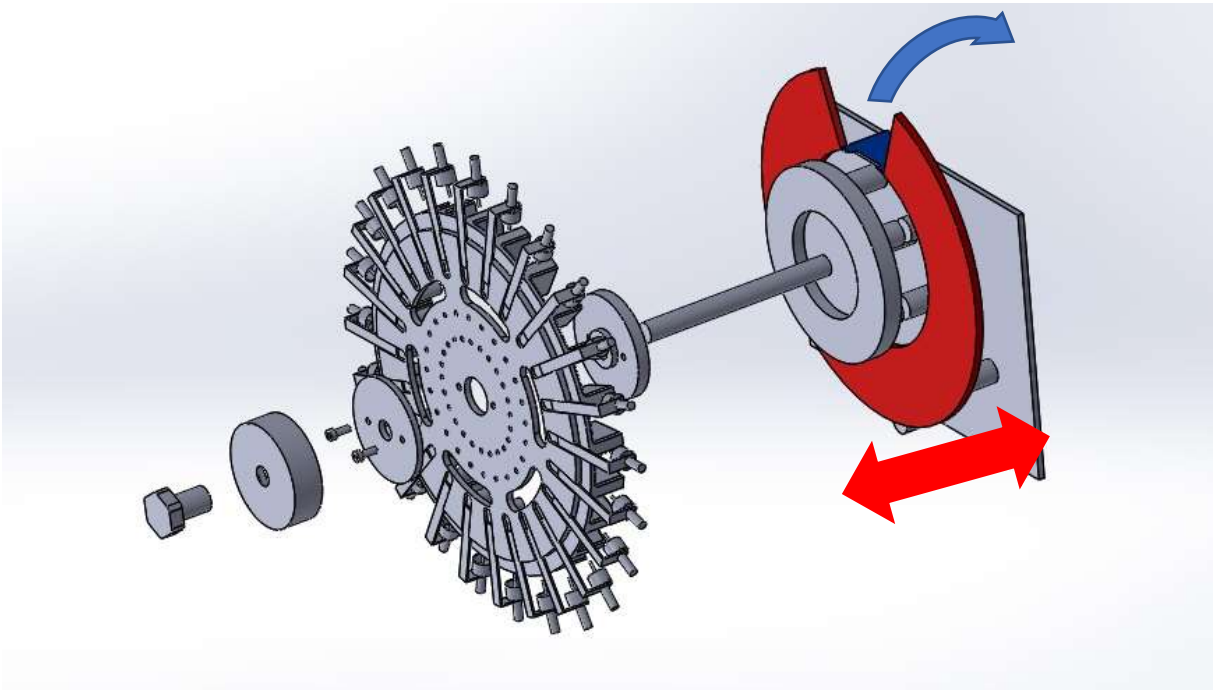


Figure 4.12- Blowing machine breakdown showing its main components.

In order to tackle the problems stated above, the following ideas were implemented:

First of all, the normal screws used to fix the blowing devices' position were replaced with spring plungers (figure 4.13). With this modification, the time to perform the height adjustment dropped down from 30 minutes to less than 10, with a total cost of 571.2€ and annual savings estimated at 20.7k€.

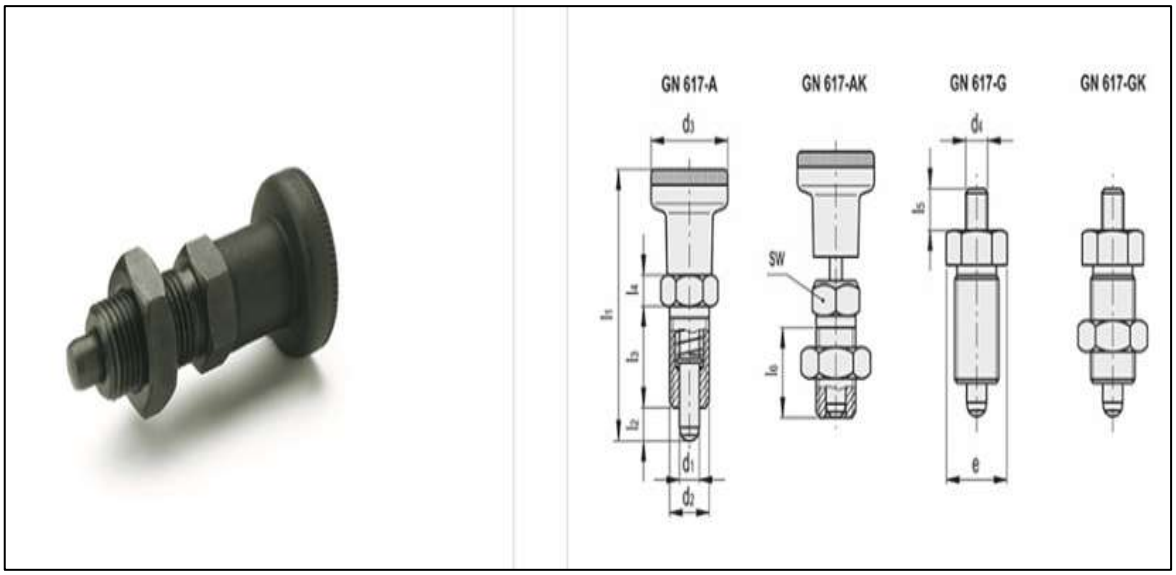


Figure 4.13- Spring plungers used to eliminate screws and reduce time needed to set the blowing devices' height.

When performing the brainstorming, the question "why do we have 2 different blowing wheels?" came up, which someone answered stating that the machine has to work with two different bottle diameters. But, therefore, someone else asked: "then why do we need to change the bottle support position?".

Analysing the operations, it was noticed that 2 different and complex operations were performed basically because the variable "bottle diameter" can take two different values. One of these two activities should be eliminated if efficiency is willing to be achieved. Since changing the position of the bottle's support was complex, difficult and needed special training, it was decided to delete this operation completely.

Following the guidelines that Shingo stated for dies standardization (Shingo, 1983), the width of the biggest blowing wheel (the one corresponding to 150 and 200 ml) was increased by 8 mm (the difference between the two bottle diameters). With this modification, it was no longer needed to change the bottles support position nor the bottles intake part, thus eliminating activities that accounted for more than 20 minutes (figure 4.14).

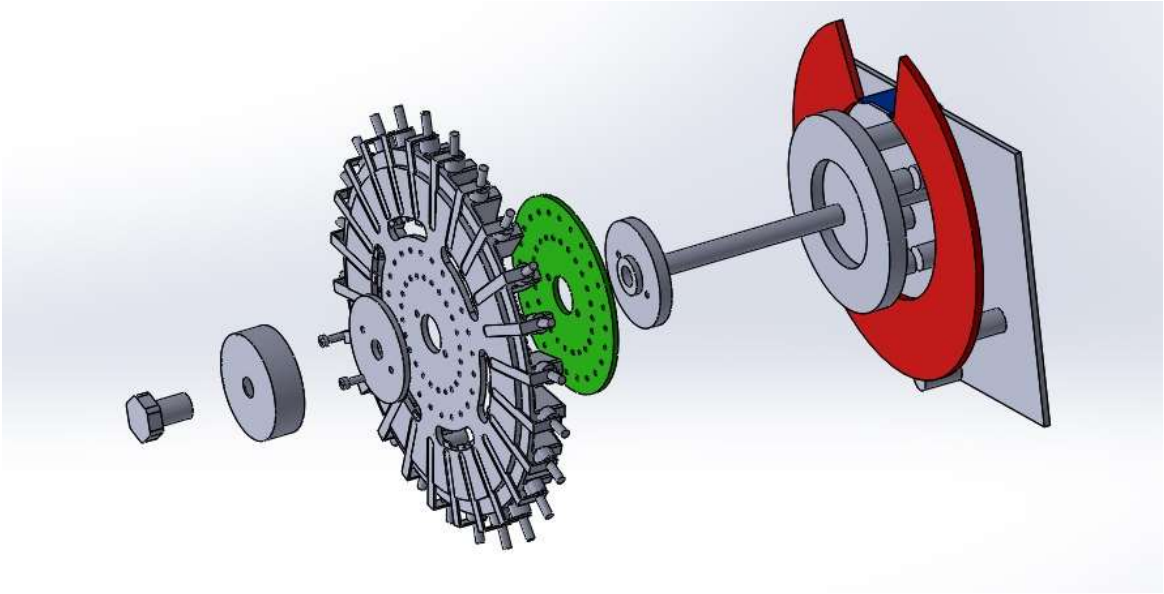


Figure 4.14-Modification made to the blowing wheel in order to eliminate operations. The green part mounted on the blowing wheel increased its width by 8mm.

Lastly, the trolley of Figure 4.15 was designed, which allowed to manoeuvre the blowing wheel without manually supporting its weight, and also to keep the not used blowing wheel stored next to the machine. This step did not have a significant impact in terms of minutes saved, but it certainly increased the operations safety and simplicity, since the workers did not have to move manually such a heavy item and the operation could be performed by one person alone.

