NOVA SCHOOL OF SCIENCE & TECHNOLOGY

DEPARTMENT OF CHEMISTRY

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Bachelor of Science Degree in Chemical and Biochemical Engineering

# THROUGHPUT INCREASE OF AN API PRODUCTION PROCESS BY 10%

MASTER OF SCIENCE IN CHEMICAL AND BIOCHEMICAL

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**Throughput increase of an API production process by 10%**

*Believe you can*
*and you're halfway there.*

*-Theodore Roosevelt*

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# Abstract

This dissertation aims to increase the throughput of an Active Pharmaceutical Ingredient (API) process by 10%, focusing on three fronts: golden Cycle Time reduction, downtime reduction, and yield improvement. Identifying the bottleneck and ensuring maximum batch overlap, would improve the bottleneck efficiency, allowing the manufactured quantity to increase in a set period.

The API is chemically synthesized in batch production mode with four intermediates and a final product. Eight batches were previously manufactured with an average throughput of 1.26 kg/day; therefore the target was to increase it to 1.38 kg/day. By identifying the bottleneck, ensuring batch overlap, and recording and analysing downtimes it was possible to achieve throughput increase on Intermediate 1 by 105%, Intermediate 3 by 60%, Intermediate 4 by 37% and Final Product by 35%. On Intermediate 2 the throughput decreased 16%.

The throughput of the API accounted for the production time of all intermediates and Final Product but only the manufactured quantity of Final Product, revealing a value of 1.35 kg/day, a 7% increase. This did not meet the target and the main reason for this was the production of only two batches of Final Product, whilst an extra two batches of Intermediate 3 and one batch of Intermediate 1, that accounted for a higher total production time, were not used.

The main conclusions were: the three fronts were efficient in increasing productivity for each intermediate; to improve the APIs' throughput, the team would have to focus more on the changeover between intermediates to ensure the bottleneck was always running; the yield results were lower than the baseline, therefore by studying the mass balance and implementing corrective and improvement actions this would lead to a higher throughput, since it would improve the process yield.

**Keywords:** API, throughput, Cycle Time, downtime, yield, bottleneck efficiency

# Resumo

Esta dissertação tem como objetivo o aumento do *throughput* de um Ingrediente Farmacêutico Ativo (API) em 10%, focando-se em três vertentes: reduzir o *golden Cycle Time,* reduzir o *downtime* e aumentar o rendimento. Ao identificar o gargalo de cada processo e assegurar a sobreposição máxima de lotes, aumentar-se-ia a eficiência do gargalo*,* permitindo aumentar a quantidade produzida num dado período.

O API é sintetizado quimicamente em modo *batch* com quatro intermediários e Produto Final. Anteriormente foram produzidos oito lotes deste API com um valor médio de *throughput* de 1.26 kg/dia, logo o objetivo é aumentá-lo para 1.38 kg/dia. Identificando o gargalo, garantindo a sobreposição de lotes e registando e analisando os *downtimes* foi possível aumentar o *throughput* do Intermediário 1 em 105%, do Intermediário 3 em 60%, do Intermediário 4 em 37% e do Produto Final em 35%. O *throughput* do Intermediário 2 diminuiu 16%.

O *throughput* do API contabiliza o tempo total de produção de todos os intermediários e Produto Final, mas apenas a quantidade produzida de Produto Final, revelando um valor de 1.35 kg/dia, um aumento de 7% em relação ao histórico. A causa principal para este valor não ter atingido os 10%, foi o facto de se terem produzido apenas dois lotes de Produto Final, quando dois lotes de Intermediário 3 e um lote de Intermediário 1 não foram utilizados em produção, mas contabilizaram um maior número de horas.

As conclusões mais importantes foram: as três vertentes em estudo foram eficazes no aumento de produtividade em cada intermediário; para melhorar os resultados do API, a equipa teria de se focar na transição entre intermediários; os resultados de rendimento foram inferiores aos históricos, pelo que estudando o balanço de massa e implementando ações corretivas e de melhoria, ter-se-ia um valor mais elevado de *throughput,* dado o aumento em rendimento.

**Palavras-chave:** API, *throughput, Cycle Time, downtime*, rendimento, eficiência do gargalo

# Contents

# List of Figures

# List of Tables

# List of Abbreviations

| | |
|---|---|
| **API** | Active Pharmaceutical Ingredient |
| **BPR** | Batch Production Record |
| **BTS** | Build To Schedule |
| **CAPA** | Corrective Action Preventive Action |
| **CAPD** | Computer Aided Process Design |
| **CBB** | Cleaning Between Batches |
| **cGMP** | Current Good Manufacturing Practices |
| **CMO** | Contract Manufacturing Organization |
| **CT** | Cycle Time |
| **DCM** | Dichloromethane |
| **DTD** | Total Dock To Dock Time |
| **FDA** | Food and Drug Administration |
| **FMEA** | Failure mode and effects analysis |
| **FTT** | First Time Trough |
| **GC** | Golden Cycle |
| **HSE** | Health, Safety, and Environment |
| **IPC** | In-Process Control |
| **JIT** | Just In Time |
| **KF** | Karl-Fischer |
| **KPI** | Key Performance Indicators |
| **LT** | Lead Time |
| **MT** | Manufacturing Technique |
| **OEE** | Overall Equipment Effectiveness |
| **PDCA** | Plan, Do, Check, Act |
| **QC** | Quality Control |
| **RCA** | Root Cause Analysis |
| **RPN** | Risk Priority Number |

| | |
|---|---|
| **SRM** | Starting Raw Material |
| **SW** | Standard Work |
| **SWIP** | Standard Work in Progress |
| **THF** | Tetrahydrofuran |
| **TPM** | Total Productive Maintenance |
| **VSM** | Value Stream Mapping |

# 1. Framework

This project aims to increase the throughput of an Active Pharmaceutical Ingredient (API) by 10%, to comply with the market needs. This API serves as a treatment for lung cancer, which has the advantage to reduce the common side effects in different patients when compared with other treatments. Therefore, Hovione must ensure the team is doing their best to deliver medical solutions to those in need of it, enhancing this way the importance of achieving the goal for this project.

The sustainability of the throughput increase must be ensured, always having, in consideration two variables: cost and impact, both in Health, Safety and Environment (HSE) and quality. It is also important to guarantee that the cGMP (current Good Manufacturing Practices) are followed strictly with any improvement action.

Over the years, Lean Production Systems have been proved as an effective way to turn the production process efficient regarding costs, process quality, time, and flexibility, which are the main goals of a pharmaceutical company.

## 1.1 Case Study

This production line is constituted by four main equipment, listed in Table 1.1, and it is incorporated on the Contract Manufacturing Organization (CMO) business, although it is temporarily dedicated to the API in question.

Table 1.1: Main equipment used in production of the API

| Equipment Code | Characterization | Capacity |
|---|---|---|
| **RV4001** | Glass-Lined Reactor | 4 000 L |
| **RH4001** | Hastelloy Reactor | 4 000 L |
| **TC2401** | Tank | 2 000 L |
| **FSEC101** | Sintered Filter Dryer | 1 $m^2$ |

This API is a relatively new product in the company, starting its demo-batch in 2019, performing the process validation between July 2019 and January 2020 and the first commercial campaign started in May 2020; this study will focus on improving the 3rd commercial campaign's production.

It is chemically synthesized in batch production mode, its production process consists of five production steps, as Figure 1.1 shows.

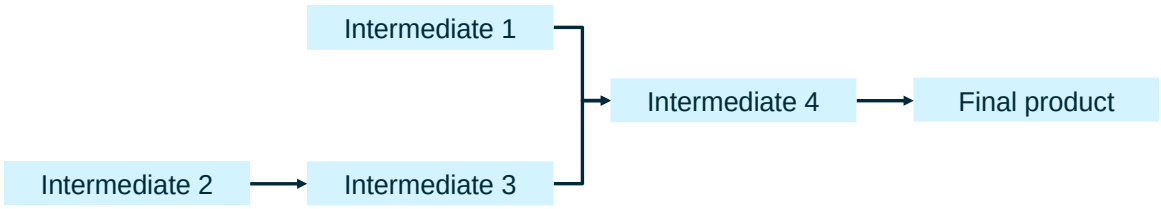


Figure 1.1: API production process

The optimum sequence of production starts with Intermediate 2, followed by Intermediate 1, Intermediate 3, Intermediate 4, and Final Product. This sequence guarantees the release of Intermediate 2 before the start of Intermediate 3 production.

The quantity of Starting Raw Material (SRM) for each step is represented in Table 1.2.

Table 1.2: Starting raw material quantity of the production steps

| Intermediate | SRM (kg) |
|---|---|
| **Intermediate 1** | 50 |
| **Intermediate 2** | 50 |
| **Intermediate 3** | 55 |
| **Intermediate 4** | 80 |
| **Final Product** | 60 |

In Figures 1.2 to 1.6, the production process of each intermediate is detailed.

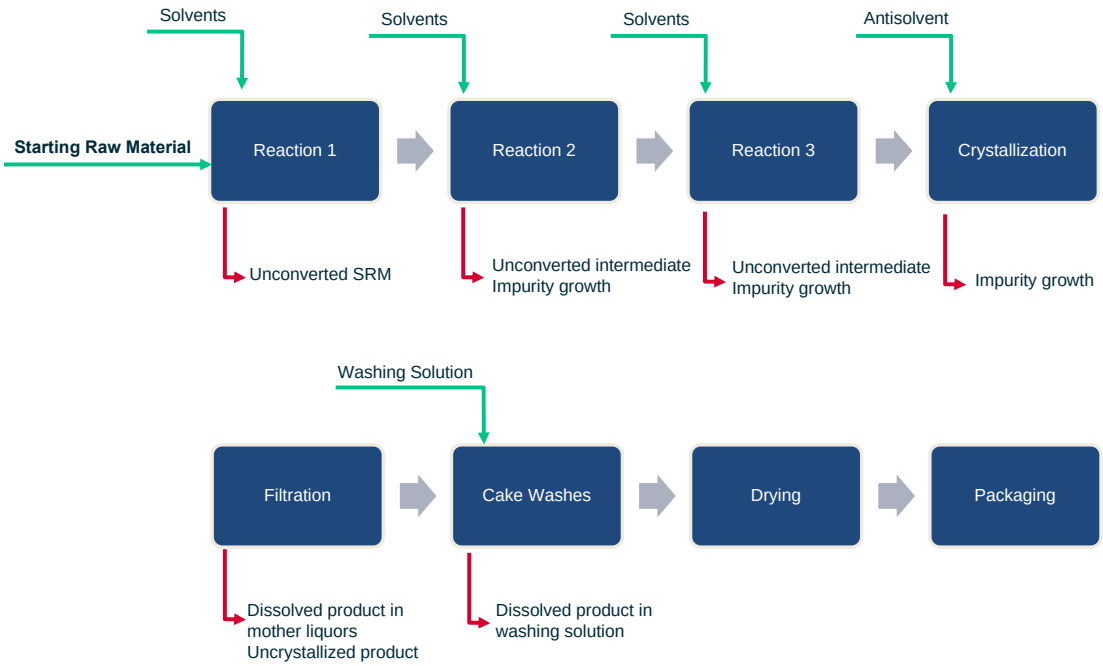


Figure 1.2: Production process of Intermediate 1

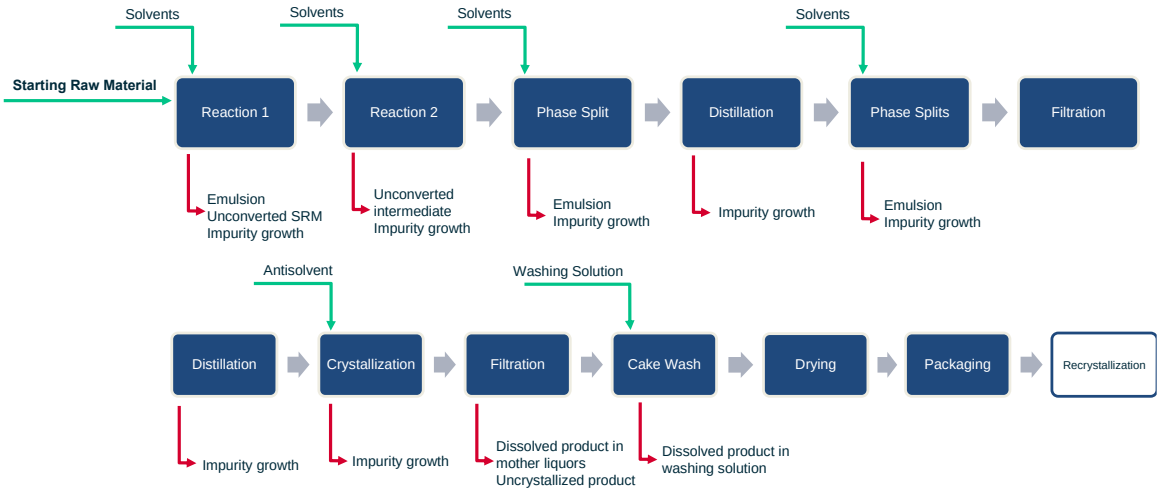


Figure 1.3: Production process of Intermediate 2

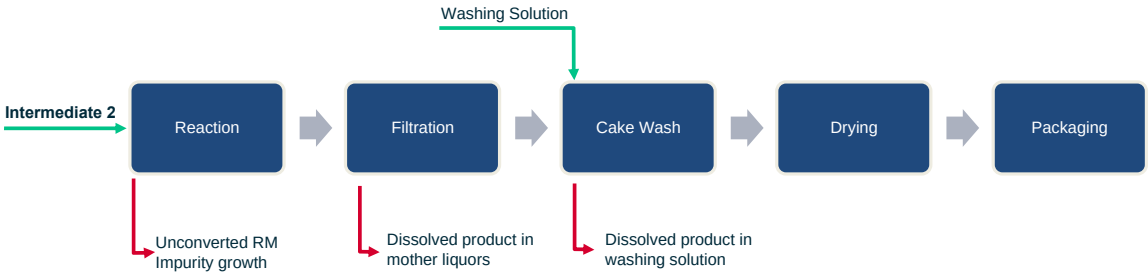


Figure 1.4: Production process of Intermediate 3

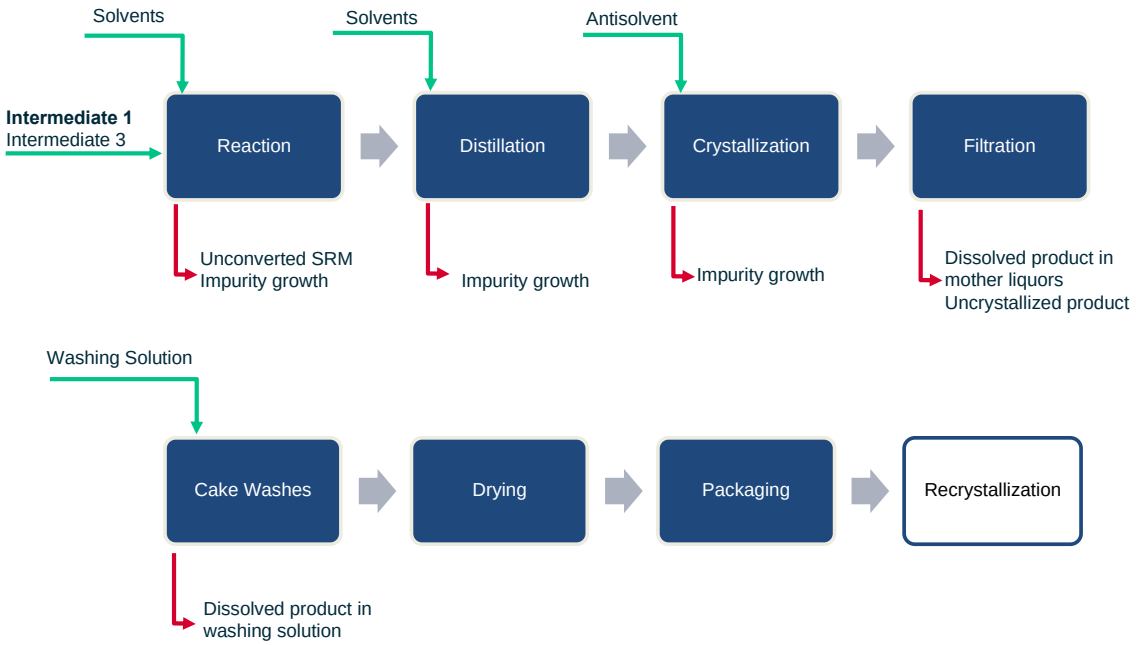


Figure 1.5: Production process of Intermediate 4

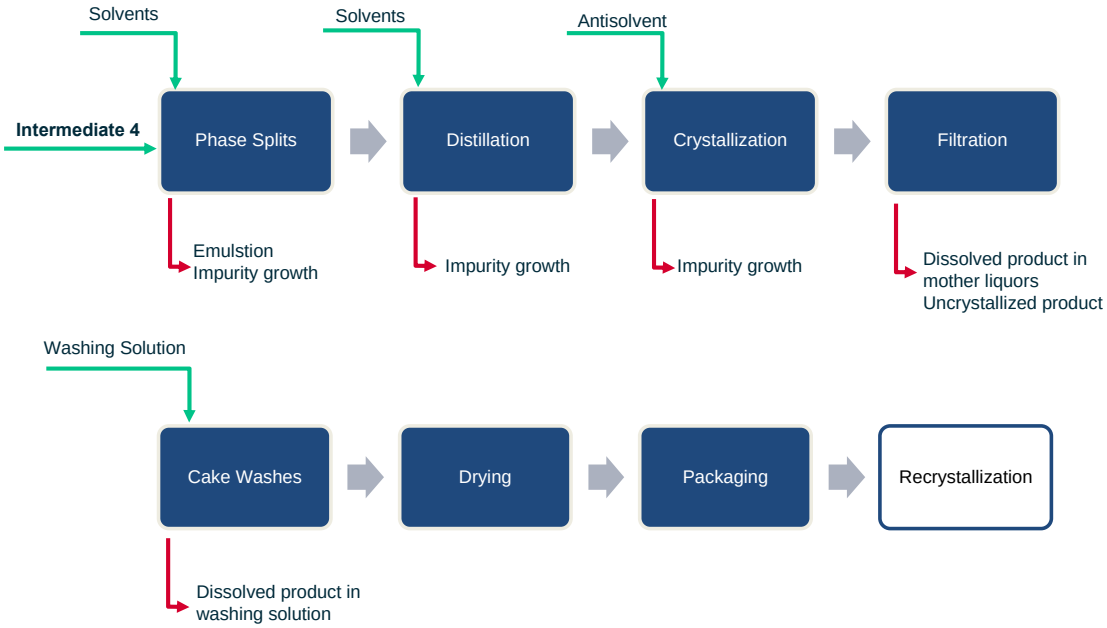


Figure 1.6: Production process of Final Product

- **Cycle Time, yield, and throughput**

Table 1.3 resumes the status of the processes in terms of current average Cycle Time and molar yield at the start of this project.

Table 1.3: Status of the processes (average Cycle Time and average molar yield)

| Intermediate | Average Cycle Time | Average Molar yield (%) |
|---|---|---|
| **Intermediate 1** | 5d - 22h | 65.1 |
| **Intermediate 2** | 8d - 11h | 69.7 |
| **Intermediate 3** | 5d - 4h | 93.0 |
| **Intermediate 4** | 12d - 1h | 84.5 |
| **Final Product** | 8d - 1h | 90.9 |

Table 1.4 reveals the campaign's throughput. Note that the number of batches and the manufactured quantity relates to the output of the API (Final Product) and not the sum of all intermediates; whilst the total available time reflects the process from start to finish (Intermediate 1 to Final Product).

Table 1.4: Baseline throughput

| Campaign | Number of batches | Manufactured quantity (kg) | Total Available Time (h) | Throughput (kg/day) |
|---|---|---|---|---|
| **Validation** | 3 | 168.64 | 2 832 | 1.43 |
| **Commercial #1** | 2 | 122.80 | 2 003 | 1.47 |
| **Commercial #2** | 3 | 138.42 | 3 826 | 0.87 |

## 1.2 Objectives

The main goal for this project is to increase the throughput by 10% by:

- Golden Cycle Time reduction;
- Downtime reduction;
- Yield improvement.

This will be achieved by:

1. Defining the throughput baseline for the processes;
2. Identifying the bottleneck, and golden cycle for each process;
3. Yield analysis and mass balances;
4. Defining and supporting the implementation of the continuous improvement plan to reduce the Cycle Time.

# 2. State of the art

This chapter highlights the different approaches to a throughput analysis, to better explain each method and elaborate on the reasoning behind the chosen ones; followed by a brief introduction to Lean concepts, continuous improvement, and root-cause analysis, all to support the throughput increase study. Through different researchers the relationship of Lean and performance both in the industry and the pharmaceutical industry is explored, to serve as a foundation for the study.

## 2.1 Throughput concepts

Throughput can be defined in different ways, according to the purpose of the analysis. Pinto defines throughput as the rate at which an organization generates money by selling products or services [1]. This definition incorporates other departments such as marketing and sales, which will not be targeted in this study.

Therefore, in this context, throughput is defined as the amount of product produced within a period. Equation 2.1 represents the simple calculation for throughput [2]:

$$\text{Throughput} = \frac{\text{Batch size}}{\text{Effective batch time}} \tag{2.1}$$

Where the batch size corresponds to the amount of final product manufactured and the effective batch time is defined as the time interval between the start of two consecutive batches; since process steps that utilize different pieces of equipment can run at the same time, the effective batch time can be less than the actual time required to complete a batch.

Based on Equation 2.1 it is evident that throughput depends on the batch size and number of manufactured batches; therefore, to increase the throughput there is the option to increase the batch size or the number of batches produced in the considered period, by decreasing the Cycle Time for the process. FDA's "Post-approval changes to drug substances: guidance for the industry" has a chapter on recommendations for those who want to make changes to a drug substance manufacturing process, including scale changes; however this is not applicable in this case, since

the client is the owner of the Manufacturing Technique (MT) and would be responsible for filing if necessary [3].

According to Koulouris et al. (2000) throughput analysis of batch processes aims at identifying opportunities for increasing annual production by identifying and eliminating size and scheduling bottlenecks. In a general matter, a bottleneck consists of any resource that creates a strangle or hinders the normal functioning of a system [1]; they can be classified as size bottlenecks, which limit the amount of material that can be processed per batch, and scheduling bottlenecks, these limit the number of batches in a certain period due to having the longest total occupancy time[1] [2].

## 2.2 Lean

Lean methodology alongside Six Sigma has been used in manufacturing industries to create value by eliminating waste and reducing variation [1].

Lean is considered a philosophy, originated in the ’40s with the Toyota Production System, intending to eliminate waste systematically and create value [4]. Value is defined as the activities that interest the client and that he is willing to pay for [5]; only value justifies the existence of an organization. Waste, or in Japanese *Muda,* refers to any activity that consumes resources but creates no value [5], and it was characterized as different types [1,5]:

**Defects:** Product defects or quality issues

**Inventory**: Presence of unused material, or materials in holding points

**Motion:** Movements that may cause injury in the manufacturing environment

**Over-processing:** Refers to overusing resources or using them wrongly

**Overproduction:** Producing what is not necessary, when it is not necessary, in unnecessary quantities

**Transportation:** Transportation refers to unnecessary movements of the product without its condition suffering alterations

**Waiting:** The time that people or equipment lose whilst waiting for something, e.g., an authorization or a quality result

Analysing the previous list, overproduction can be considered the worst type of waste because it leads to a stock increase, which is another type of waste; and it unnecessarily occupies resources, consumes materials and energy.

[1] time interval from the start of the first step hosted by the equipment to the end of the last step hosted by the same equipment

Lean is known for its seven main principles: identify the stakeholders, define value, value stream mapping, create flow, establish pull, seek perfection and always innovate [1].

### 2.2.1 Continuous Improvement

To implement lean thinking, one must go through change, which relies on continuous improvement. Continuous improvement ensures performance improvement and superior quality of the products and/or services by encouraging the workers' proactivity to solve problems and challenges. According to Covey, a habit is an interception between knowledge, desire, and knowing how to do it [7]. Therefore, to implement continuous improvement, one must have the knowledge and understand why there is the need for this and what do to in that sense, to adopt continuous improvement habits.

A basis of continuous improvement is the PDCA cycle which is known as the circle of continuous improvement or Deming's circle, it is a facilitator for lean, not a tool. It is divided into four parts, as Figure 2.1 shows [1].

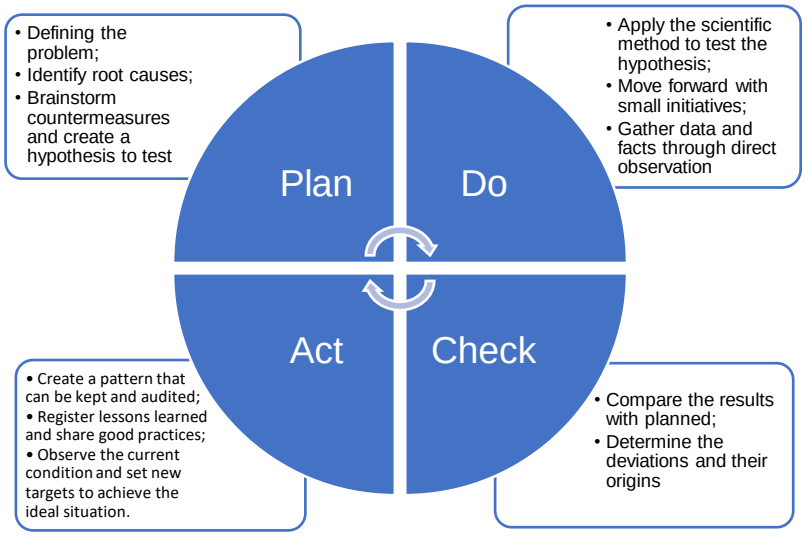


Figure 2.1: PDCA Cycle

Although it is divided into four parts, the time spent on each of them should not be equivalent; planning should be the longest task to truly tackle the problem at hand in the best way possible.

*Hourensou* is a method developed in Japan, to facilitate and promote communication between all hierarchy levels in the organization . It results from the combination of three Japanese words, which mean report, update and consult. Using this method, floor workers can unilaterally communicate information to their managers for them to make decisions based on current and accurate data [1].

Lastly, standardizing ensures a firm ground for continuous improvement, by guaranteeing that everyone performs all actions the same way. By ensuring repeatability, that is, one worker always performs a task the same way; and reproducibility, all workers perform it the same way, predictability is achieved, therefore the process is more reliable and controllable, ergo a process

with low standard deviations. Notice that a standardized process is easily taught, improved, documented, audited, and transferable.

### 2.2.2 Lean Methodologies

As mentioned previously, value is the core of lean philosophy, so it is important to follow value along the production process. The value stream consists in identifying every action required to design, order, and make a product. This allows to sort these actions into three categories [5]:

- the ones which create value as it is perceived by the customer;
- those that do not create value but are required by the product development and cannot be eliminated yet;
- the actions that do not create value and can be eliminated immediately.

Once the value stream is defined, there is the need to map every process and flow to take the actions required to eliminate waste.

In the 60's a philosophy called Total Productive Maintenance was created to "ensure that every machine in a production process is always able to perform the requires tasks being so that the production is never interrupted" [5]. However, this method was improved to intervene in the whole process; now settling on five pillars: eliminate waste; install planned maintenance, executed by the technicians; install autonomous maintenance, executed by the operators; train personnel; design TPM where it is discussed the possible improvements on the machines [1].

### 2.2.3 Lean Tools

Before exploring lean tools, there are two basic concepts to define: Cycle Time – the time between consecutive batches, is defined by the longest operations; and lead time – necessary time for production, which includes productive and non-productive time.

Most of the lean tools rely on visual resources, such as the **Seven Basic Quality Tools** [8]:

- The **Cause-and-effect Diagram**, also known as Ishikawa Diagram, resembles a fishbone where probable causes for the problem at hand are grouped into categories, which are later analysed and confirmed that it was an isolated event, otherwise, it should be divided into sub-causes.

  The categories into which the causes should be divided started with Dr. Ishikawa as the 4M [9], and later developed into the 6M.

  **Methods:** Variation originated from different components, scheduling, procedure, etc.

  **Materials:** Variation associated with design and quality

  **Machine:** Variations allied with design, installation, suppliers, etc.

  **Measurement:** Variations arising from different measurement units.

  **Man:** Variation related to skill, training, resources, communication, etc.

  **Mother Nature:** Variation due to location, time, temperature in which the process occurs.

- The **check sheet** consists of a data form where that should be easily registered; it is used when there is a need to analyse a process based on facts and not opinions. Whilst creating the check sheet the situation must be clearly defined, the format of the sheet should be conceived, and the data collection period should be defined.
- A **Histogram** is a graphic representation of quantitative data grouped by frequency classes. Essentially it is a bar graph that supplies information regarding the values' dispersion and localization.
- The **Scatter Diagram** is used to identify a potential relationship between two or more variables, using a correlation coefficient, known as r, which quantifies the relation degree between the variables; and a determination coefficient, known as $r^2$, which measures the quality of the adjustment.
- A **Pareto Chart** is a frequency distribution of data arranged by category; with this chart, it is easy to visually identify the most frequently occurring types of defects, since roughly 80% of the consequences come from 20% of the causes.
- The **defect concentration diagram** consists of drawing the various types of defects on the different views of the product; this way it can be determined if the location of the defects conveys useful information about the potential causes of the defects.
- The **Control chart** is a monitoring technique used to detect the occurrence of assignable causes of process shifts; it can also be used to estimate the parameters of a process and therefore determine the process's capability.

Lean thinking has several other tools that can help achieve the desired state, such as Value Stream Mapping (VSM), 5S, and Standard Work (SW) [1].

**Value Stream Mapping**, as the name indicates, is a tool used to map the value stream taking into consideration both materials and information flows. This method relies on observation; therefore, it is best to create it whilst on the shop floor, during a Gemba Walk; it includes an "as-is" mapping and focuses on the "to be" status [10]. There are other alternatives to map the value stream such as flow diagrams, bubble diagrams, swimlane, and spaghetti diagrams.

**5S** is a tool named after five Japanese words that refer to a set of practices that strive to reduce waste and improve the performance of people and processes by maintaining the optimum conditions of the workspace. It has immediate consequences after its application, such as decreasing rework, increase in safety, and decrease in waiting times. Note that to achieve the next step, the previous one must be solidified, and it must be ensured that the deviations from the standard are visible.

**Sort** (*Seiri*): Guarantee that in the workspace only remains equipment, tools, and necessary materials; define an area to act on, question every object, red tag the unnecessary objects, and do monthly audits to review the objects

**Set** (*Seiton*): Reorganize the objects left in the workspace; define specific locations for each material

**Shine** (*Seiso*): Cleaning of the workspace

**Standardize** (*Seiketsu*): Rely on standardized work to help sequence a 5S audit

**Sustain** (*Shitsuke*): Create habits to sustain the workspace

An **A3 report** is a tool used to put into practice the PDCA cycle. This one-page report contains all the information regarding the process with visual support. It typically includes:

**Background**: A description of the problem

**Current Condition:** Description of the process, time limits, layout, etc.

**Goal:** The goal for the process

**Root Cause Analysis**: Usually done using an Ishikawa Diagram and the 4M's

**Countermeasures:** Actions for the identified root causes

**Effect Confirmation**: Tasks and timeline for the project

**Follow-up Actions:** Post-implementation tasks to ensure the solutions are maintained

**Standard Work** stands on three main pillars:

| | |
|---|---|
| **Takt Time** | The rate at which products or services must be supplied to satisfy demand (internal or external) |
| **Sequence** | The sequence in which the activities must be ensured, whilst takt time and with no risk associated |
| **SWIP** | Standard Work In Progress: number of units per work post, to promote a smooth and continuous workflow |

There are three documents of Standardized Work: Production Capacity Sheet – it is used to confirm the real capacity of each step of the process and identify bottlenecks; Standardized combination table- combines the machine's Cycle Time, manual work and motion in a visual way, and allows the evaluation of man-machine interaction and level the work according to Takt Time; Standardized work chart – shows the sequence of motions of the operators during a full shift, locates equipment, materials and work posts [11].