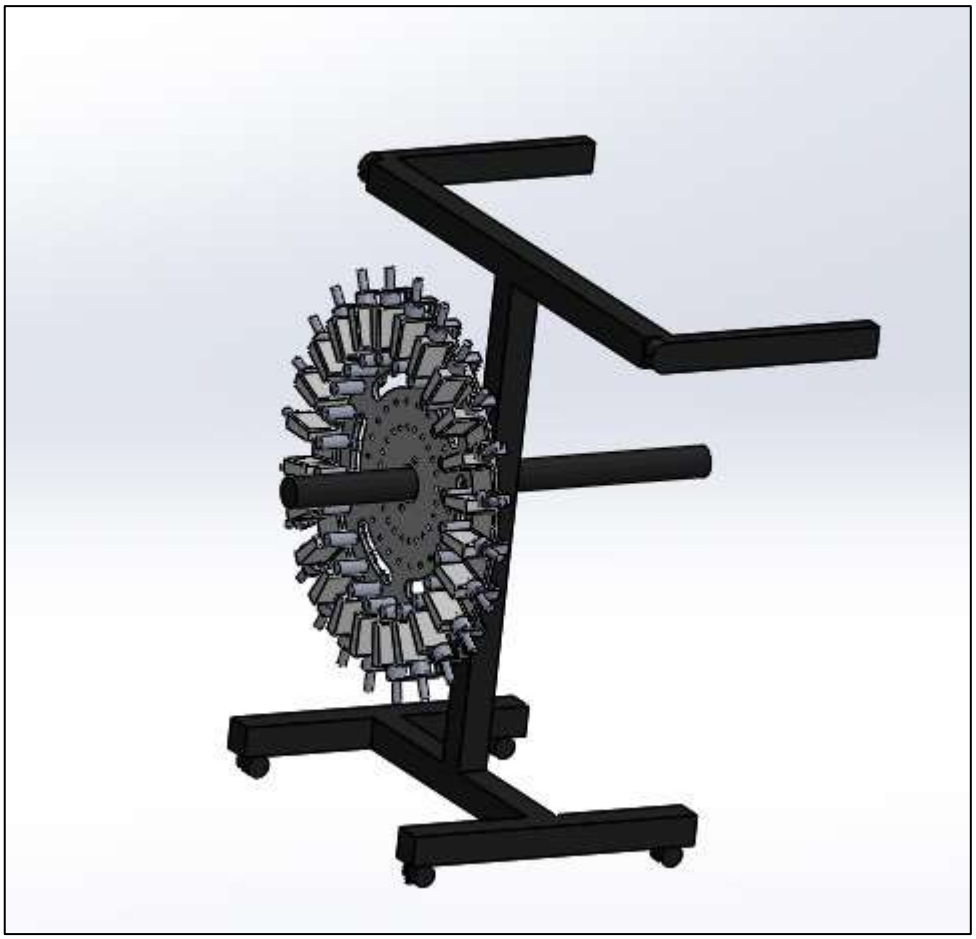


Figure 4.15-Trolley used for mounting the blowing wheel

Additionally, with the trolley it is possible to hold the blowing wheel by its centre axis, avoiding the buckling that the blowing devices' supports suffered on the past due to the fact that the blowing wheel was laid vertically against a wall, thus supporting all its weight with the blowing devices' support.

With the modifications stated above, the operation can now be performed in 5 minutes for a total change and 10 minutes for a partial change. It can be performed by any operator (since no longer adjustments should be made) and it became a much safer operation. The total investment was 2,326€, which allowed to save more than 52.3k€ annually.

Stage 4: Streamline and reduce internal work

During this step, several bolts were changed by hand lever screws in order to streamline internal operations. Also, several modifications were made with the purpose of eliminating adjustments as much as possible, which was achieved by predefining the correct position by means of colour marks and similar systems. These modifications did not caused substantial savings in terms of time, but the investment was insignificant and the operations were significantly simplified, allowing for new operators to perform the activities even without a thorough training.

Figure 4.16 and 4.17 show the evolution of the duration of type C changeovers over time. As can be seen, when the project started the mean duration was 7.34 hrs for total changes and 4.02hs for partial ones. By the time the project was formally closed, these values dropped down to 5.57hs and 2.94hs respectively.

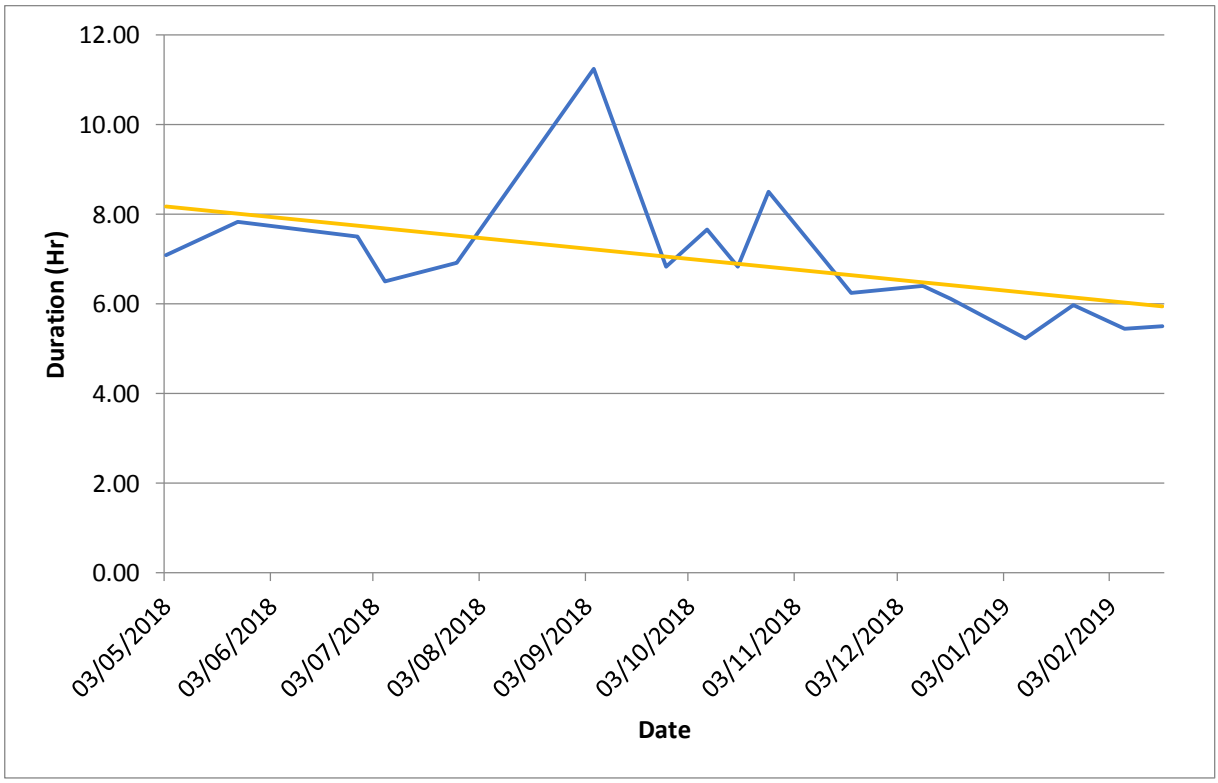


Figure 4.16-Evolution of Total Type C CO duration over time.

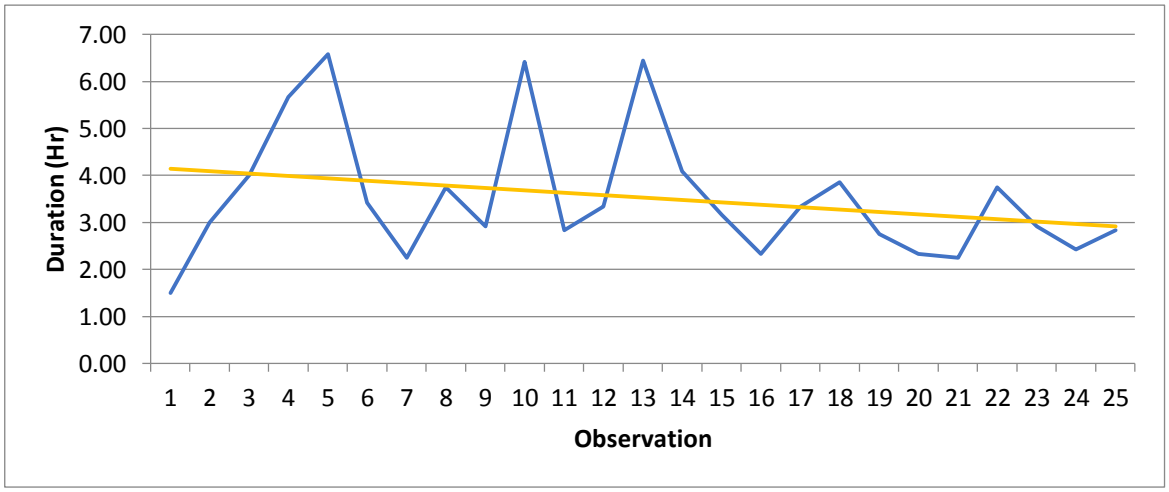


Figure 4.17- Evolution of Partial type C CO duration over time

To sum up, the methodology was applied focusing mostly on technical modifications. Satisfactory results were achieved by simplifying operations. Due to the constrained time to run the project, the modifications were mainly made on the blowing machine, but the same approach can be extended to the rest of the production line. The author believes that the operations composing the type C CO should became as simple as possible (or even eliminated) in order to achieve the full potential of parallelization of activities. In that way, at least theoretically, the aforementioned changeover can achieve durations of 1 hour or lower.

4.4. Reducing Unplanned Stops

As it was commented in chapter 3, the maintenance activities were basically corrective maintenance interventions. This is the logical case expected from an organizational structure in which the maintenance operators are directly subordinated to the production managers.

Since unplanned stops represented 45% of total availability losses, it was decided to analyse on a deeper level which were the main contributors. Information was taken from the logbooks in order to create a database. From this latter one, it was possible to estimate MTBF and MTTR per machine for the FY2019 (Figure 4.18 and Figure 4.19). As can be seen, the case packager was the machine with the highest mean time to repair (around 30 minutes) as well as the one with the lowest time between failures (9.63 hours).

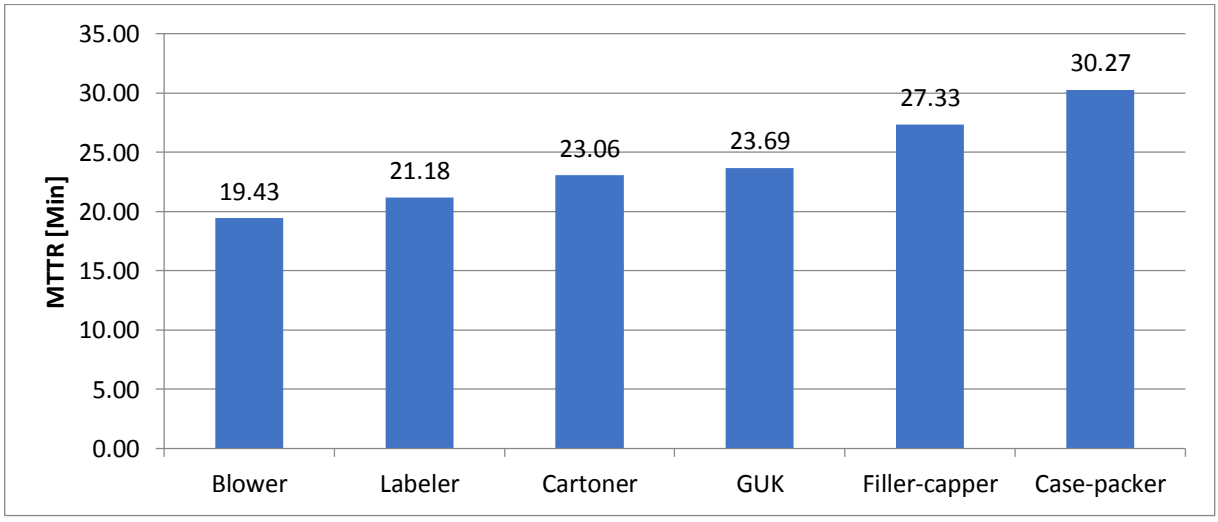


Figure 4.18-MTTR concerning the different machines of the oral solution production line

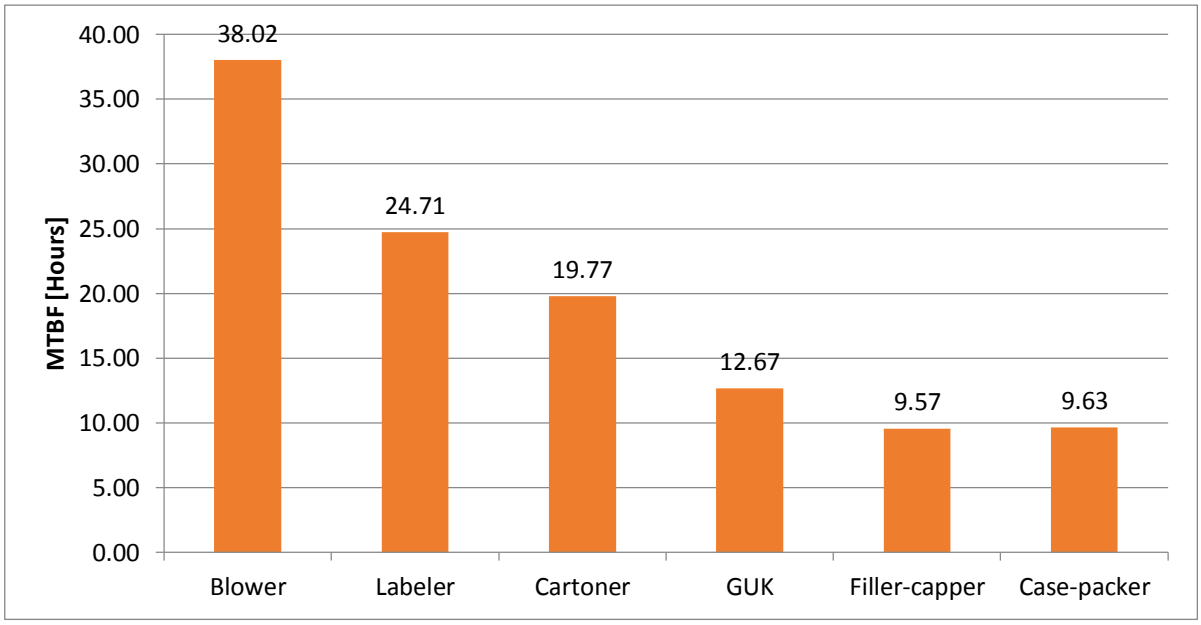


Figure 4.19-MTBF concerning the different machines of the oral solutions production line

The maintenance interventions were further broken down by type of problem, with the results and description presented in figure 4.20and table 4.9, respectively. As can be seen, the main single contributor was the case-packager machine and, in particular, the problem presented during the final operation (closing the case). It was also noticed that this problem was strongly interrelated with the type C changeover. A meeting was conducted in order to eliminate (or at least reduce) the downtime due to this cause, with the Ishikawa diagram of figure 4.19 as a result.

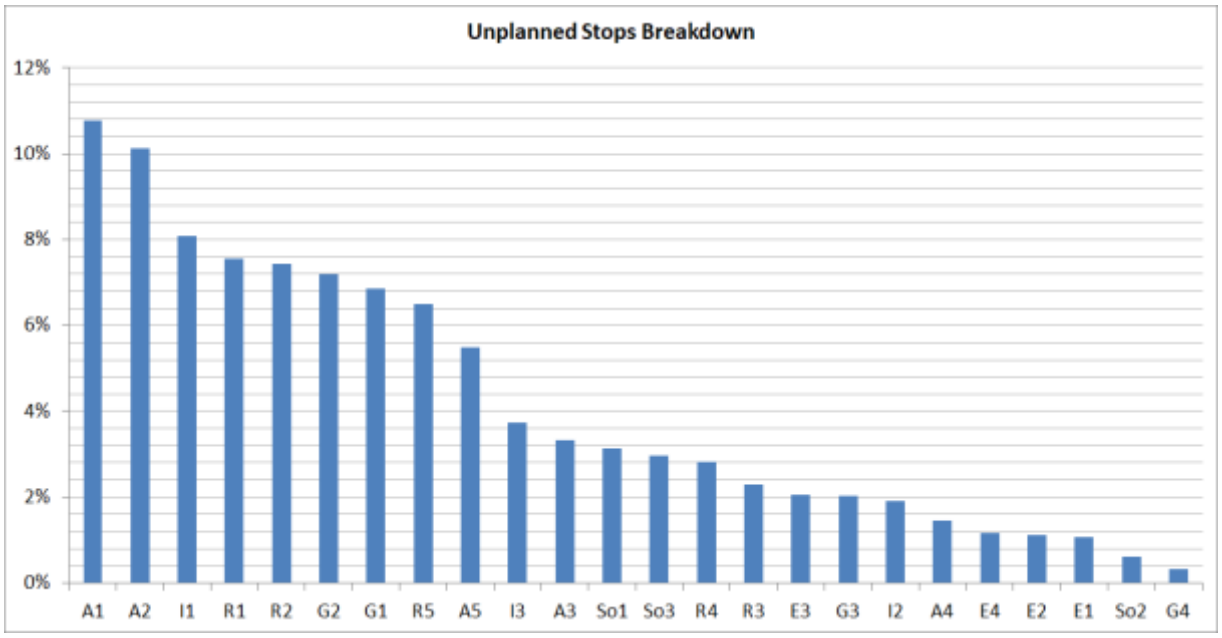


Figure 4.20 -Breakdown of downtime due to machine failure

A1	**Case closure related problems**
A2	**Problems related to the insertion of leaflet, bottle and measuring devices inside the case**
A3	**Problems related to the case intake**
A4	**Problems related to the bottle conveyor**
A5	**Other problems regarding the case packager machine**
E1	**Cocked labels**
E2	**Creased labels**
E3	**Problems with the stamp**
E4	**Other problems regarding the labeling machine**
G1	**Blockage**
G2	**Problems with leaflet withdrawal**
G3	**Problems with the barcode reader**
G4	**Other problems regarding the leaflet folder**
I1	**Problems concerning the carton holder**
I2	**Problem concerning the insertion of cases inside the carton**
I3	**Other problems regarding the cartoning machine**
So1	**Tilted blowing devices**
So2	**Problems concerning the rotational buffer (bottles fall of, bottles do not get into the blowing wheel, etc.**

So3	**Other problems regarding the blowing machine**
R1	**The syringes leak**
R2	**Problems with the automatic pre capping operation**
R3	**problems with the automatic cap tightening operation**
R4	**Problems with the control cameras**
R5	**Other problems regarding the filling and capping machine**

Table4.9- Description of the types of problems that caused a mechanical intervention.