Focusing on eliminating the current gap from standard and get to the root causes of the problem, can be achieved by Root Cause Analysis (RCA). This analysis gathers several other tools, such as 5 whys, 5 Whys Tree, 5W2H, FMEA, Affinity Diagram, and Is/Is Not. It also relies on previously mentioned tools, the Pareto Chart and Ishikawa Diagram.

The **5 whys** tool, as the name indicates, is based on the question "why", and follows the subsequent flowchart represented in Figure 2.2.

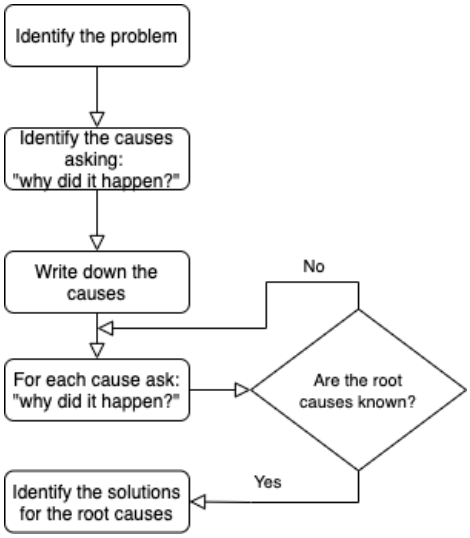


Figure 2.2: Process flowchart for 5W [1]

This tool is useful when tackling a single direct cause, however, it might be the case where there are more than one direct cause bringing the need to use a tool known as **5 why's Tree** [12]**.**

The 5 whys tool should not be confused with **5W2H**, which focuses on the questions: What?, Why?, Where?, When?, Who?, How?, How Much?. Through these explanatory factors, the problem can be visualized clearly and objectively. It also serves as a tool for creating strategic planning, since it defines exactly what the company must do to achieve the stipulated goals.

**Failure Mode and Effect Analysis** (FMEA) is a preventive technique orientated to identify the failure modes of a product, process, or service and supply orientations to reduce or eliminate the risk associated with those failures [13]. In this analysis it is considered a failure when something does not fulfil a function or does not function according to specifications; a failure mode consists of why the failure was produced; and an effect consists of the consequence of the failure mode occurrence, in the product. The process should follow a similar order as:

1. Gather a team
2. Gather and analyse information
3. Functional analysis
4. Identify failure modes
5. Determine the effects
6. Analyse the severity of the effects (G);
7. Determine the causes
8. Determine the occurrence (O) and detection difficulty (D) indexes for the failure modes
9. Calculate and analyse de Risk Priority Number (RPN=GxOxD)
10. Elaborate an action plan focused on the entries with the highest RPN

Table 2.1 summarizes the RCA tools, focusing on advantages and disadvantages of each one, allowing for a better understanding regarding the situations where each one is better suited.

Table 2.1: Root Cause Analysis Tools

| Tool | Description | Purpose | Advantages | Disadvantages |
|---|---|---|---|---|
| **Pareto chart** | A bar graph where the lengths of the bars represent frequency and are arranged with longest bars on the left and the shortest to the right. | Find the few direct causes that are contributing to the most effects | Visual graphic | It may be hard to read for those who are not familiar with the concept |
| **Ishikawa Diagram** | A diagram which shows the possible causes of an event | Group problem causes into categories (such as 4M, 6M, …) | Easy to use<br>Visual<br>Promotes structure | Difficulty in dividing the problems into categories and identifying the root cause from there |
| **5 whys** | A method that explores the underlying cause-and-effect of a problem | Discover the root cause of a single cause | Easy to use<br>Finds the root cause | Requires a wide knowledge of the problem<br>Only analysis one cause at a time |
| **5 whys tree** | A method that explores the underlying cause-and-effect of a problem | Narrow down and eliminate possible causes in a diagram | Considers more than one cause | Requires a wide knowledge of the problem |
| **FMEA** | Systematic method for evaluating a process | Identify the failure modes of a process to reduce or eliminate the associated risk | Promotes structure<br>Identifies areas of concern | Requires a wide knowledge of the process<br>Dependent on the team<br>Risk of being too detailed |

**Key Performance Indicators**, known as KPI, are a set of measurable indicators that support the purpose and goals of the organization, whilst helping identify sources of variation. There are different types of KPI such as operation, financial, etc. Table 2.2 illustrates four primary lean metrics [14].

Table 2.2: Most used KPI in operations

| | First Time Through (FTT) | Total Dock to Dock Time (DTD) | Build to Schedule (BTS) | Overall Equipment Effectiveness (OEE) |
|---|---|---|---|---|
| **Definition** | Percentage of finished product that guarantee quality requirements. | Time between unloading the raw materials and release of finished product for expedition | Percentage of planned items for a certain day, produced in the right day, volume and sequence | Measures availability, performance and quality typically for the bottleneck |
| **Connection to Lean** | Zero defects / Zero Waste | Zero defects / Zero Waste<br>Continuous flow and JIT | Align capacity with market demand | Availability, speed, and quality |
| **Advantages** | Improves the process's quality<br>Reduces the need for stock<br>Reduces the need for replanning<br>Increases BTS and OEE values | Reduces the need for stock<br>Reduces the need for replanning<br>Increases BTS and OEE values<br>Reduces working capital | Reduces Setup times<br>Ability to achieve clients' expectations and increase wallet share | Reduces processing time and DTD<br>Stabilized and predictable processes, increase BTS |

## 2.3 Lean and the pharmaceutical industry

The pharmaceutical industry has a slower moving adjustment pace to manufacturing efficiency and productivity, due to high costs and all the concern of regulatory problems whilst revalidating process changes. However, as mentioned in the first chapter, the FDA through the PAT initiative, supports innovation and efficiency in a cGMP environment. This is a framework that provides a "set of scientific principles and tools supporting innovation and a strategy for regulatory implementation that will accommodate innovation". In its essence, PAT is a system that thrives so that quality is integrated in the products by design and not by testing it into products; it designs, analyses and controls manufacturing through timely measurements of raw materials, in-process materials, the process itself and critical quality [15].

Table 2.3 compares some aspects between cGMP and lean manufacturing [11,12].

Table 2.3: Comparing cGMP and lean manufacturing

| **Area** | **cGMP** | **Lean** |
|---|---|---|
| Purpose | Ensure product effectiveness<br>Prevent harm | Reduce waste<br>Create value |
| Focus | Product development, manufacturing, and quality assurance | Value stream |
| Approach to manufacturing | Quality first | Quality balanced with productivity |
| Improvement | Regulated and prudent | Continuous and simultaneous |
| Goals | Follow validated processes<br>Prevent deviation | Reduce cost<br>Improve quality<br>Decrease Cycle Time<br>Reduce inventory<br>Improve delivery |
| Tools | Personnel qualifications<br>Personal hygiene<br>Organization of the workspace<br>Documentation<br>Validation and qualification<br>Audits | VSM<br>5S<br>5W<br>A3 report<br>FMEA<br>Standard Work |

Fundamentally lean pharma determines how the current manufacturing procedures can be modified to support improvements while maintaining the technical standards, to ensure no risk to the product. This can be achieved by standard work, clear relationships between customer and supplier, simple flow, and scientific improvement [16].

In the pharmaceutical world, Corrective Action and Preventive Actions (CAPA) have been implemented to detect patterns and trends in nonconformities and other system problems, which then are the focus of a root cause analysis to identify causes and preventive actions, as the name indicates. This analysis should start by in identifying the problem, evaluate its magnitude (assessing risk as well), investigate and assign responsibility, and lastly analyse and document the root cause of the problem [18].

**So how does the pharmaceutical industry face throughput increase in a batch plant?**

The basis of continuous improvement is to implement habits that focus on problem solving and facing challenges. Due to companies being more aware of the need for employee qualification and motivation, Petrusch et al. (2019) implemented a Lean Learning Factory to respond to these needs and by displaying specific examples of the process and exercises to face the challenges, it was possible to increase the willingness of employees to participate in these sort of trainings and their know how to implement the concepts in daily challenges [19].

Koulouris et al. (2000) provide a systematic analysis for batch plants, where they define metrics that will characterize bottlenecks, through processing and utilization times. And conclude that the overall throughput can be improved by increasing batch sizes until a size bottleneck is reached, and later proceed with one of the three routes [2]:

- "increase the number of cycles per batch for the limiting procedure;
- rearrange the equipment assignment so that equipment with larger capacity is utilized for the limiting procedure;
- introduce new equipment."

Whilst this paper considers a single-product plant, which is similar to the case study at hand, it does not account for process time variability [2].

Petrides et al. (2002) affirm that to increase plant throughput, changes in batch size and Cycle Time reduction are effective, so they suggest the following strategy [20]:

- increasing batch size until one cyclical step operates at 100% use capacity;
- if the equipment uptime[2] is low, one should increase the number of cycles per batch for that equipment;
- if the maximum batch size is reached focus on Cycle Time reduction by eliminating bottlenecks;
- if a time bottleneck is caused by a single step with very long Cycle Time then a new equipment should be introduced;
- if a time bottleneck is caused by an equipment, then secondary operations should be moved to a non-bottleneck equipment (such as heating material) and lastly if the bottleneck analysis suggests buying new equipment, it is suggested to evaluate the overall project economic state, do not focus sole on the throughput increase.

Computer Aided Process Design (CAPD) can also be a tool to throughput increase since they allow for a systematic identification of the process bottleneck. Tan et. al (2006) published an article on debottlenecking a batch pharmaceutical production process where they define minimum Cycle Time of the process as the minimum time possible between the start of two consecutive

[2] Ratio of equipment's occupancy time over the plant Cycle Time

batches, therefore, the longest occupation time of the bottleneck equipment. Using a scheduling tool, it is possible to identify different improvement schemes which provide different minimum Cycle Times by changing the layout or adding a new equipment. The best outcome proved to reduce the minimum Cycle Time in 30 hours, increasing the annual production rate in 162% [21].

Jully et al. (2007) applied CAPD to a batch pharmaceutical production, and through two different approaches, one where the raw material feed was increased to the maximum capacity of the equipment and the second where new equipment was introduced, the annual process throughput was increased in 25% [22].

Papavasileiou et al. (2007) wrote on how to optimize manufacturing of pharmaceutical products with process simulation and production scheduling tools; through an example where the process already operates at its maximum batch size, reducing the Cycle Time of the time bottleneck equipment was the only option for throughput increase. The scheduling tool proved to minimize late orders and reduce inventories, by generating accurate production schedules, which allowed for a better capacity analysis and debottlenecking tasks [23].

Velumani & Tang (2017) used a discrete event simulation in a tire manufacturing process to help identify how the production proceeds in a specific batch size as well as production bottlenecks; by including the pull-out based changes the process time was reduced as well as reductions to the bottleneck, tardiness and increase in the production efficiency [24].

Karam et. al (2018) implemented SMED in a pharmaceutical industry to decrease changeover times. First, they analysed the data and defined the baseline capability, and did a root-cause analysis for the observed standard deviation; after externalizing and implementing simultaneous steps, an A3 Changeover scheme was created to assure visual guide for the team, this way each person had access to a task, target, and the changeover steps. By involving the operators in this process, their ideas were key to a successful implementation. The changeover time decrease by 30%, and by completing the control phase and further improvement it is expected to have a total decrease near 37% [25].

In a general manner, reducing Cycle Time can be the obvious choice for companies which do not have the current ability to increase batch size. With this is mind, several articles are written on how to proceed with this reduction.

PAT implementation on different companies has proven to reduce production Cycle Times, improved manufacturing efficiency, reduced rejects, and increased production operating time [26].

To facilitate the process analysis and debottlenecking tasks, it has been proven by different authors that implementing production scheduling tools in the manufacturing of pharmaceuticals generates feasible production schedules and enables the process engineers to efficiently handle process delays and equipment failures (reducing downtime) [15, 22, 23].

Several authors consider that bottleneck control in real-time production, optimizing the initial buffer adjustment, and predicting order lead times can lead to improvements in production and reducing the manufacturing Cycle Time [24, 25].

Byrne et al. (2021) developed a 7-step customized problem-solving methodology, as seen in Figure 2.3, to reduce downtime in a manufacturing site without affecting the production required to fulfil demand whilst increasing product quality [31]:


Figure 2.3: Seven-step problem-solving methodology [31]

- Step 1: focuses on identifying top losses within a production line, using a VSM; data was also gathered regarding the OEE for production line downtime and production time losses.
- Step 2: Loss stratification serves to narrow the scope of the problem.
- Step 3: Next, projects are prioritized according to their benefit, impact, and the necessary resources.
- Step 4: According to the authors, the team required to solve the problem is supposed to be diverse in terms of knowledge and should be composed of 3 to 7 people.
- Step 5: The problem-solving step should start with an A3 report, followed by developing the 5W; a standard work instruction should also be developed; a Gemba Walk should be performed to visualize the different types of defects and granularity around the number of stops. After gathering the line issues, a root cause and preventive action should be assessed.
- Step 6: This can be completed with a Future VSM, where the ideal state of the manufacturing system is represented.
- Step 7: Is very important to keep similar problems from happening again, as well as implementing similar ideas and methodologies in similar production processes.

With this methodology, the plan successfully determined root causes and implemented corrective actions; eliminated the problems under investigation without negatively impacting cost, production time, or product quality [31].

## 2.4 Course of action

According to all the previously listed information, my suggested approach to throughput increase of the API would be to first define the problem, following the PDCA cycle. I would make sure to gather a team and explain our goal to make sure everyone is focused on it. Then gather all the historical data of the process and map it, through a VSM, for example, where it would be ensured that the production process is well understood. Later it is important to define the baseline for all matters, such as throughput, Cycle Time, downtime (using a Pareto diagram), and molar yield.

A FMEA exercise would be done on all intermediates to predict if a batch size increment is possible.

Through the Cycle Time analysis, I would determine the longest operations and evaluate if it would be possible to reduce their duration, to reduce the Cycle Time. This is where the identification of the bottleneck would be possible, allowing a greater focus on this equipment. By understanding the process and identifying the bottleneck, it would be possible to plan the batch overlap that would lead to a greater bottleneck efficiency. Using a scheduling tool would generate feasible production schedules and enable the process engineers to efficiently handle process delays.

Following the gather of the downtime events, a Pareto chart would be used to identify the most repetitive cause, and later on, a cause-and-effect diagram would be created to ensure root-cause analysis. Afterward, the previous CAPA could be checked to ensure that the proper actions are currently in place.

After these studies were conducted, I would implement *Hourensou* meetings, where a report from the previous day would be presented and the chosen KPI, such as throughput adherence, Cycle Time adherence, yield adherence, downtime, would be discussed, ensuring that the “Check” part of the PDCA Cycle. To ensure knowledge management, an A3 report would be created so that products with similar manufacturing processes, can benefit from the lessons learned during this project.

A yield increase would increase the throughput; therefore, a mass balance study should be conducted for all the processes. A sampling strategy would have to be put in place, to identify the steps where yield losses could occur, such as sampling of the aqueous and organic phases, mother liquors, and washing solution. The analytical method errors must be taken into account [32, 33].

# 3. Methodology

This chapter presents a detailed account of the methodology adopted to conduct this research, which was based on the literary review and the decisions from both the technical production team and the Operational Excellence team at Hovione.