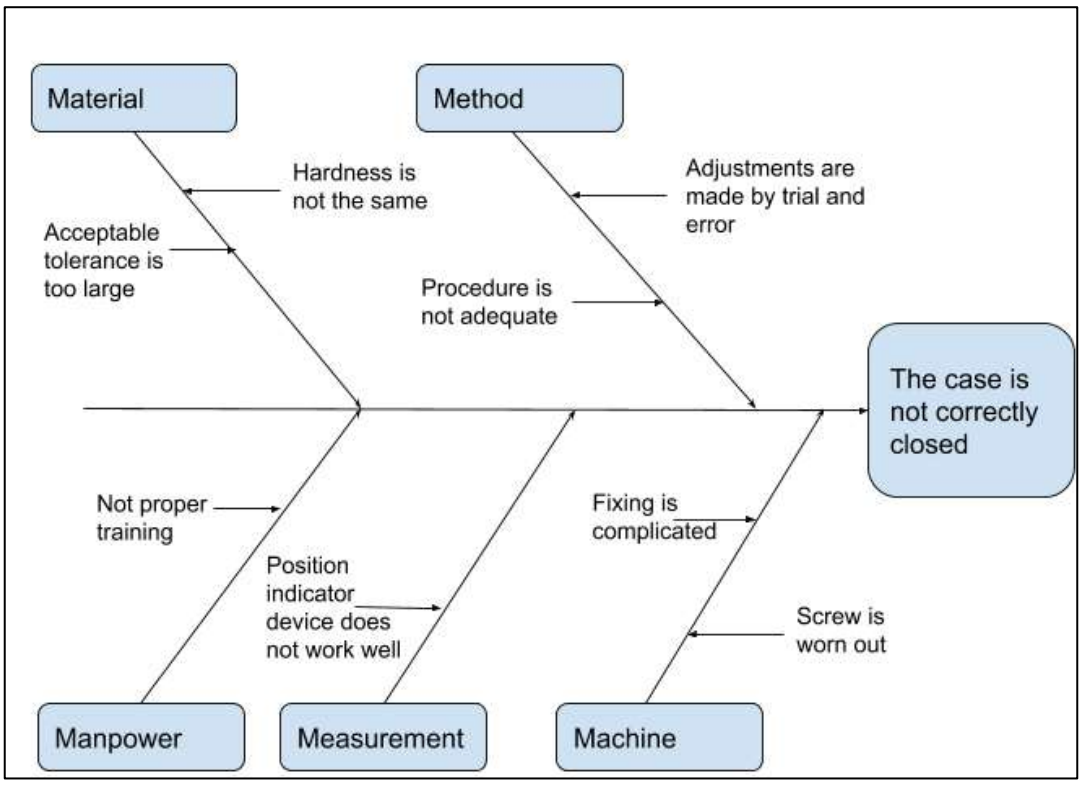


Figure 4.21-Ishikawa diagram analysing the causes of the defect A1

The reduced space did not allow the existence of normal blocking devices and therefore the pieces were not 100% fixed while operating. This caused the necessity to readjust the devices' imposed position from time to time. Eventually, the position indicators were worn out, which caused the line operators to not rely anymore on the SOPs to perform the type C CO. Figure 4.20 shows the part of the machine that performs the closing operation. As can be seen, even the smallest change in the inclination would be amplified due

to the length of the piece. The fixer screw should be properly tighten, otherwise quality problems are likely to occur.

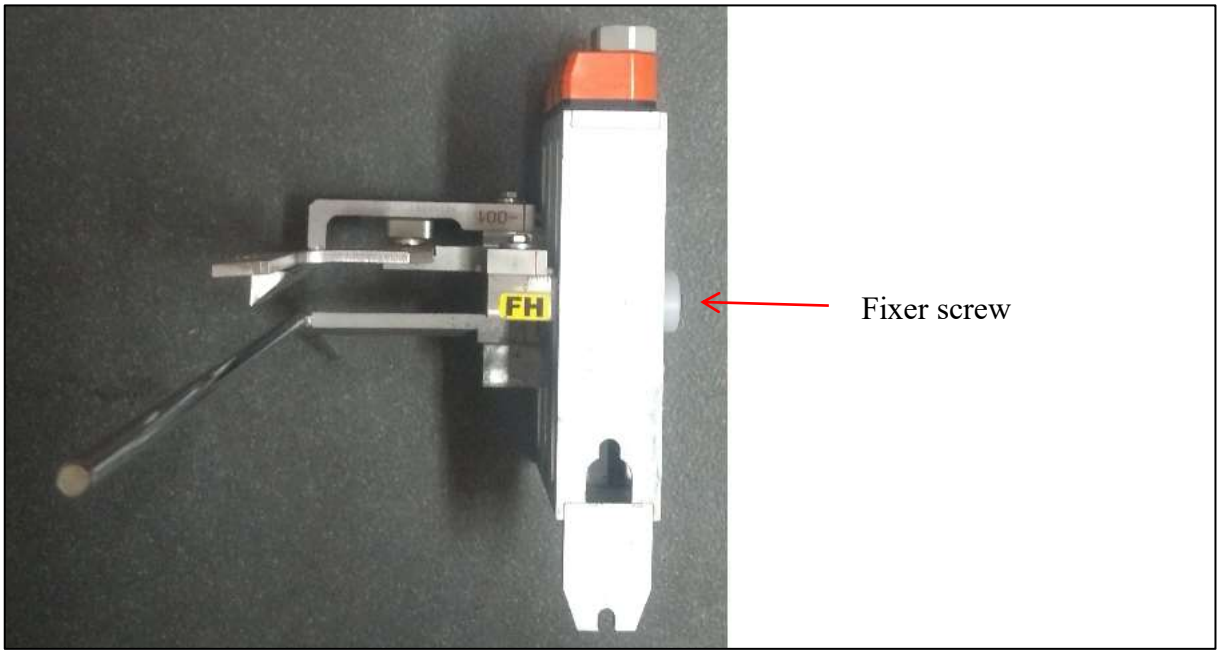


Figure 4.22- Part of the case packer machine in charge of closing the case.

As a solution, the team suggested to install flat clamping levers, suitable for this particular application. With the clamping levers, the operators could tighten the pieces once on site and with one easy movement. It was expected that, once the correct position is set, the piece would remain in that same position.

Also, with an easy to adjust mechanism, the operators would be more likely to loosen up and tighten the screws before and after making the adjustments, Therefore this modification also would have an impact in the type C changeover, since with the position sensors working correctly, it would be possible to set the correct position of the device immediately and with one touch.

Another more innovative proposal suggested a technical modification that would buttress the horizontal arm in two points instead of one. In fact, with the extra bolt (shown in

green in Figure 4.23), the vertical allowance would be reduced to a minimum while eliminating the necessity to loosen and tighten up the fixing bolt whenever the position had to be changed.

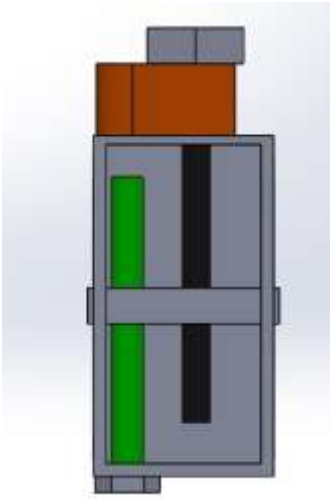


Figure 4.23-technical modification suggested to reduce the defects on the case closure operation.

Among the two alternatives, the second one was chosen because of the mechanism's simplicity. The cost was almost insignificant and, thus, no financial analysis was made in order to evaluate the proposal. The modification was applied immediately and, as it had been predicted before, both MTTR and MTBF significatively improved, as figure 4.24 shows.

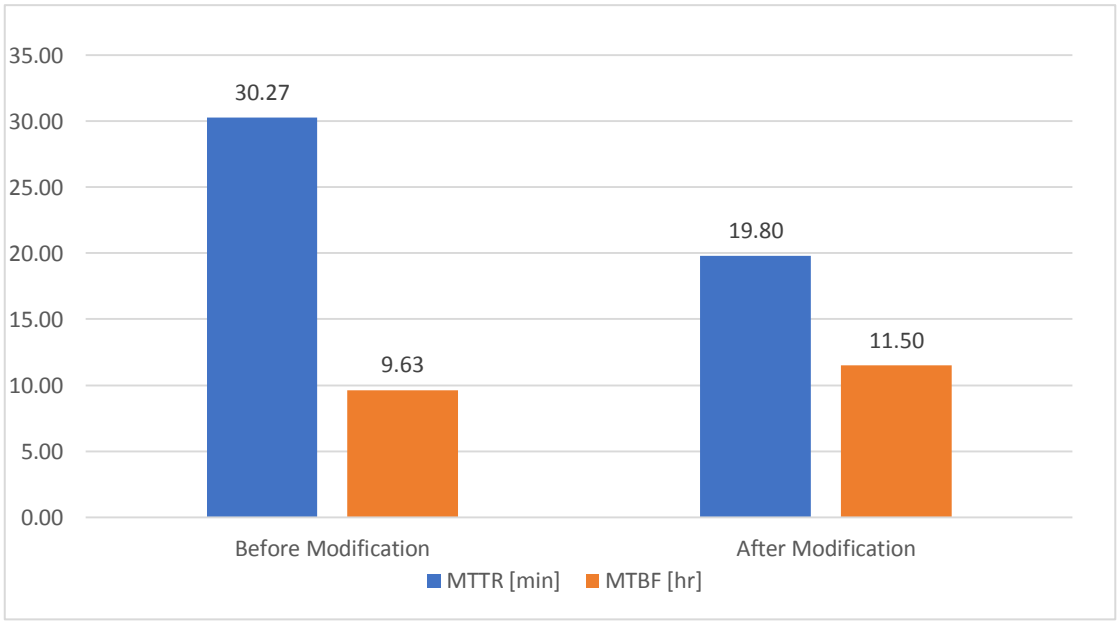


Figure 4.24-MTBF and MTTR for the case packer before and after the technical modification

Chapter 5- Results and Conclusions

During the strategic phase, a 5% increase in OEE for the oral solutions production line was set as the target. A thorough analysis identified the greatest inefficiencies happening in the availability domain. Concretely, both changeovers and breakdowns were substantially reducing the time available to produce and, therefore, 4 interdependent projects were carried out with the purpose of achieving the target aforementioned.

By applying the SMED methodology and cause root analysis, it was possible to increase the availability factor by 7% (that is, from a monthly-mean value of 70.67% when the analysis started to 75.21% when all the four interdependent projects were implemented). Results can be appreciated in Figure 5.1.

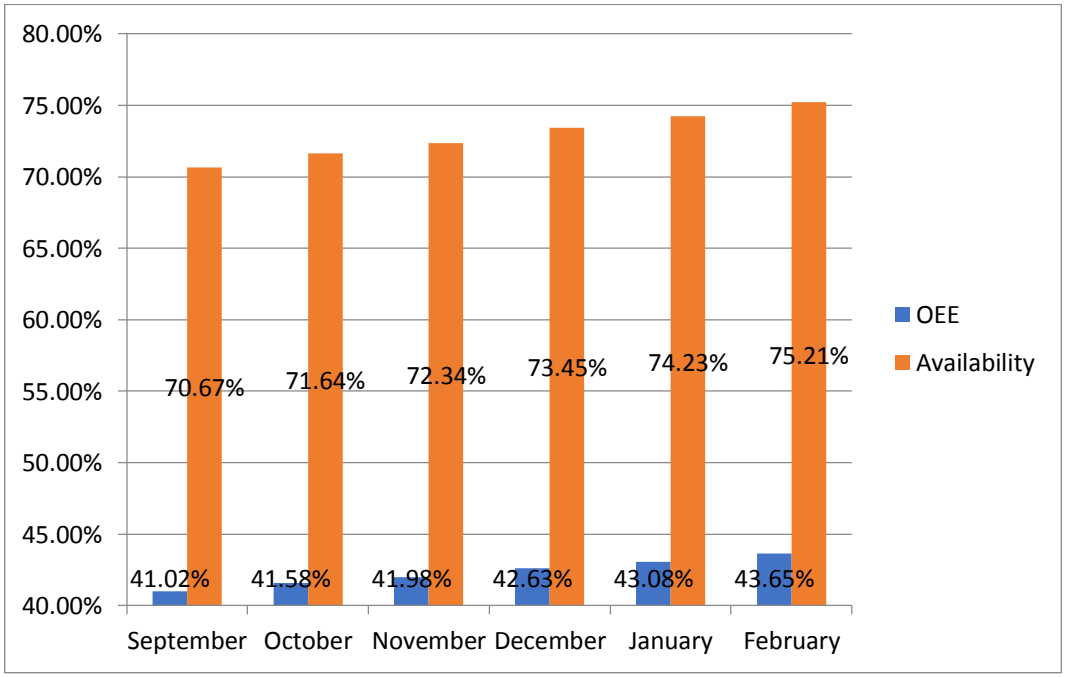


Figure 5.1- Evolution of OEE and Availability

After the successful implementation of kaizen activities, OEE raised from 41% to 43.65%, which was considered a success by the cross-functional teams. In addition, the

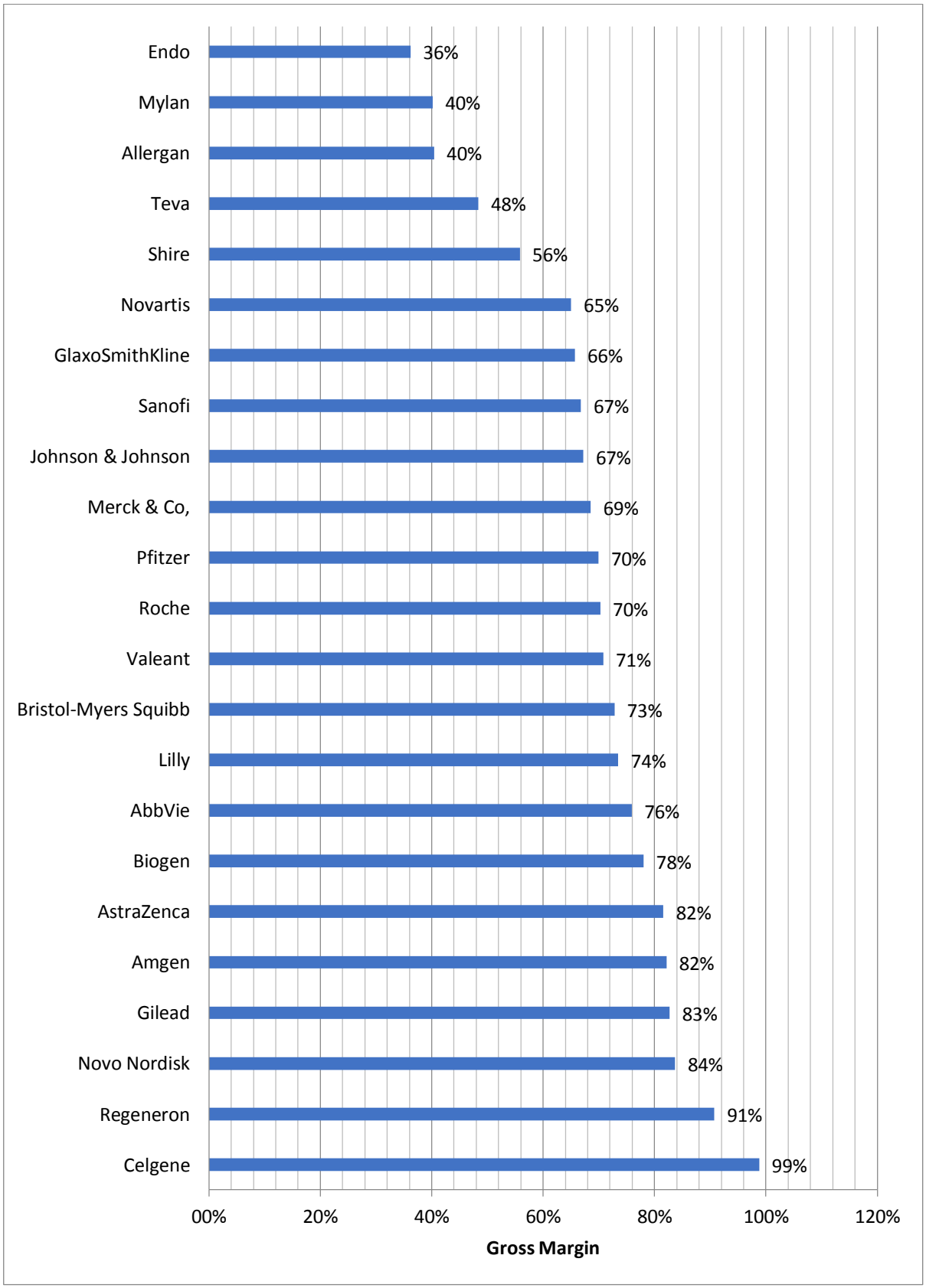
collaboration framework served to empower many of those who, in the past, had been passive and subjugated, so that they came forward with important data and constructive ideas and contributed much to the successful implementation of solutions. Involving people form the shop floor in the decision-making process helped to demonstrate the value of working together in teams, both in tackling problems and in implementing solutions on an everyday basis.

However, from a strictly formal point of view, the projects were not successful, since the 5% OEE increase target set during the strategic phase was not achieved. This shortcoming can be linked to the fact that, during the strategic phase, the goal was set having in mind that type B CO duration could also be reduced. An assumption that happened to be wrong during the implementation phase, when the team realised no time reduction could be achieved without reducing or externalizing the washing cycle in the storage tank.

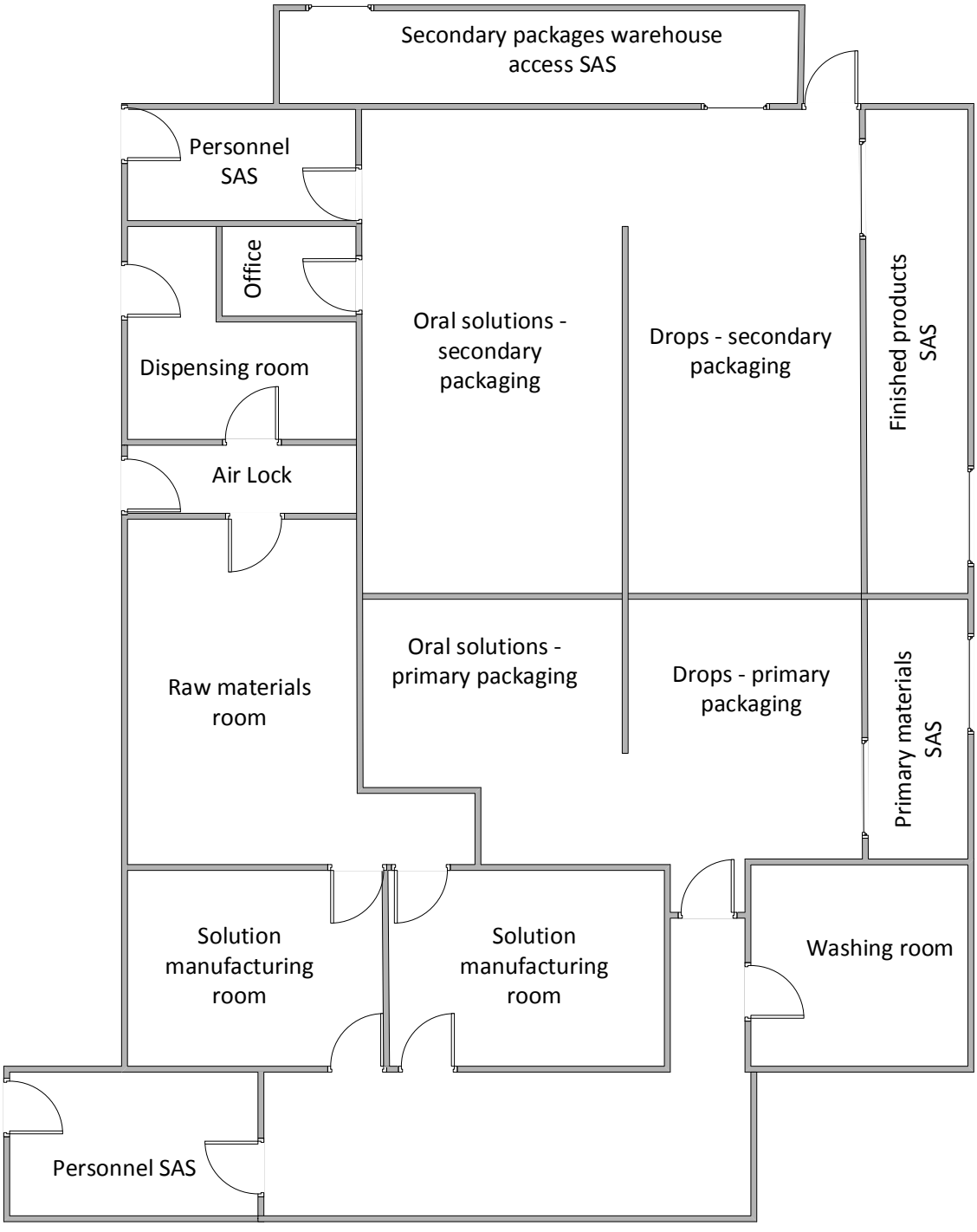
Another deterrent is found in senior management, which having on average 20 years inside the pharmaceutical industry, are not concerned about the continuous improvement philosophy. In fact, it is not seen as a strategic competence and thus, virtually no resources are committed to it. Unfortunately, this is true even in the case of CDMO, where the core business relies mainly upon the ability to deliver items in the right quantity, with the expected quality and at a competitive cost.