The APIs' throughput is calculated by Equation 3.1, where the output is the quantity of Final Product obtained in each campaign; the total available time reflects the campaign lead time (considers the difference between the end of Last Batch and the start of the 1st batch) without the shutdown periods and overlapping of batches.

$$\text{Throughput} = \frac{\text{API output (kg)}}{\text{Total available time (h)}} \tag{3.1}$$

The goal was to increase the APIs' throughput by 10%, to keep this in mind throughout the campaign, Cycle Time targets for each intermediate were established. Using Equation 3.2 it is possible to calculate the target Cycle Time for each batch of all intermediates.

$$\text{Target Cycle Time for intermediate x} = \frac{\text{Average output of intermediate x (kg)}}{\text{Target throughput (kg/h)}} \tag{3.2}$$

The average output considered all previously manufactured batches and the target throughput was set for an increase of 10% compared to the baseline of each intermediate.

During the duration of the project, daily meetings known as TOP15, due to their 15-minute duration, were implemented to review the last 24-72h of production line execution, understand the causes of lost time or anticipations and act immediately to put in place mitigation actions to prevent reoccurrence; further information on this meeting can be found in Figure I.1 of Annex A.

TOP60 (1 hour duration) meetings were implemented on a weekly basis, to review the weeks top losses in the production line and ensure mitigation actions have been put in place, review the progress in reducing CT on the bottleneck and review the improvement actions for yield; further information on this meeting can be found in Figure I.2 of Annex A.

In Figure 3.1 the followed methodology is represented under the project's goal, focusing on three fronts to achieve it. This plan resembles a PDCA cycle due to its phases: plan, do, check, and act.

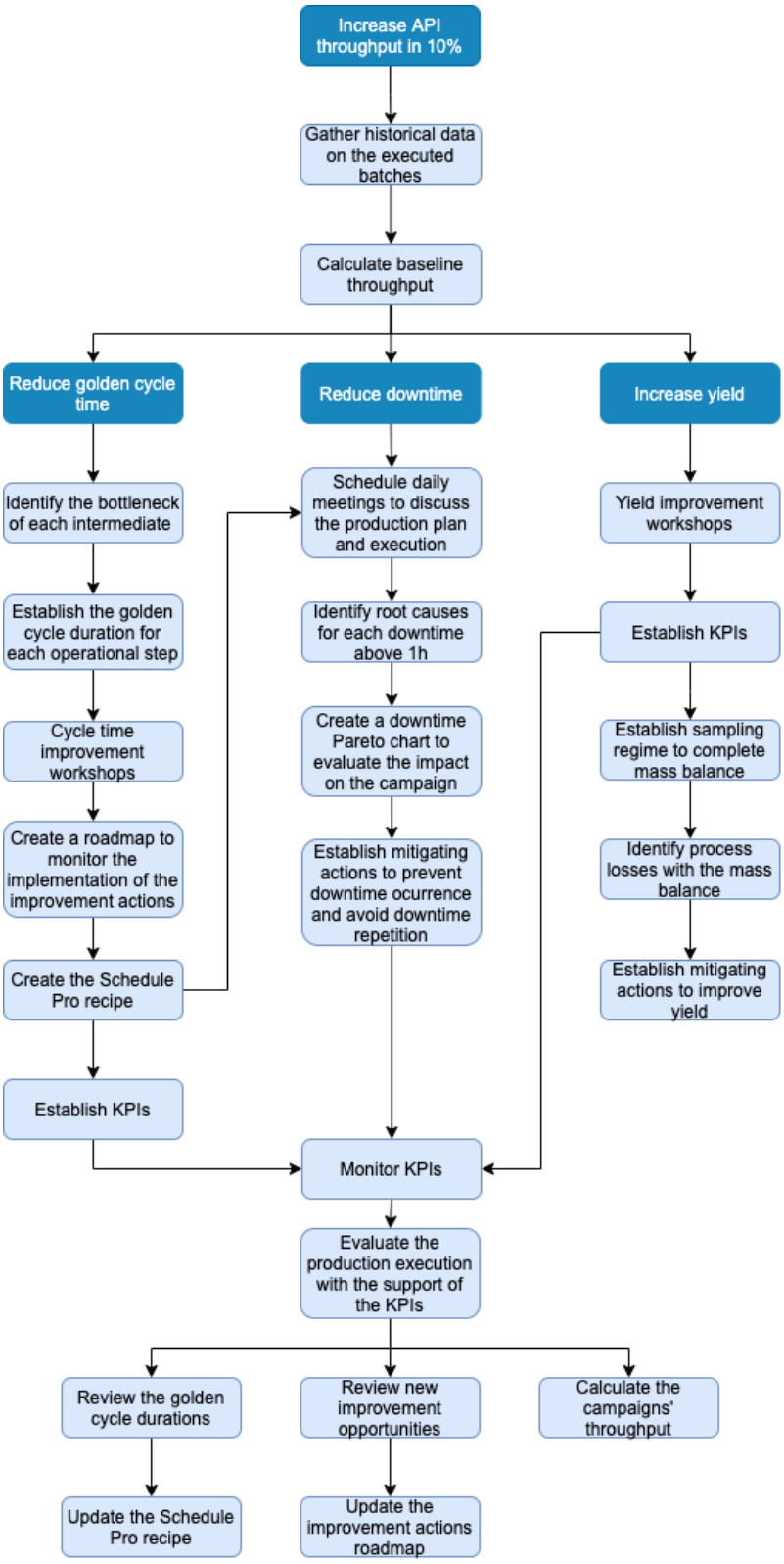


Figure 3.1: Diagram of the projects' methodology

## 3.1 Golden Cycle Time Reduction

To improve the processes' Cycle Time, the goal was to ensure the bottleneck was always running at maximum speed, eliminating idle times; this is easily done when the equipment is used downstream to the bottleneck, however, if there is equipment used upstream to the bottleneck it is necessary to define trigger points so that the bottleneck is not affected by possible downtime. The bottleneck equipment is defined as the equipment with the highest total occupancy time, Figure 3.2 serves as an example of how the bottleneck was defined for each of the intermediate steps.

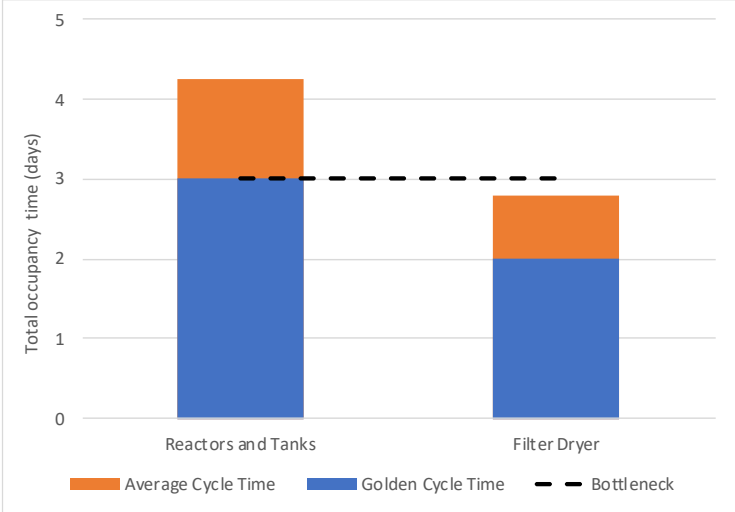


Figure 3.2: Example for bottleneck identification

Using the baseline data, the golden Cycle Time duration was established by Equation 3.3.

$$\text{Golden Cycle Time} = \sum_{i=1}^{n} \min\left(\text{bottleneck step } i\right) \tag{3.3}$$

These Cycle Times had to be validated by the production team, to see if they were feasible and replicable in terms of the current resources and restrictions. Of course, there are exceptions to this equation, since there are operations that are related between them, for example, a faster filtration can indicate that the mother liquors were not properly pulled therefore the drying can take longer – these operations should be evaluated together by batch.

Besides planning for success by achieving the golden Cycle Time in each batch, there was also the goal to challenge the team in improving the golden CT itself. This was done with different workshops for each intermediate, where the bottleneck steps with the longest execution times, in the previous batches, were made a priority and the focus of the brainstorm. In these workshops, the production engineers and the supporting operational excellence team brainstormed different actions that would improve the process. The actions from these sessions were displayed in a plot that analysed complexity and value. An example is showed in Table 3.1 and Figure 3.3.

Table 3.1: Example of improvement opportunities

| Action | Opportunity | Action description | Potential impact | Potential effort |
|---|---|---|---|---|
| **1** | Sample drying after 8h of temperature stabilization | Collect samples both after 4 and 8h after temperature stabilization since the sample always meets the criteria | 4h | 18h |
| **2** | Stirring profile during drying is not standardized | Evaluate *DeltaV*™ data and establish standards according to sampling results and the shortest duration | 8h | 8h |
| **3** | Temperature stabilization is visually identified by the operators | Evaluate *DeltaV*™ data to establish the variation of the temperature in a set period, for example, 30 minutes, to help the operators define "stable temperature" | 0.5h | 8h |

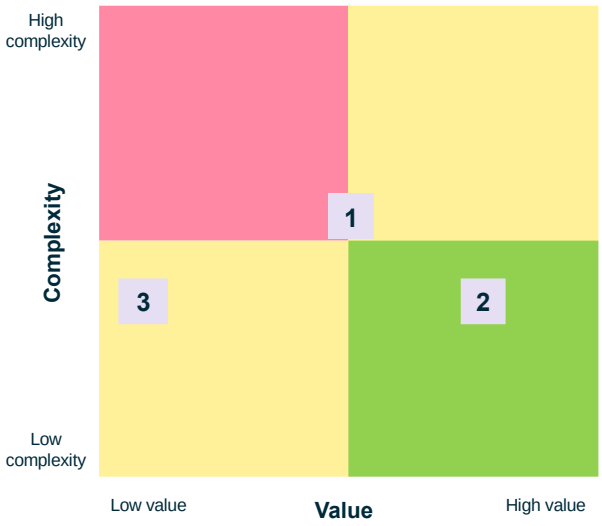


Figure 3.3: Example of complexity and value plot of the improvement opportunities

The potential impact referred in Table 3.1 reflects the hours saved on the average Cycle Time, and the potential effort reflects the time invested by the team on implementing the action. After analysing the plot, the actions should be reviewed to establish priorities and ensure everyone is aware of their responsibilities in implementing them.

The KPI used for this parameter was the bottleneck efficiency, calculated by Equation 3.4.

$$\text{Bottleneck Efficiency} = \frac{\text{Golden Cycle Time}}{\text{Start of bottleneck steps of batch } n+1 \; - \; \text{Start of bottleneck steps of batch } n} \tag{3.4}$$

## 3.2 Downtime Reduction

In previous campaigns, the few recorded downtimes were associated with either the start of the batch or the finish of the batch. With the implementation of the golden Cycle Time and the occupation of the bottleneck planning strategy, it is important to track each step to better understand the process. The operators insert the real-time of each operation into the *SchedulePro*™ software

from Intelligen, Inc. and daily in the TOP15 meeting, the delays over one hour are mentioned to discover the root cause; this method was chosen since the delays over one hour are the ones with greater impact on the process and the company does not have resources and capacity to investigate all the delays.

The KPI for downtime consists of a chart similar to a Pareto, where the downtime will be represented against the Cycle Time. Figure 3.4 serves as an example.

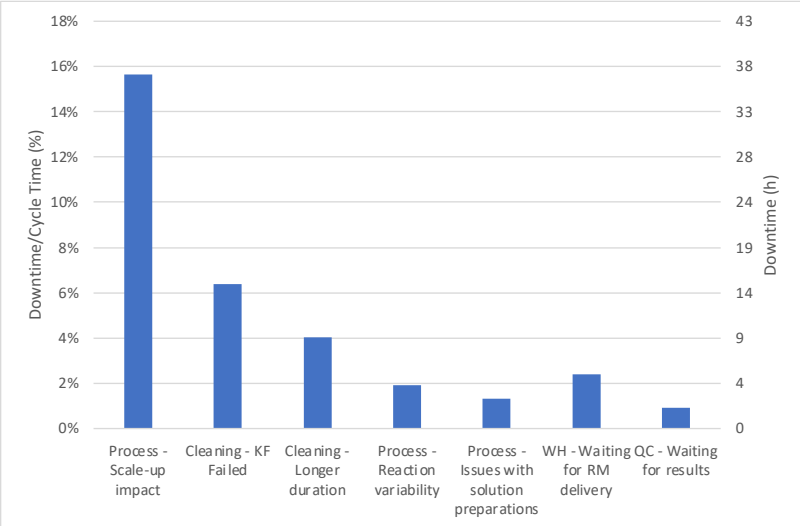


Figure 3.4: Example for recorded downtime

## 3.3 Yield Improvement

The molar yield values were calculated using Equation 3.5.

$$\text{Molar yield (dry basis)} = \frac{\frac{\text{Packed product (g)}}{\text{Molecular weight } (\frac{\text{g}}{\text{mol}})} \times \text{Assay } \left(\%\frac{\text{w}}{\text{w}}\right) \times \text{ (1-\% of solvents)}}{\frac{\text{Starting Raw Material (g)}}{\text{Molecular weight } (\frac{\text{g}}{\text{mol}})}} \quad (3.5)$$

To increase yield, a mass balance study was performed to identify the main losses and implement corrective actions. The first step consists in identifying every possible loss of product, this was done whilst studying each intermediate process flow, in Figures 1.2 to 1.6 from Chapter 1. Reaction steps have IPC samples in place, therefore it is possible to assess unconverted SRM, however, it was necessary to implement new informative samples, to measure the loss of product in operations like phase splits, filtration, and washes. This mass balance is considered incomplete, since it was focused on yield, to characterize the transformation of SRM in product as well as account for possible physical losses. The unconverted SRM was estimated by comparing peak areas from the reaction samples; the remaining samples had an assay analysis that allowed to estimate the amount of product present by Equation 3.6.

$$\text{Loss product (kg)} = \text{Assay } \% \left(\frac{\text{w}}{\text{w}}\right) \times \text{Volume (L)} \times \text{Density } \left(\frac{\text{kg}}{\text{L}}\right) \quad (3.6)$$

When the production of each intermediate came to an end, there was a review meeting to discuss its performance. These meetings focused on the operations with the highest difference from the golden cycle (either longer or shorter), and steps that had an impact on quality, to discover the root cause and improve in the next campaign; the golden cycle was reviewed, and the *SchedulePro*™ Recipe was updated.

# 4. Analysis and discussion of results

This chapter will present the results achieved for each of the intermediates and Final Product, by detailing the production plan that was followed and analysing the performance in each of the focus areas.

## 4.1 Throughput targets

The API baseline throughput values are represented in Table 1.4, in Chapter 1. Considering the average throughput of the previous campaigns (validation – with three batches of each process- and two commercial - a total of five batches for each process), the target throughput for this campaign is 1.38 kg/day.

To increase the throughput there is the option to increase the batch size, there was a FMEA conducted, previously to this study, to assess this option for Intermediates 1 and 2. A scale-up for Intermediates 3, 4, and Final Product is not possible since the equipment, mainly the filter dryer, would no longer be suitable for the volumes in question. Previously, Intermediate 2 had high losses of yield associated to the scale-up batch, therefore in this campaign there will only be a scale-up of the Intermediate 1 batches, from 50 kg to 100 kg of SRM.

To monitor the process throughout of the campaign, there were throughput and Cycle Time targets set for each intermediate, available in Table 4.1. The throughout target for the intermediates was set for a 10% increase.

Table 4.1: Throughput baseline and targets for the intermediates

| Intermediate | Baseline total available time (h) | Baseline total output (kg) | Baseline Throughput (kg/day) | Target Throughput (kg/day) | Expected output (kg) | Target Cycle Time |
|---|---|---|---|---|---|---|
| Intermediate 1 | 1 198 | 475.09 | 9.52 | 10.47 | 59.39 | 5d -16h |
| Intermediate 2 | 1 628 | 436.52 | 6.44 | 7.08 | 54.57 | 7d - 16h |
| Intermediate 3 | 808 | 315.88 | 9.38 | 10.32 | 39.49 | 3d - 19h |
| Intermediate 4 | 2 324 | 660.56 | 6.82 | 7.50 | 82.57 | 11d |
| Final Product | 1 362 | 429.86 | 6.88 | 7.57 | 55.75 | 7d - 8h |

Note that the targets for Intermediate 1 were established for 50 kg batches; the targets will only be adjusted for 100 kg batches after this campaign.