Nonetheless, it has been clearly demonstrated that Japanese management techniques can be successfully transplanted from industries such as car manufacturing and consumer electronics to pharmaceutical production. In fact, the packaging of pharmaceutical components is full of improvement opportunities. As happened with the car industry, the necessity to increase productivity will rise only when the market ceases to expand and regulations became more severe regarding prices.

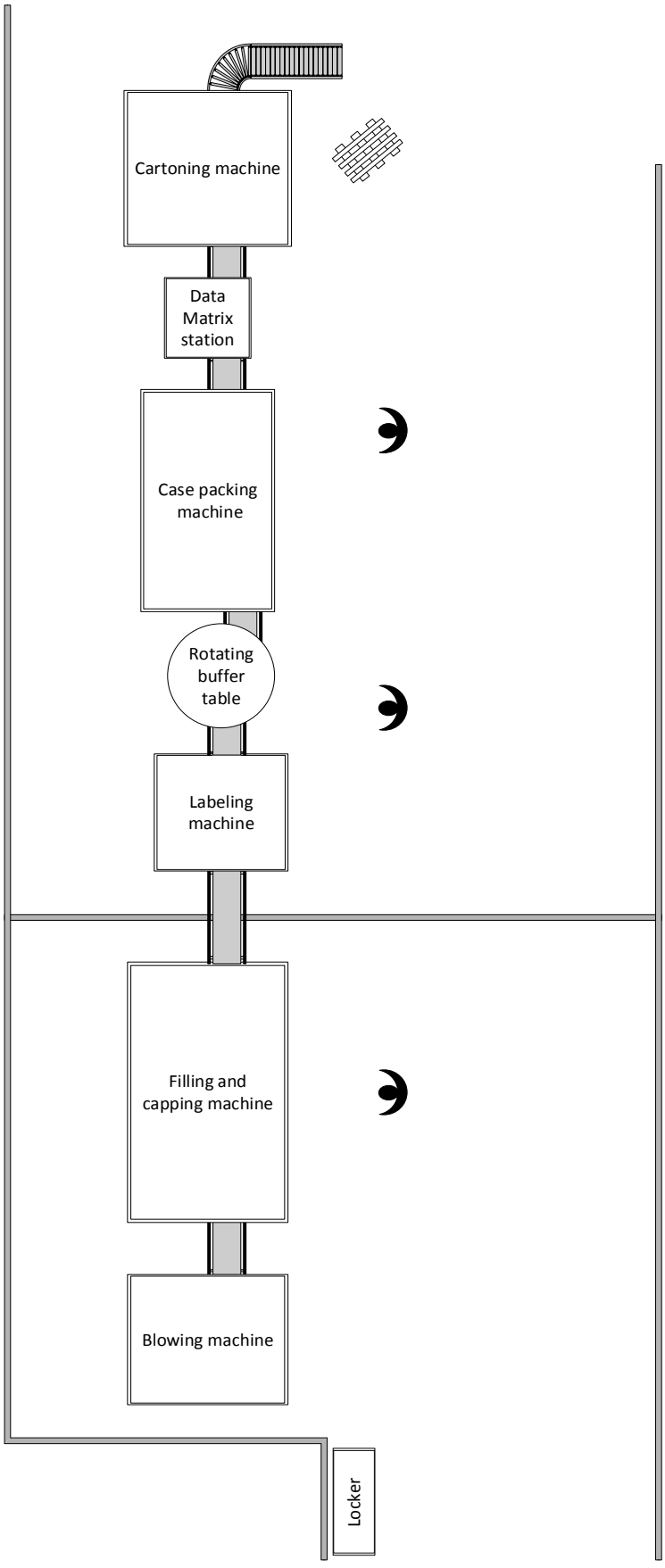
Appendix 1- Gross Margin for the most representative pharmaceutical companies worldwide



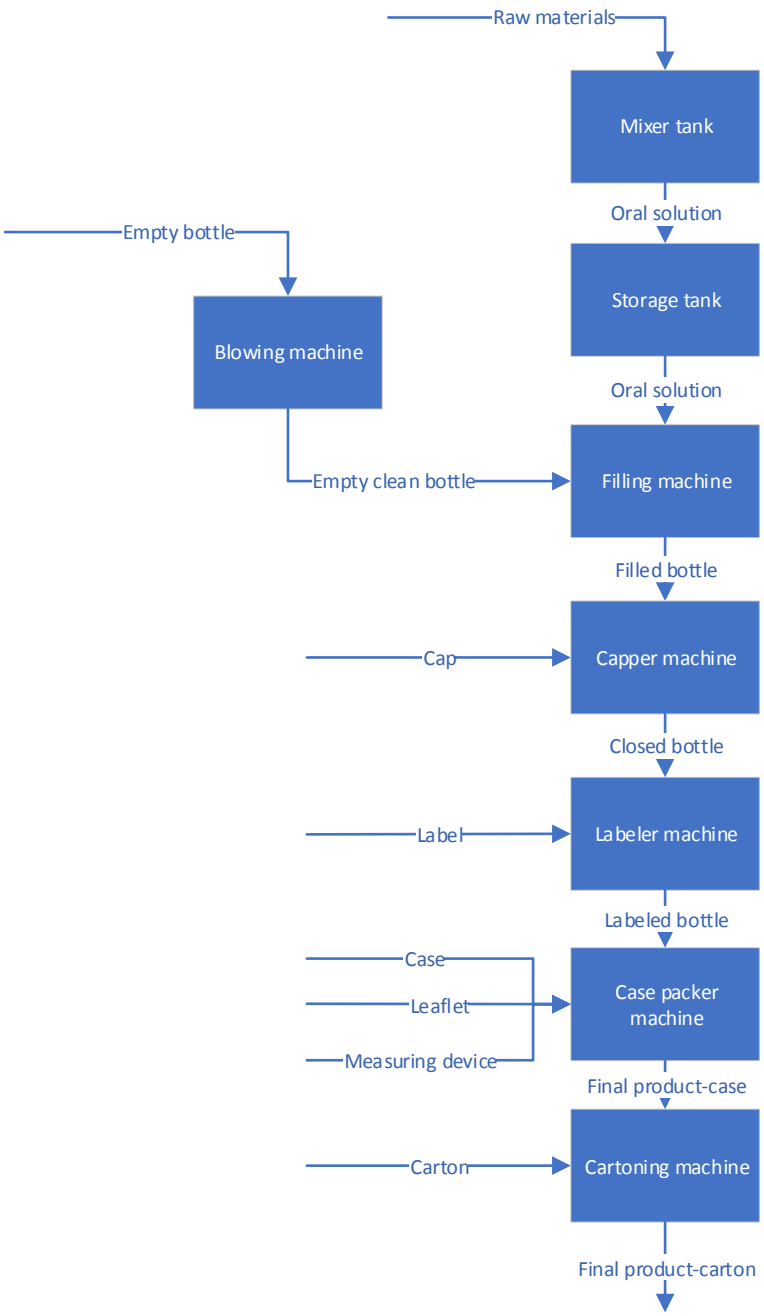
Appendix 2- Oral solutions production plant layout