## 4.2 Bottleneck identification

Table 4.2 represents the bottleneck – the equipment or set of equipment with the highest total occupancy time- for each intermediate. This was achieved with the aid of Appendix A. The times of occupancy for each equipment include the average duration of the cleaning procedures since it is necessary to execute these steps to start the next batch.

Table 4.2: Bottleneck identification of the intermediates

| Intermediate | Bottleneck |
|---|---|
| **Intermediate 1** | Reactors and Tanks |
| **Intermediate 2** | Reactors and Tanks |
| **Intermediate 3** | Filter Dryer |
| **Intermediate 4** | Filter Dryer |
| **Final Product** | Reactors and Tanks |

## 4.3 Production Plan

The production plan for this campaign is present in Figure 4.1.

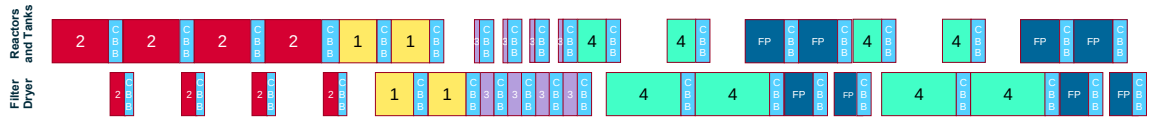


Figure 4.1: Production plan for the campaign

As mentioned in the methodology chapter, the goal is to keep the bottleneck running and plan to start the next batch as soon as the bottleneck is available. Even though the team had this in mind, it was not possible to implement it in every intermediate.

Due to a mitigation plan in place, after the failed scale-up attempt in the previous campaign, it was not possible to start the Cleaning Between Batches (CBB) immediately after the first cake wash. The overlap of Intermediate 2 batches is represented in Figure 4.2.

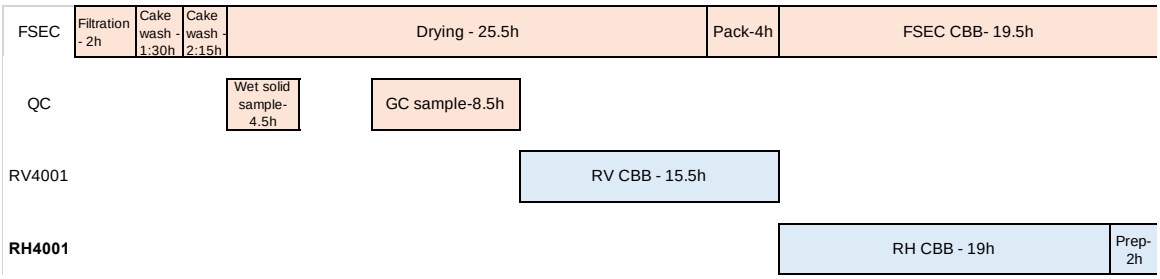


Figure 4.2: Batch overlap for Intermediate 2

The batches of Intermediate 1 were scale-up batches (from 50 to 100 kg of SRM) and the plan was to start the second batch as soon as the reactors were cleaned.

On the changeover from Intermediate 1 to Intermediate 3, it was not possible to optimize the utilization of the reactor set, due to a quality constrain. A batch of Intermediate 3 can only be started when it is assured that the FSEC will be available to perform the filtration, since for this process no holding points were validated. A similar approach was executed for the changeover between batches of Intermediate 3, as represented in Figure 4.4.

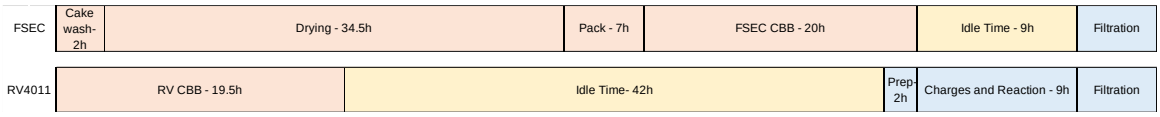


Figure 4.3: Changeover plan between Intermediate 1 and Intermediate 3

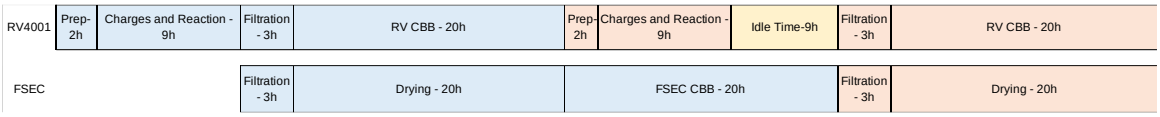


Figure 4.4: Batch overlap for Intermediate 3

The changeover plan between Intermediate 3 and Intermediate 4, represented in Figure 4.5, is simpler since the bottleneck is the same. For this changeover, there would always be planned idle time on the bottleneck, since the drying, packaging and cleaning of Intermediate 3, is faster than the cleaning and operations leading to the filtration of Intermediate 4; the ideal plan would be to start the preparations immediately after the RV CBB, reducing the idle time in 14 hours, however this was not possible to implement due to a team decision to wait for the drying IPC sample results.

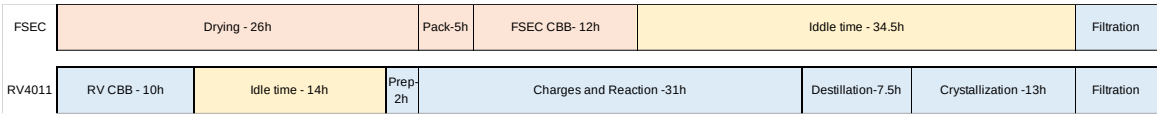


Figure 4.5: Changeover plan between Intermediate 3 and Intermediate 4

The plan for Intermediate 4 batch overlaps is represented in Figure 4.6.

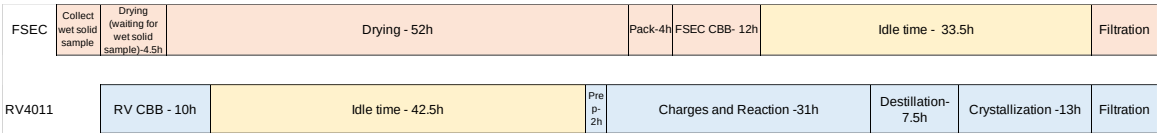


Figure 4.6: Batch overlap for Intermediate 4

The changeover plan between Intermediate 4 and Final Product is represented in Figure 4.7 and the batch overlap for the latter is in Figure 4.8. This changeover entails a bottleneck change, therefore there was planned idle time for the Final Products' bottleneck, since it was not possible to start the batch before having the result from the wet solid sample. During the batch overlap for Final Product, there is planned idle time of 1.5 hours, due to waiting for results.

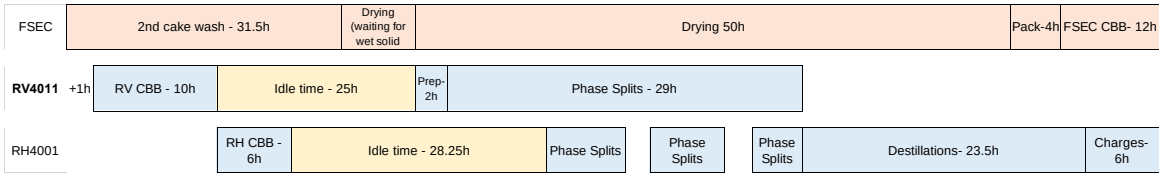


Figure 4.7: Changeover plan between Intermediate 4 and Final Product

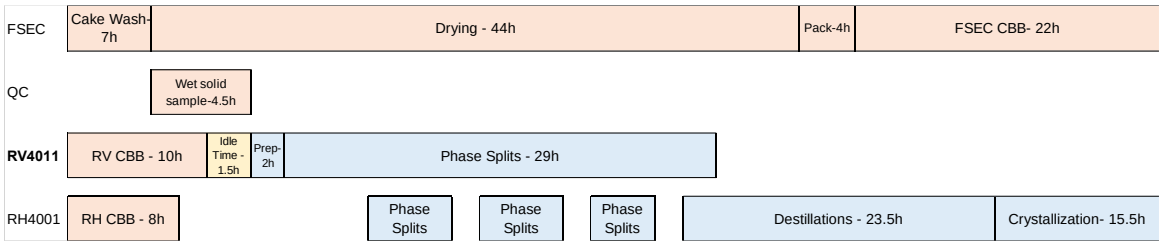


Figure 4.8: Batch overlap for Final Product

## 4.4 Golden Cycle Time Reduction

### 4.4.1 Efficiency targets

Table 4.3 illustrates the golden Cycle Time, Baseline and target values for average Cycle Time and bottleneck efficiency.

Table 4.3: Baseline and target values for CT and bottleneck efficiency

| Intermediate | Baseline Average CT | Golden CT | Baseline Bottleneck Efficiency | Target CT | Target Bottleneck Efficiency |
|---|---|---|---|---|---|
| Intermediate 1 | 5d - 22h | 4d - 2h | 69.3% | 5d - 16h | 72.1% |
| Intermediate 2 | 8d - 11h | 4d - 19h | 56.6% | 7d - 16h | 62.2% |
| Intermediate 3 | 5d - 4h | 1d - 21h | 36.5% | 3d - 19h | 49.5% |
| Intermediate 4 | 12d - 1h | 6d - 6h | 52.0% | 11d | 57.0% |
| Final Product | 8d - 1h | 4d - 6h | 52.7% | 7d - 8h | 57.8% |

Note that the baseline considers all batches from the validation and two commercial campaigns.

### 4.4.2 Improvement opportunities

With the aid of the production engineers and the supporting operational excellence team, the improvement opportunities of the processes were studied, and it was necessary to estimate the impact and effort before going forward with the implementation. The potential impact reflects the hours saved on the average Cycle Time and in Appendix B the potential effort is detailed for each improvement opportunity.

- **Intermediate 1**

For Intermediate 1, the improvement opportunities, represented in Table 4.4 and Figure 4.9, were focused on the reactions.

Table 4.4: Improvement opportunities for Intermediate 1

| Action | Opportunity | Action description | Potential impact | Potential effort |
|---|---|---|---|---|
| **1** | Reaction 3 reaches a plateau after about 9h but runs for 20h | Increasing aliquot in sample preparation to catch more solids; ensure sampling procedures are done consistently and correctly on the production side | 10h | 15h |
| **2** | Improve the conversion of reaction 3 | Study a faster NaOH transfer to increase the conversion rate of the reaction | Undetermined | 8h |
| **3** | The second sample of Reaction 2 always meets the criteria | Take the 2nd sample 1h after the 1st, instead of 3h; Note: if the QC doesn't deliver the result after 3h, sample again | 2h | 19h |
| **4** | Reaction 1 sample release is 2h over the time established by the QC team | Update the analytical method instruction | 2h | 15h |

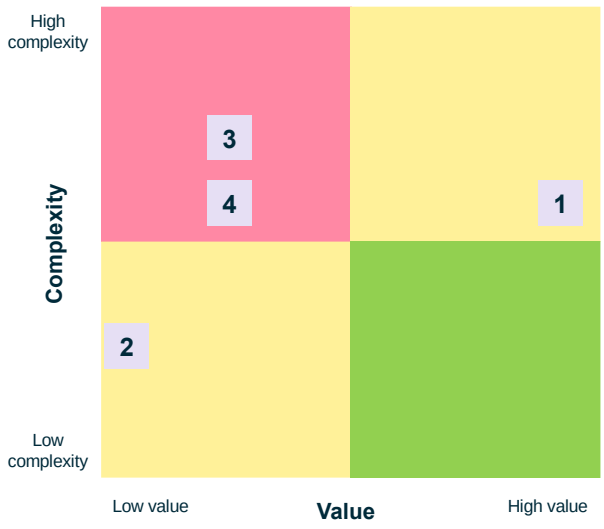


Figure 4.9: Complexity and value of the improvement opportunities for Intermediate 1

Due to these batches being the first attempt of a scale-up, the team did not want to risk testing action #2. All other actions were implemented, actions #1 and #4 proved effective since the QC waiting downtime reduced drastically compared to the previous batches; the additional sample for #3 did not meet the criteria.

- **Intermediate 2**

The improvement opportunities for Intermediate 2 are represented in Table 4.5 and Figure 4.10.

Table 4.5: Improvement opportunities for Intermediate 2

| Action | Opportunity | Action description | Potential impact | Potential effort |
|---|---|---|---|---|
| **1** | Time for sampling Reaction 1 is 24h and the sample always meets the criteria | Take additional sampling after 20h to evaluate if the threshold is reached earlier | 2h | 18h |
| **2** | Heating and cooling operations with long durations | Evaluate *DeltaV*™ data to establish the heating/cooling profile and identify possible improvements | Undetermined | 6h |

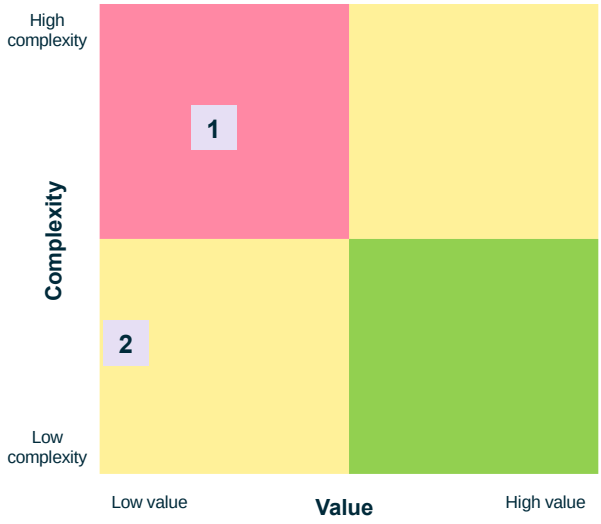


Figure 4.10: Complexity and value of the improvement opportunities for Intermediate 2

The Technical Services chemist provided evidence that during the laboratory trials, the reaction reached the threshold only after 24 hours and that was no sufficient basis to trial the sample from action #1, therefore this was not implemented. After analysing the data from action #2, it was concluded that the team was executing these operations the best they could, with the right settings on the jacket temperature and switching to a high performance pump at the right moment (when the flow rate decreases).

- **Intermediate 3**

Intermediate 3 has a very low Golden Cycle (GC), so any improvement will provide a high increase in productivity. The improvement opportunities represented in Table 4.6 and Figure 4.11 were focused on the drying step.

Table 4.6: Improvement opportunities for Intermediate 3

| Action | Opportunity | Action description | Potential impact | Potential effort |
|---|---|---|---|---|
| **1** | Sample drying after 8h of temperature stabilization | Collect samples both after 4 and 8h after temperature stabilization since the sample always meets the criteria | 4h | 18h |
| **2** | Stirring profile during drying is not standardized | Evaluate *DeltaV*™ data and establish standards according to sampling results and the shortest duration | 8h | 8h |
| **3** | Temperature stabilization is visually identified by the operators | Evaluate *DeltaV*™ data to establish the variation of the temperature in a set period, for example, 30 minutes, to help the operators define "stable temperature" | 0.5h | 8h |

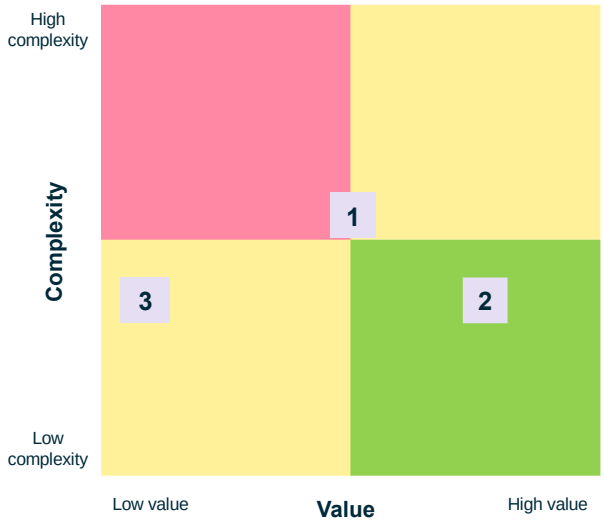


Figure 4.11: Complexity and value of the improvement opportunities for Intermediate 3

Action #1 revealed that the sample did meet the criteria after only 4 hours. Actions #2 and #3 led to a more standardized drying process and even a new GC record.

- **Intermediate 4**

Intermediate 4 was the product with the highest number of improvement opportunities since the filtration and drying steps have a lot of variability associated. Even though some of the steps do not bring immediate value to the process, they will prove of value in future campaigns. These opportunities are represented in Table 4.7 and Figure 4.12.

Table 4.7: Improvement opportunities for Intermediate 4

| Action | Opportunity | Action description | Potential impact | Potential effort |
|---|---|---|---|---|
| **1** | The filtration cake feed is not standardized | Establish fixed quantities of cake feeding | 4h | 10h |
| **2** | Standardize compaction time | Measure final volume of mother liquors | 8h | 6h |
| **3** | Standardize end of filtration steps | Identify relation between SRM and final mother liquors + washing volume | Undetermined | 4h |
| **4** | Standardize end of filtration steps | Measure the hourly flow rate of the mother liquors and washing solution | N/A | 8h |
| **5** | Crystallisation | Standardize the cooling ramp between the reflux temperature and the cooling temperature | Undetermined | 8h |
| **6** | Temperature stabilization is visually identified by the operators | Evaluate *DeltaV*™ data to establish the variation of the temperature in a set period, for example, 30 minutes, to help the operators define "stable temperature" | 0.5h | 8h |
| **7** | Stirring profile during drying is not standardized | Evaluate *DeltaV*™ data and establish standards according to sampling results and the shortest duration | 3h | 18h |
| **8** | Sample drying after 8h of temperature stabilization | Collect samples both after 4 and 8h after temperature stabilization | 4h | 8h |

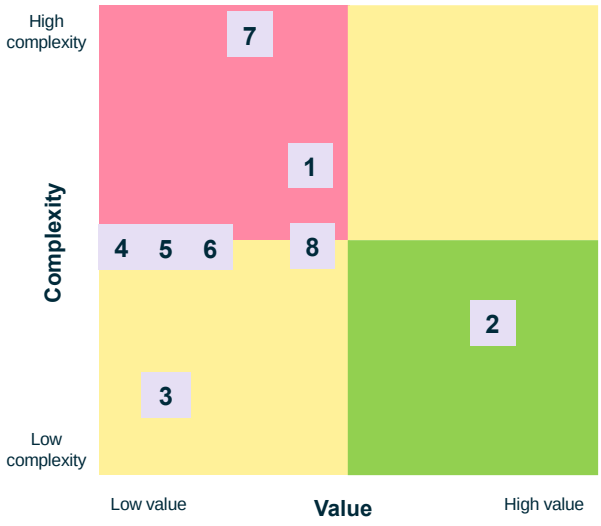


Figure 4.12: Complexity and value of the improvement opportunities for Intermediate 4

Action #1 was set as portions of 150L at a time with a 30-minute waiting hold, this was followed during the first batch but not in the second, having doubled the feeding time; therefore, this opportunity proved valuable and should be followed in future campaigns. Due to the tight production schedule, it was not possible to implement actions #3 and #5. Action #2 was executed however it did not allow to reduce the compaction time; further actions should be defined. Actions #6, #7, and #8 had a positive impact on the process and led to a new GC record, as presented in Chapter 4.4.3.

- **Final Product**

Finally, the improvement opportunities for the Final Product, present in Table 4.8 and Figure 4.13 proved to be the ones with the highest potential effort to implement since it needed a lot of additional studies, support from Technical Services, client approval, and change in the filing.

Table 4.8: Improvement opportunities for the Final Product

| Action | Opportunity | Action description | Potential impact | Potential effort |
|---|---|---|---|---|
| **1** | Cleanings between phase splits | Eliminate cleanings | 4.5h | 20h |
| **2** | In each phase split the organic phase is collected in the RH then transferred back to the RV to proceed with the next phase split | Evaluate how to minimize transfers between RV & RH during phase splits | 1.5h | 32h |
| **3** | There are four distillation steps, which summed have a long duration | Discuss with chemists the possibility to change the conditions with an appropriate software | 3h | 11h |
| **4** | The distillations' purpose is to replace dichloromethane (DCM) with acetone but there is not a sample at the end of each one | Test the DCM quantities after each distillation | 3h | 11h |

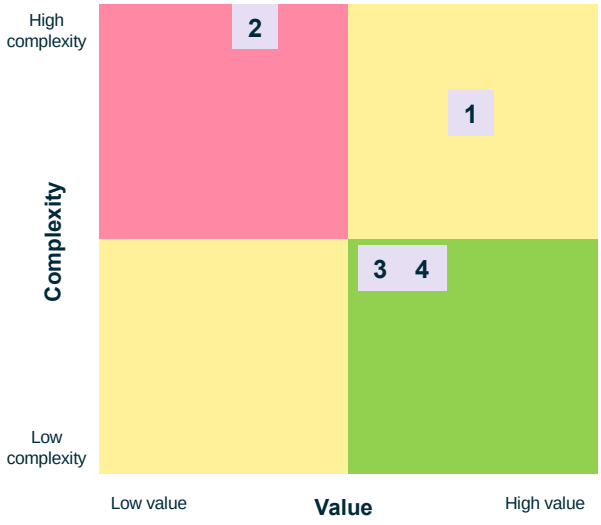


Figure 4.13: Complexity and value of the improvement opportunities for the Final Product

With the close deadline of the summer shutdown, the team was not able to implement any of the improvement actions.

### 4.4.3 Final results

In Table 4.9 the average batch Cycle Time of this campaign is compared to the baseline and golden Cycle Time.

Table 4.9: Results for average batch Cycle Time

| | Golden Cycle Time | Baseline Average CT | Average batch CT | Cycle Time comparison | Comments |
|---|---|---|---|---|---|
| **Intermediate 1** | 4d – 2h | 5d - 22h | 6d - 1h | +2% | Good results for a scale-up campaign<br>Batch overlap was ensured |
| **Intermediate 2** | 4d – 19h | 8d - 11h | 9d - 8h | +11% | The mitigation plan did not allow focus on this improvement project |
| **Intermediate 3** | 1d – 21h | 5d - 4h | 2d - 11h | -52% | The batches started as soon as possible according to the team, achieving great results.<br>With planned idle time, there is still more room to improve |
| **Intermediate 4** | 6d -6h | 12d - 1h | 9d - 8h | -23% | The batch overlap strategy was used correctly<br>This campaign did not present the need for reprocessing, which happen frequently on previous batches |
| **Final Product** | 4d – 6h | 8d - 1h | 6d - 15h | -18% | The batch overlap strategy was used correctly<br>This campaign did not present the need for reprocessing, which happen frequently on previous batches |

Although none of the batches performed below the golden Cycle Time, due to the improvement actions and standardization there were several operations in each of the intermediates that revealed a new best time, this can be found in Appendix C. After the campaign, the team evaluated what led to this improvement, to replicate it in the future, and updated the *SchedulePro*™ recipe to match the new golden cycle.

The KPI used to measure the reduction of the golden Cycle Time was the bottleneck efficiency since the goal was to ensure the bottleneck was always running at maximum speed, eliminating idle times. The following sub-points allow for a detailed study on each intermediate where the bottleneck efficiency is calculated, and it is possible to identify new golden Cycle Time.

- **Intermediate 2**

Before this campaign, a scale-up batch revealed a great loss in yield, so it was agreed to return to batches of 50 kg with additional precaution measures to ensure quality. The impact of this mitigation plan is evident in the results since steps such as phase splits and drying had a longer duration due to additional sampling and more caution whilst performing the operations.

As mentioned in Chapter 4.3, there was no batch overlap for Intermediate 2, decreasing the bottleneck efficiency. Figure 4.14 represents the production execution of this intermediate.

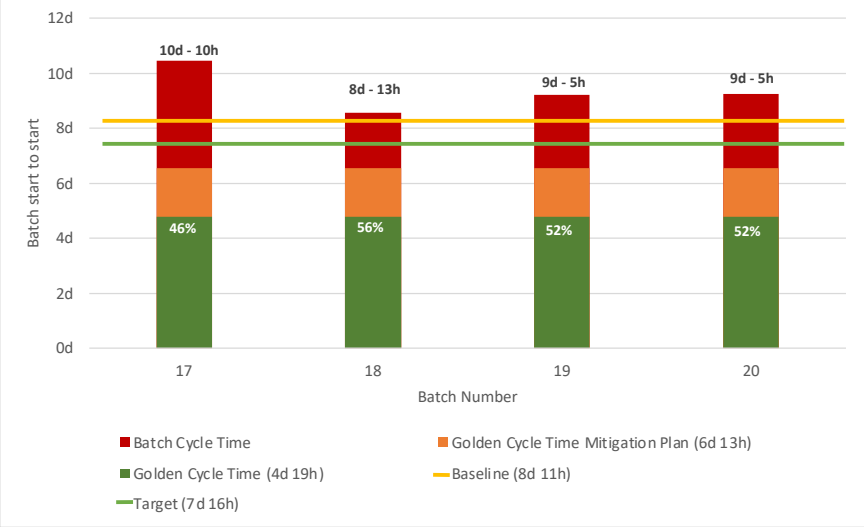


Figure 4.14: Bottleneck efficiency analysis for Intermediate 2

Batch 18 presented the best results of this campaign since it had smaller delays associated with operations such as distillations, crystallization and drying; it was also the only batch where it was possible to parallelize the CBB of the RH4001 with the drying and packaging, which allowed for the preparations of the next batch to start a few hours after the end of packaging.

Batch 17 was the longest due to it being the first batch with the mitigation plan in place; after that, it is possible to see an improvement trend due to the change in the team's behaviours and mindset. However, no batch met the target of 62.2% bottleneck efficiency.

Evaluating the data, if the approach was to overlap batches, the average bottleneck efficiency could have been 66.7%, saving this campaign a total of 8 days and 15 hours. The average batch Cycle Time increased 21 hours, an 11% increase.

- **Intermediate 1**

In Figure 4.15 the bottleneck efficiency analysis is represented for Intermediate 1.

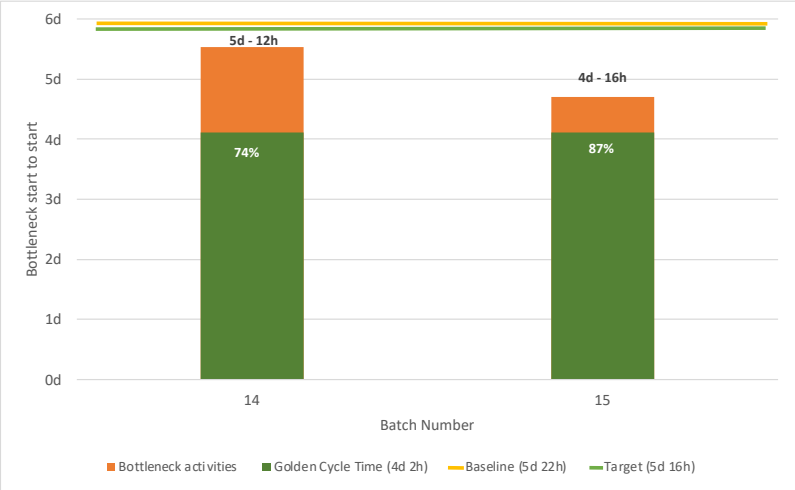


Figure 4.15: Bottleneck efficiency analysis for Intermediate 1

With a scale-up it is expected that some operations last longer, mainly the filtration, drying and packaging. As mentioned in Chapter 4.3, the strategy was to start the RV4011 CBB after the cake washes, which did happen, thus two of the most time-consuming operations where parallelized with the start of the next batch, contributing to a higher bottleneck efficiency.

The improvement actions also contributed to these results, with actions #1 and #4 proving a greater efficiency from the QC team to deliver the sample results.

Since between Intermediate 1 and Intermediate 3 there is a bottleneck change, for the bottleneck efficiency of batch 15 (Intermediate 1), the end time was considered as the end of the RV cleaning and not the start of the Intermediate 3s' batch.

Both batches performed above the bottleneck efficiency target. When assessing the average batch Cycle Time (considering start to start of batches), this increased by 3 hours, ergo -2%, a great result for a scale-up.

- **Intermediate 3**

As mentioned in Chapter 4.3, there was planned idle time for the bottleneck of Intermediate 3, in Figure 4.16 the non-bottleneck activities are represented and are relative to the operations that occur in the reactors.

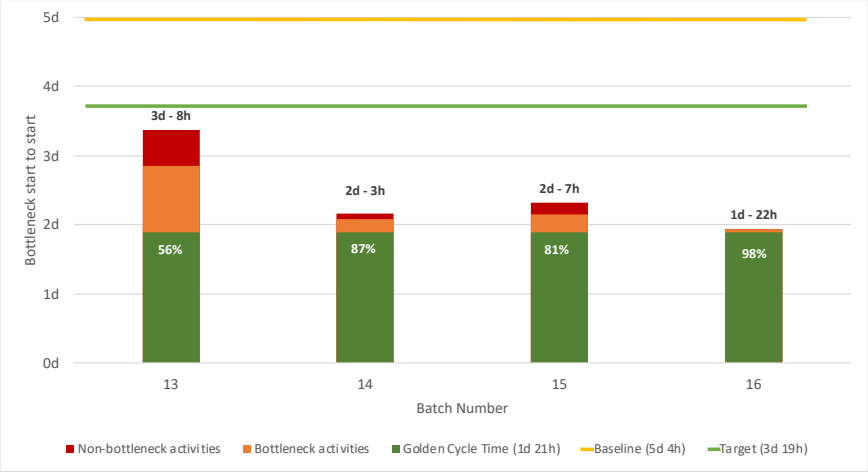


Figure 4.16: Bottleneck efficiency analysis for Intermediate 3

In this campaign, Intermediate 3 showed a high improvement on the Cycle Time due to standardizing the drying and implementing a new sampling regime as improvement actions. The downtimes were also lower, as discussed in the next sub-chapter. All batches met the target, however there were no bellow the Golden Cycle Time. The average batch Cycle Time decrease 2 days and 16 hours, 52% from baseline, this was the highest average Cycle Time decrease of intermediates when comparing to the baseline.

- **Intermediate 4**

Figure 4.17 represents the bottleneck efficiency for Intermediate 4.

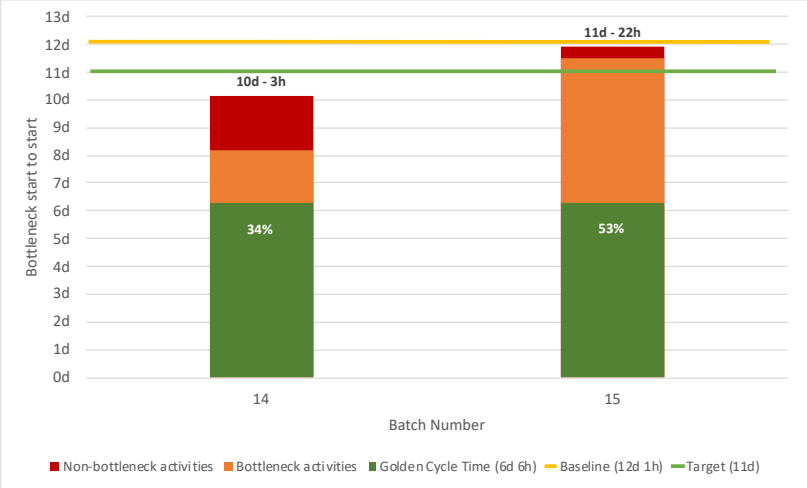


Figure 4.17: Bottleneck efficiency analysis for Intermediate 4

Due to the complications in both batches during the filtration and filter cake wash steps, the bottleneck efficiency target was not met. However, batch 14 was manufactured under the target Cycle Time. The average batch Cycle Time decreased 2 days and 17 hours, revealing a decrease of 23%, this was the best result in terms of Cycle Time reduction.