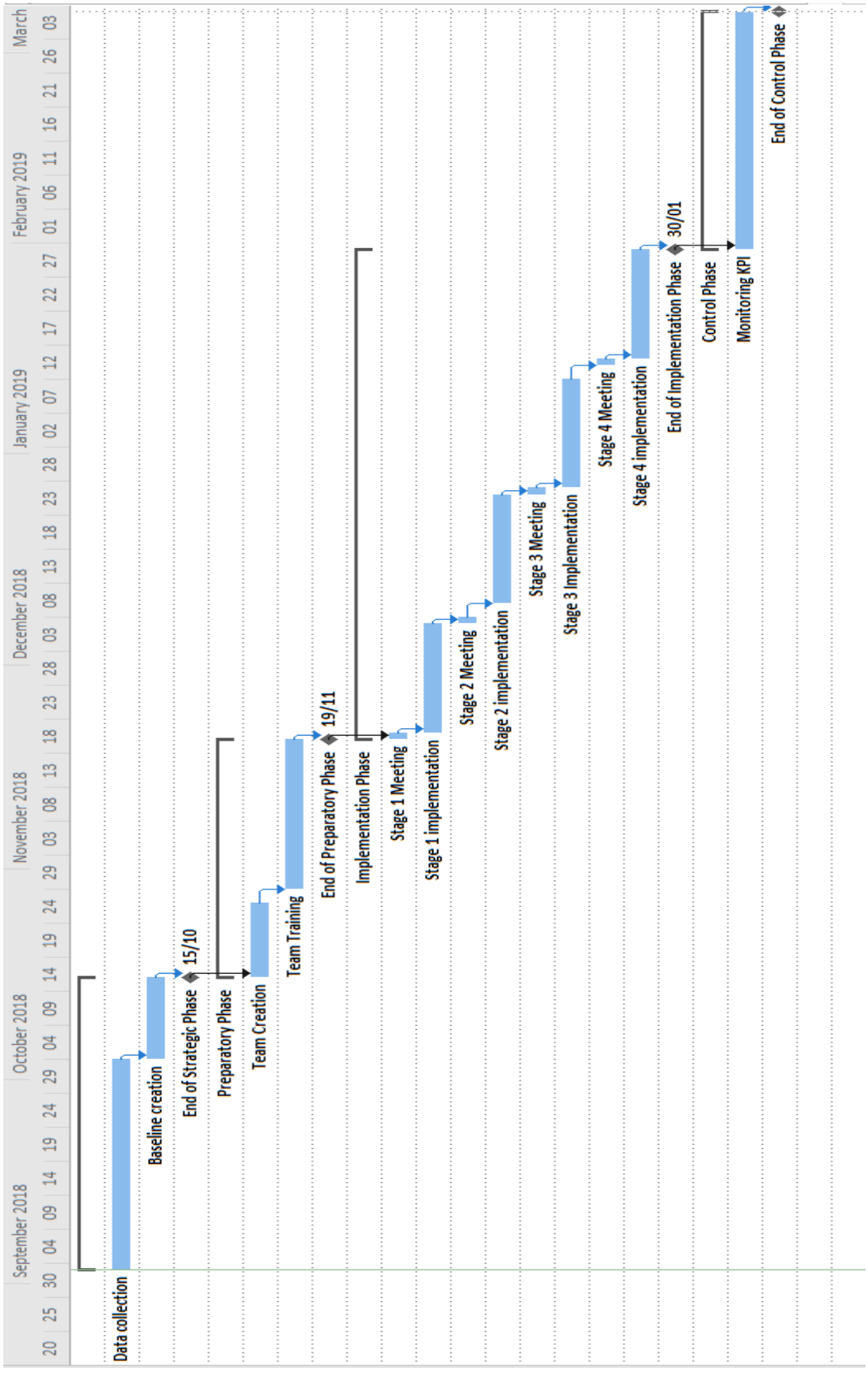
Appendix 3- Oral solutions production line layout



Appendix 4- Oral solutions production process' flow chart



Appendix 5 – Illustrative Gant Chart showing the project schedule



Appendix 6 – List of activities performed during a Type A CO with their respective duration

N	Event Description	Time(min)	Internal	External	Eliminated
1	Fill in and close batch card product A	14	X		
2	Clear the line (remove product A materials)	4	X		
3	Take apart labeler stamp	1	X		
4	Change labeler stamp characters	8	X		
5	Reassemble labeler stamp	1	X		
6	Take apart case packager stamps	1	X		
7	Change both case packager stamps	19	X		
8	Reassemble case packager stamps	1	X		
9	Take away finished pallet	1	X		
10	Reconciliation of components	6	X		
12	Clean production floor	3	X		
13	Fill in batch documentation product B	12	X		
14	Print carton labels	3		X	X
15	Fold printed labels	4		X	X
16	Print pallet labels	5		X	X
17	Bring product B materials to the line	5	X		
18	Check type and quantity of product B materials	14	X		
19	Check stamps conformity	3	X		
21	Adjust leaflet intake GUK	6	X		
22	Adjust leaflet bar code reader GUK	6	X		
23	Tidy up workplace	3	X		
24	Put label reel product B on labeler machine	5	X		
25	Adjust labeler to match new format	4	X		
26	Load spoons	2	X		
27	Load case packaging	2	X		
28	Load cartons	2	X		
29	Load leaflets	1	X		
30	Control line clearance (QC personnel)	5	X		
31	Check conformity of variable data (Team leader)	5	X		
	Total	**146**			

Appendix 7– List of activities performed during a Type B CO with their respective duration

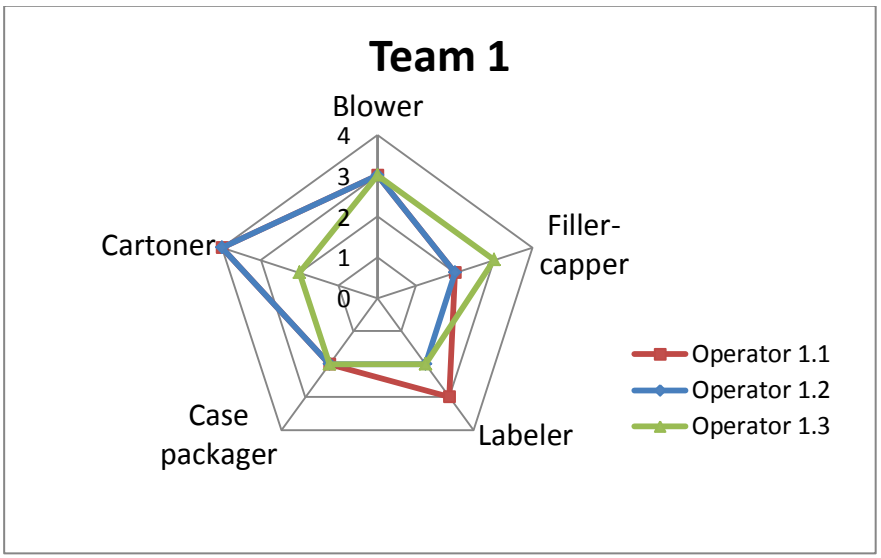
	Event Description	Time(min)
1	Remove empty bottles from the filling machine	1
2	Unscrew filling syringes	1
3	Put syringes inside a carafe	3
4	Bring a cauldron full of water next to the line	1
5	Take apart the syringes from the tank	3
6	Take apart the tank filter	2
7	Put the syringes inside the cauldron	2
8	Depurate hose and syringes	10
9	Carry the tank to the cleaning room	1
10	Disassemble the tank	4
11	Wash the tank components	4
12	Dry the tank components	2
13	Reassemble the tank	4
14	Reassemble the tank's filter	2
15	reassemble the tank's syringes	3
16	Remove air from the hoses	8
17	Clean the machine	3
18	Reassemble filling syringes	7
19	Check filling volume	3
20	Change batch number on labeler stamp	10
21	QC control primary packaging	3
22	Change batch number on case packager stamps	14
23	Check stamps conformity	2
24	Fill in and close batch card product A	10
25	Inventory not used materials	4
26	Print carton labels	1
27	Fold printed labels	1,5
28	Print pallet labels	4
29	QC control secondary packaging	3
30	Check conformity of variable data	5
	Total	121.5

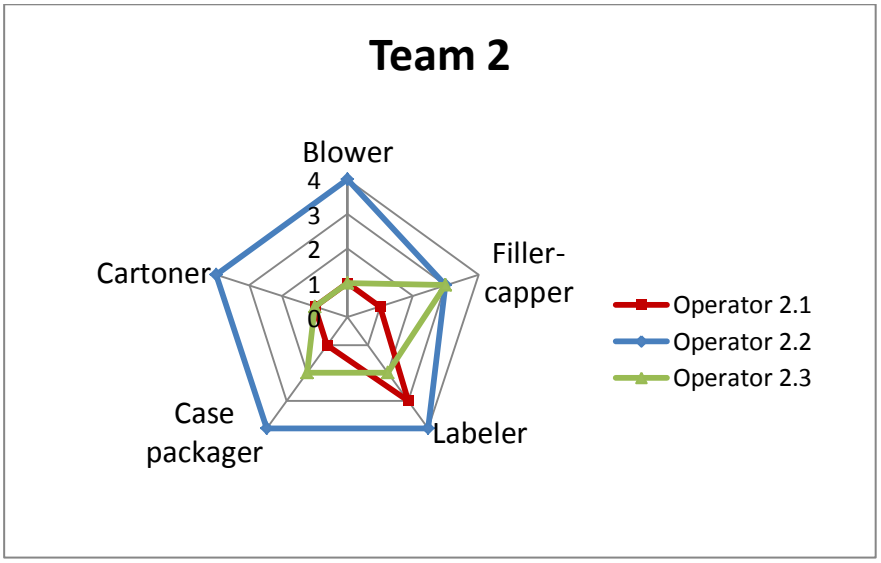
Appendix 8-NPV analysis for projects A and B when varying both the discount rate and the proportion of TOC water measurements not satisfied the first time. Data is expressed in €