- **Final Product**

The performance from the Final Product is represented in Figure 4.18.

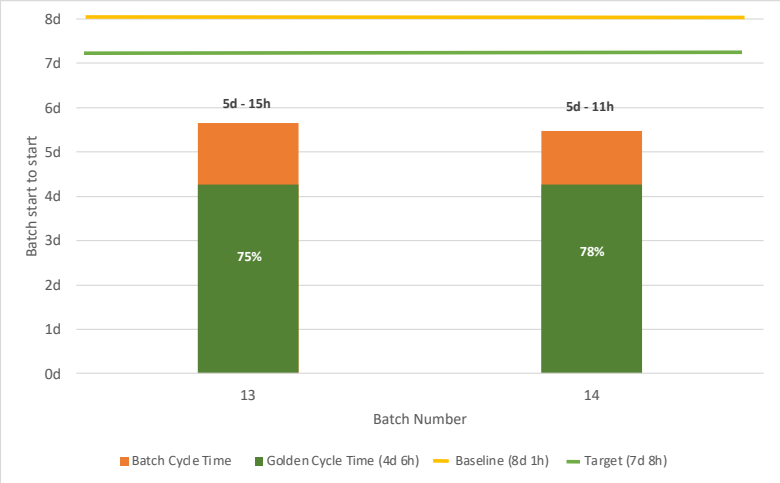


Figure 4.18: Bottleneck efficiency analysis for the Final Product

Both batches met the CT and bottleneck efficiency target. In terms of batch Cycle Time, these batches had a 18% improvement, by decreasing the average CT in 1 day and 10 hours.

This campaign was not finished since it was not possible to manufacture the remaining two batches of Intermediate 4 and Final Product, being the reason why the results are not shared.

## 4.5 Downtime Reduction

Every day, the production team evaluated the delays over one hour and recorded their root cause; this allowed the team to track what types of delays had the greater impact on the process and take mitigating actions to prevent them from reoccurring the following batches. The delays below one hour led to an unaccounted category.

- **Intermediate 2**

In Figure 4.19 it is possible to analyse the impact each type of delay had in all the batches of Intermediate 2. In Figure 4.20, the delays are reported per batch of Intermediate 2, to better understand when each type of downtime occurred and to see if was possible to avoid the reoccurrence on the following batches.

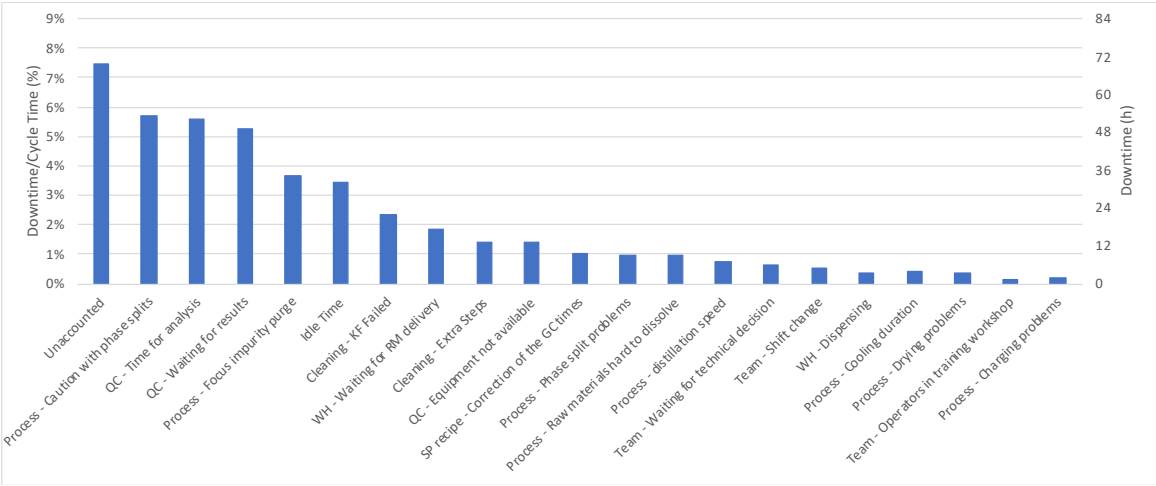


Figure 4.19: Recorded downtime in Intermediate 2

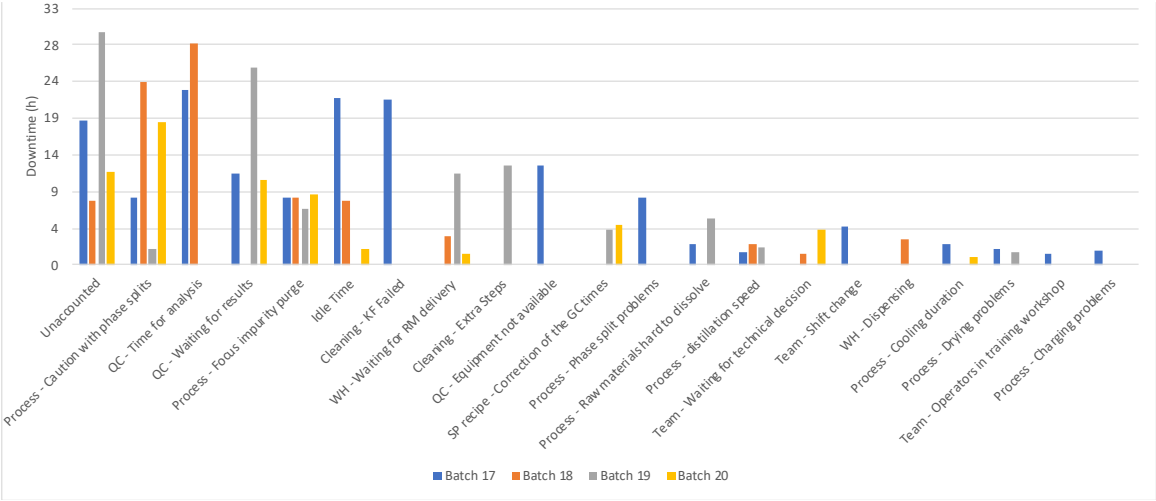


Figure 4.20: Recorded downtime per batch in Intermediate 2

As this process has so many detailed steps in the scheduling recipe, the small delays identified throughout the batches led to a high unaccounted value. The second highest downtime was related to the additional steps from the mitigation plan, so that the operators handled the phase split operations more carefully to avoid emulsions; following these four batches, the results from the phase splits will be evaluated and the team will decide if these mitigation actions should be part of the process or if they should be eliminated.

Next, there are two types of downtime related to the QC department, to avoid this, a representative from the QC team started to attend the TOP15 meetings to plan the sample analysis with real-time data.

The KF failure during the reactors cleaning was a delay reported that the team could not identify the root-cause immediately, therefor a detailed analysis had to be conducted, available at the end of this chapter.

- **Intermediate 1**

Figures 4.21 and 4.22 refer to the Intermediate 1 production.

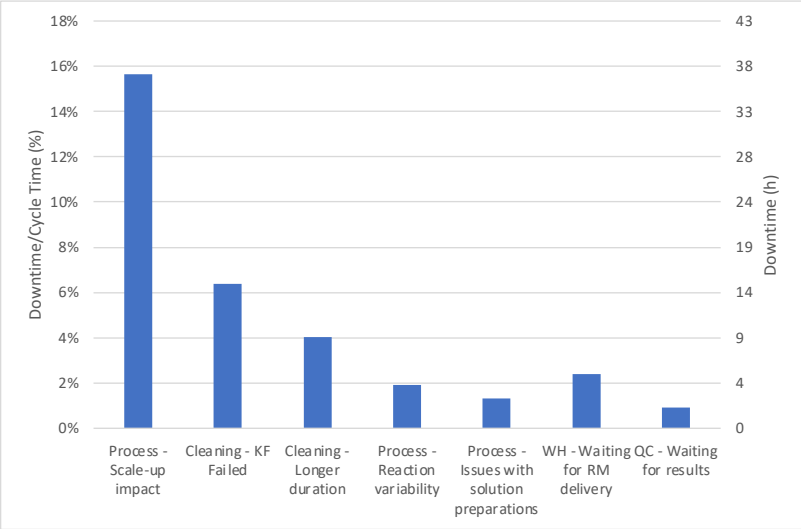


Figure 4.21: Recorded downtime in Intermediate 1

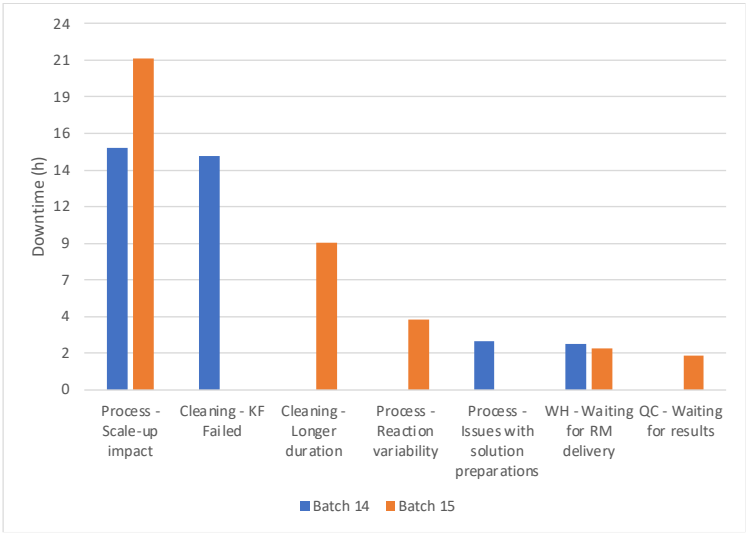


Figure 4.22: Recorded downtime per batch in Intermediate 1

The scale-up recipe of the intermediate was defined with estimated durations; therefore, it was expected to have different duration values and to update the recipe after this campaign. The first downtime column reflects the operations where there were no process issues, but the time was above the established golden duration. The downtime related to the failed KF during the cleaning had the same corrective actions as Intermediate 2, and as observed in Figure 4.22, in the second batch the analysis met the criteria.

- **Intermediate 3**

Figures 4.23 and 4.24 refer to the Intermediate 3 production.

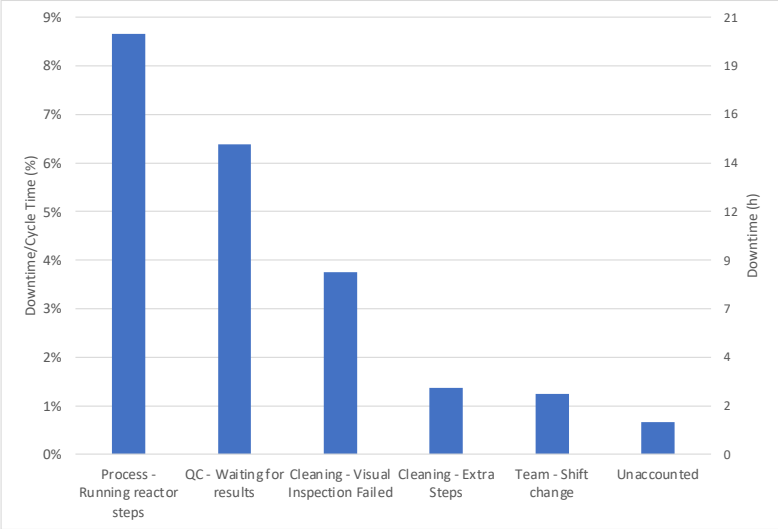


Figure 4.23: Recorded downtime in Intermediate 3

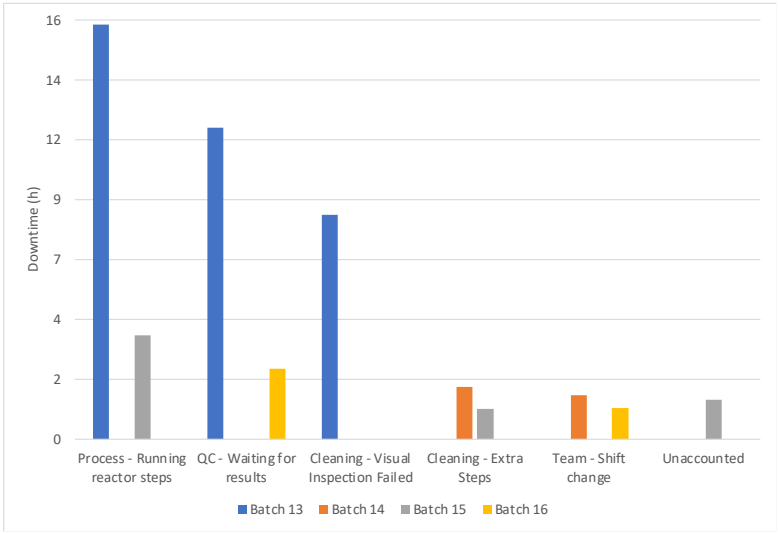


Figure 4.24: Recorded downtime per batch in Intermediate 3

From Intermediate 1 to Intermediate 3 there was a bottleneck change, hence the highest downtime related to the reactor steps on the first batch; the downtime related to the second batch was expected according to the production plan in place. Once again, the QC department has an important role in efficiency, but through close communication, it was possible to prevent further downtime in the following two batches.

- **Intermediate 4**

Figures 4.25 and 4.26 refer to the Intermediate 4 production.

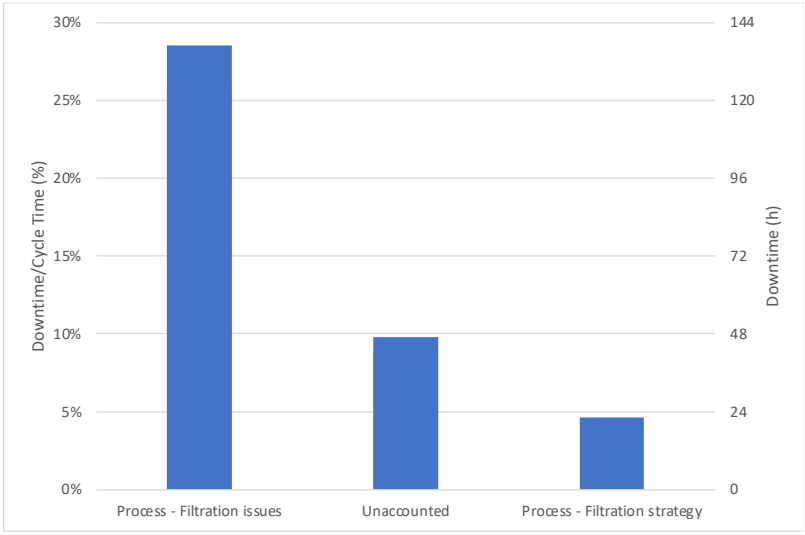


Figure 4.25: Recorded downtime in Intermediate 4

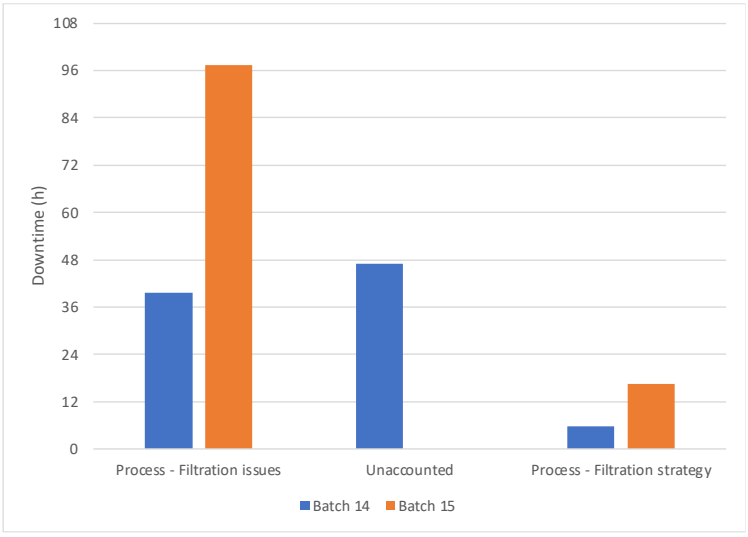


Figure 4.26: Recorded downtime per batch in Intermediate 4

Intermediate 4 has the hardest filtration process. Even with the actions to standardize it (represented by the last columns – filtration strategy), it was impossible to prevent the high delays in the cake washes (filtration issues). The cake was very compact, therefore the mother liquors were being removed at a very low flow rate.