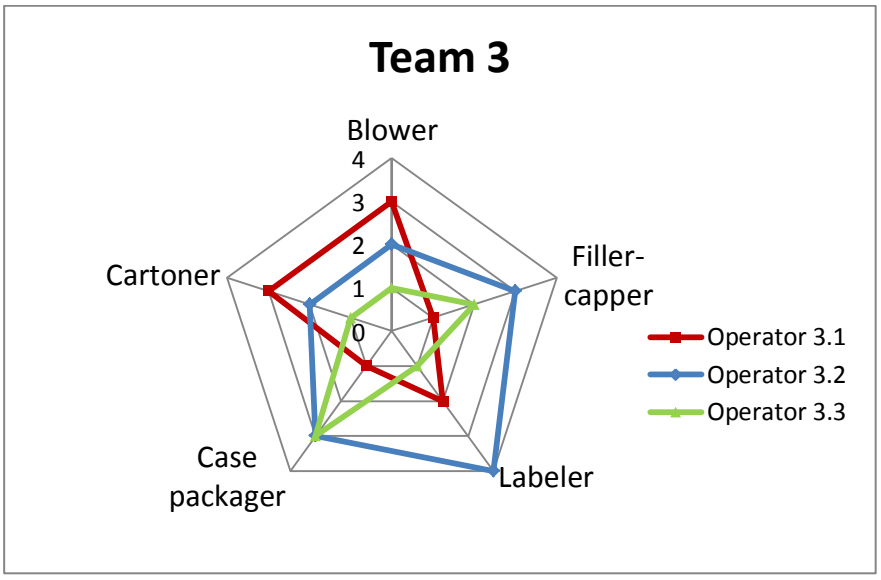
Project A		TOC not satisfied							
		0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1
Discount rate	0.015	1041530	1041530	1041530	1041530	1041530	1041530	1041529.9	1041530
	0.02	1016893	1016893	1016893	1016893	1016893	1016893	1016893.2	1016893
	0.025	992933.5	992933.5	992933.5	992933.5	992933.5	992933.5	992933.5	992933.5
	0.03	969628.5	969628.5	969628.5	969628.5	969628.5	969628.5	969628.5	969628.5
	0.035	94695.7	946956.7	946956.7	946956.7	946956.7	946956.7	946956.6	946956.7
	0,04	924897.3	924897.3	924897.3	924897.3	924897.3	924897.3	924897.3	924897.3
	0.045	903430.5	903430.5	903430.5	903430.5	903430.5	903430.5	903430.5	903430.5
	0.05	882537.2	882537.2	882537.2	882537.2	882537.2	882537.2	882537.1	882537.2
	0,055	862198.8	862198.8	862198.8	862198.8	862198.8	862198.8	862198.8	862198.8
	0.06	842397.7	842397.7	842397.7	842397.7	842397.7	842397.7	842397.7	842397.7
	0.065	823116.9	823116.9	823116.9	823116.9	823116.9	823116.9	823116.8	823116.9
	0.07	804339.7	804339.7	804339.7	804339.7	804339.7	804339.7	804339.7	804339.7
	0.075	786050.6	786050.6	786050.6	786050.6	786050.6	786050.6	786050.5	786050.6
	0.08	768234	768234	768234	768234	768234	768234	768234.0	768234
	0.085	750875.5	750875.5	750875.5	750875.5	750875.5	750875.5	750875.4	750875.5
	0.09	733960.7	733960.7	733960.7	733960.7	733960.7	733960.7	733960.7	733960.7
	0.095	717476.1	717476.1	717476.1	717476.1	717476.1	717476.1	717476.1	717476.1

Project B		TOC not satisfied							
		0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1
Discount rate	0.015	1104274	1090706	1077138	1063570	1050002	1036434	1022866.1	1009298
	0.02	1079916	1066610	1053303	1039997	1026691	1013385	1000078.7	986772.5
	0.025	1056219	1043167	1030116	1017065	1004014	990962.3	977910.9	964859.7
	0.03	1033161	1020358	1007555	994751.8	981948.7	969145.6	956342.5	943539.5
	0.035	1010722	998160.5	985599.2	973037.8	960476.5	947915.1	935353.7	922792.4
	0.04	988881.2	976555.3	964229.4	951903.5	939577.6	927251.7	914925.7	902599.9
	0.045	967619.5	955523	943426.5	931330	919233.4	907136.9	895040.4	882943.9
	0.05	946918.2	935045.2	923172.2	911299.2	899426.2	887553.2	875680.2	863807.3
	0.055	926759.4	915104.2	903449.1	891793.9	880138.7	868483.6	856828.4	845173.2
	0.06	907125.8	895683	884240.1	872797.3	861354.4	849911.6	838468.7	827025.9
	0.065	888000.8	876765	865529.1	854293.2	843057.4	831821.5	820585.6	809349.8
	0.07	869368.4	858334.4	847300.3	836266.3	825232.2	814198.2	803164.1	792130.1
	0.075	851213.2	840376	829538.7	818701.5	807864.2	797027	786189.7	775352.5
	0.08	833520.3	822875	812229.7	801584.4	790939.1	780293.8	769648.5	759003.2
	0.085	816275.5	805817.4	795359.3	784901.3	774443.2	763985.2	753527.0	743069
	0.09	799464.8	789189.4	778914.1	768638.7	758363.3	748087.9	737812.5	727537.1
	0.095	783075.1	772978	762880.9	752783.7	742686.6	732589.4	722492.3	712395.2

Appendix 9- Radar charts with Operators' ability to perform type C changeovers in the different machines that conform the line



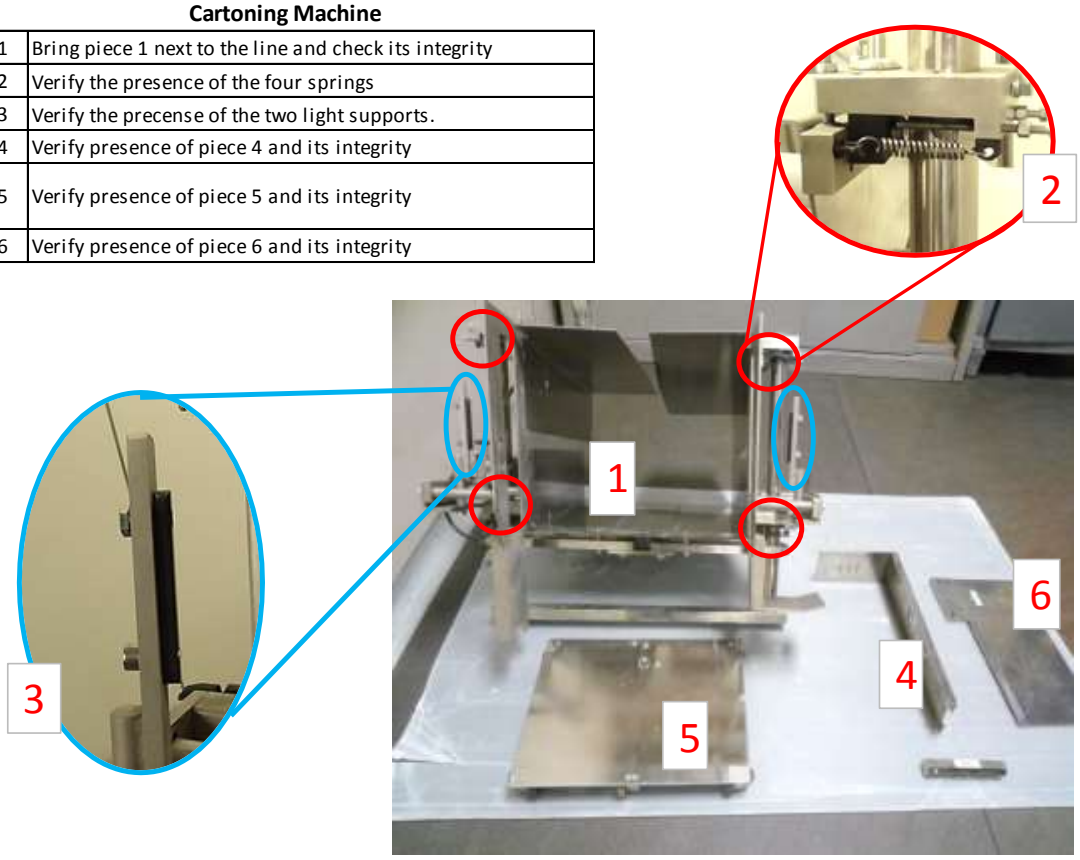




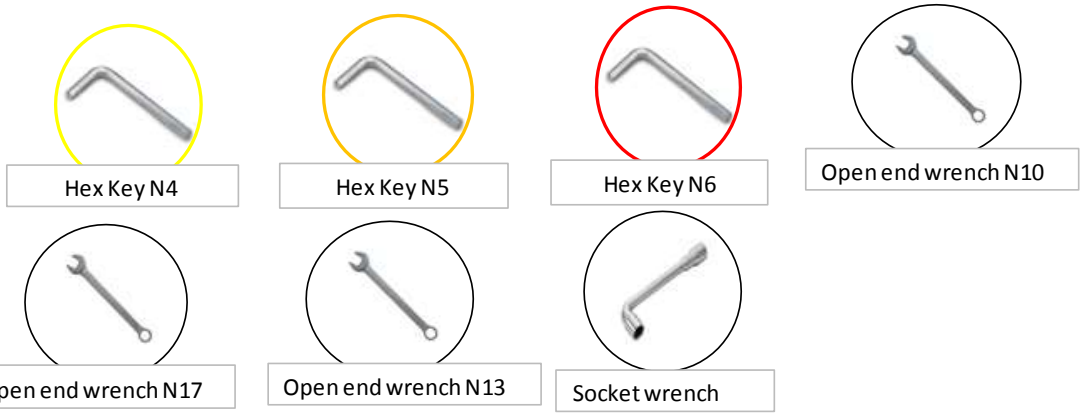
Appendix 10- Simplified version of the checklists that were made in order to collect the tools and materials needed prior to start the type C Changeover

Secondary-Tertiary Packaging Section
Cartoning Machine

1	Bring piece 1 next to the line and check its integrity
2	Verify the presence of the four springs
3	Verify the precense of the two light supports.
4	Verify presence of piece 4 and its integrity
5	Verify presence of piece 5 and its integrity
6	Verify presence of piece 6 and its integrity



Tools needed for the Type C Changeover on the cartoning machine



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