- **Final Product**

Figures 4.27 and 4.28 refer to the Final Product production.

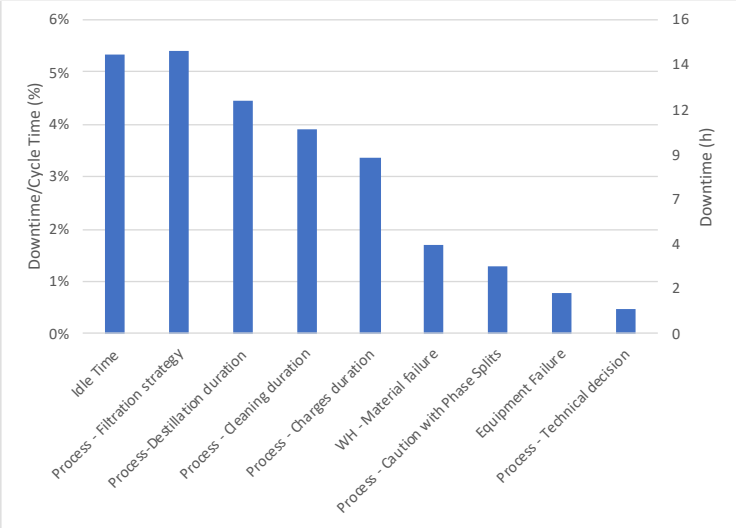


Figure 4.27: Recorded downtime in Final Product

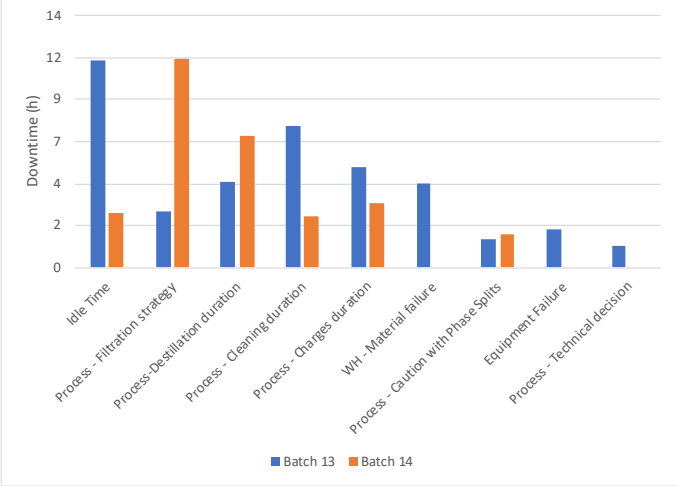


Figure 4.28: Recorded downtime per batch in Final Product

The idle time here was reported during different operations due to shift changes and training of the team at the start of the Final Product production- since in the second batch the idle time was reduced. Once again, due to standardization of the filtration, this step had longer durations than the baseline. The distillations did not present any problem but since there are four of them, the small delays account for the total downtime represented in the previous figures.

- **Root-Cause Analysis**

As mentioned in Chapter 3.2, the root-cause of every delay over one hour should be identified to implement preventive actions in the next batches. There are cases where the root-cause is not clear during the TOP15 meetings, therefore an extensive analysis needs to be performed. Succeeding, an example of root-cause analysis is detailed.

In the first batch of Intermediate 2, the cleaning of the RH4001 failed the KF analysis needed to start the next batch. The team could not identify immediately the root cause; therefore, a more detailed analysis was required. At Hovione there is a problem-solving template that gathers this information in an A3 report type; the example for this downtime can be found in Appendix D.

The goal of this cleaning is to remove all water contents from the reactor, with tetrahydrofuran (THF), since it reacts with the SRM of both the Intermediate 2 and Intermediate 1 SRM. The 5W2H tool was used to identify the problem:

| | |
|---|---|
| **What?** | KF result of the RH4001 failed on batch 17. |
| **Why?** | Criteria: ≤0.05%(w/w) Result: 0.06%(w/w) |
| **Where?** | KF Analysis in the QC laboratory |
| **When?** | During the KF analysis of the RH4001 CBB |
| **Who?** | The QC technicians detected it |
| **How?** | As a result of the analytical verification, the criteria was not met |
| **How Much?** | One Time occurrence |

This allowed to write a problem statement: In the KF analysis of the RH4001 CBB in batch 17, it was observed the presence of water above the criteria of 0.05% (w/w), impacting the start of the next batch.

Next, in Figure 4.29 the CBB procedure was mapped to help identify probable causes.

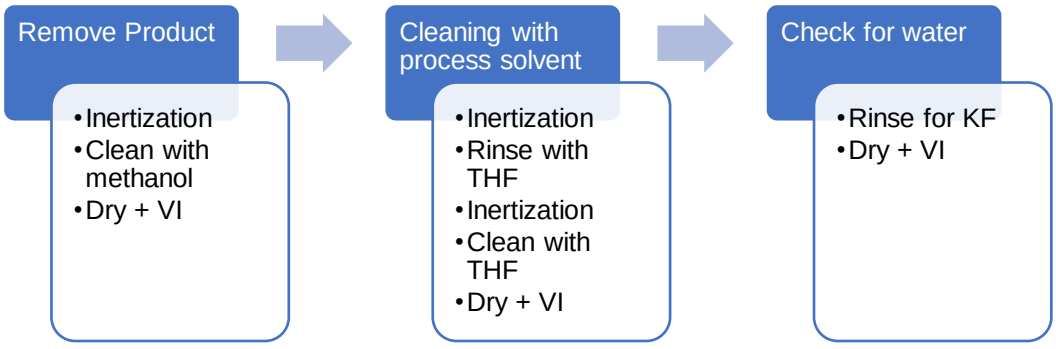


Figure 4.29: Mapping of the RH4001 CBB procedure for root-cause analysis

With the aid of the Ishikawa Diagram, Figure 4.30, the team listed the possible causes.

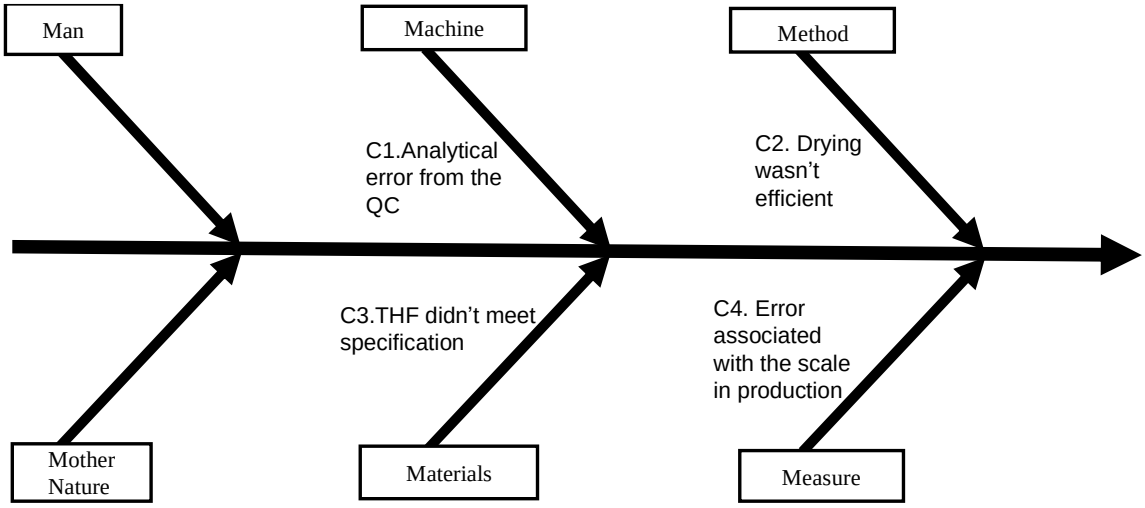


Figure 4.30: Ishikawa Diagram for the root-cause analysis

The probable causes were analysed in Table 4.10.

Table 4.10: Selection of likely causes as root-cause

| Cause | Description | Supporting evidence | Likely/Unlikely |
|---|---|---|---|
| **C1** | Analytical error from the QC | The blank value was 0.003% (w/w) | Unlikely |
| **C2** | Drying was not effective | Water residue found | Likely |
| **C3** | THF did not meet specification | Residue on evaporation and peroxides are lower in the THF used in batch 11 (which passed the KF analysis) than the one used in batch 17 | Unlikely |
| **C4** | Error associated with the scale in production | Batch Production Record (BPR) states that the scales were calibrated before the charges | Unlikely |

The only cause considered likely was C2, therefore the corrective action implemented was to increase the drying time from 30 to 90 minutes. The team was able to test the corrective action and due to its effectiveness, it was implemented in the following batches as well. The CBB performed after batches 18 and 19 met the KF criteria.

## 4.6 Yield Improvement

The baseline yield values can be found in Appendix E.

A mass balance study at the current scale was never performed for this product, and with the sampling strategy in place it was only possible to quantify rigorously the losses related to the reactions.

### 4.6.1 Yield Results

Figure 4.31 compares the molar yield results from the previous campaigns and this campaign. Appendix F details the values used for this analysis.

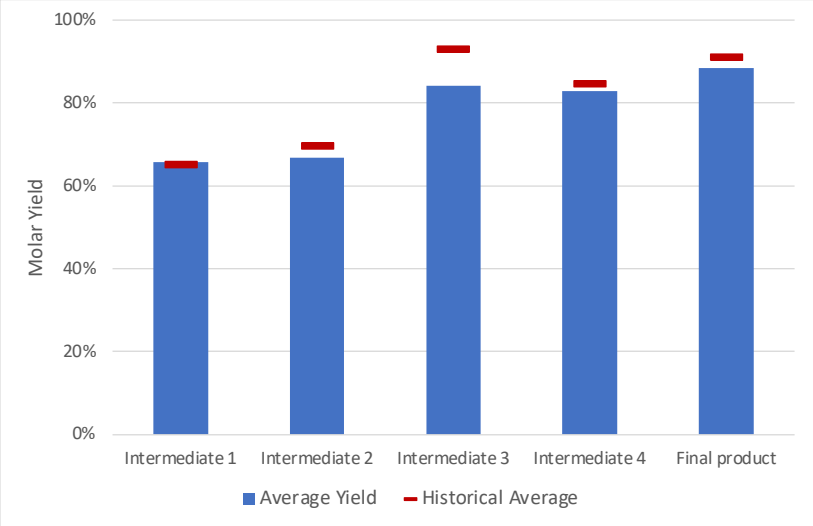


Figure 4.31: Baseline and third commercial campaign molar yield

Figures 4.32 to 4.36 illustrate the yield results obtained in this campaign.

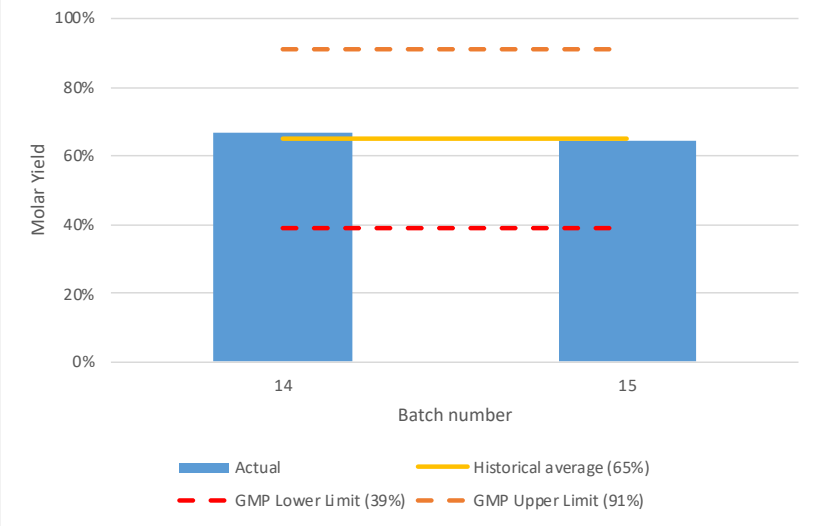


Figure 4.32: Intermediate 1 yield results

For Intermediate 1, the average yield of this campaign was higher than the baseline.

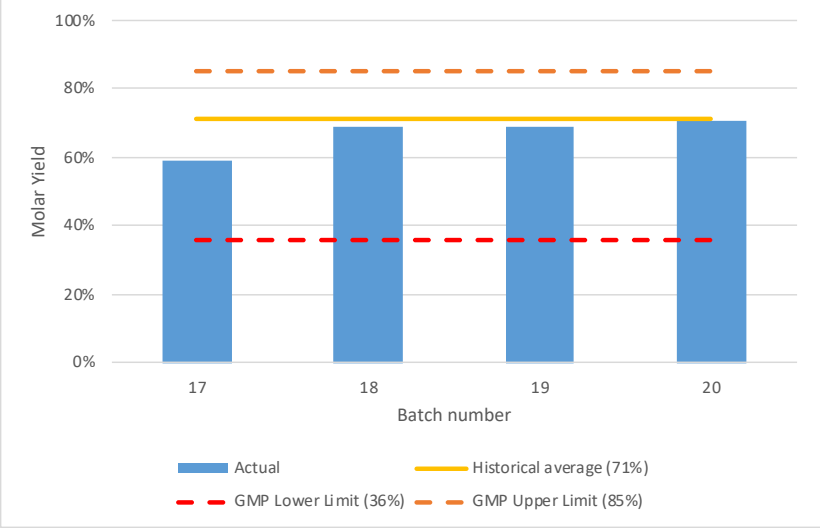


Figure 4.33: Intermediate 2 yield results

Intermediate 2 was a campaign that focused a lot on yield, due to the high loss in yield in the previous scale-up attempt, however the values did not reach the baseline. The goal was to understand the losses with the mass balance study.

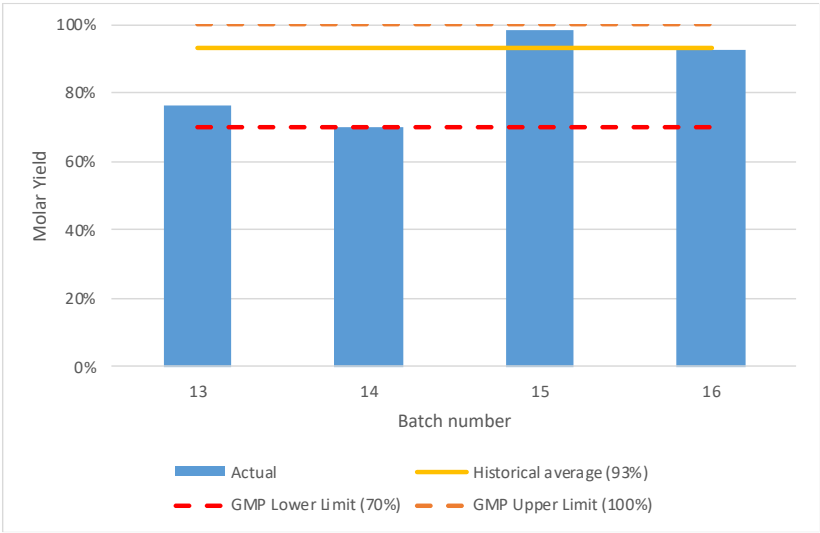


Figure 4.34: Intermediate 3 yield results

Intermediate 3 started with low yield results but in the last two batches, it was able to improve and even set a new best observed result. The mass balance study should present conclusions regarding the yield loss in the first two batches.

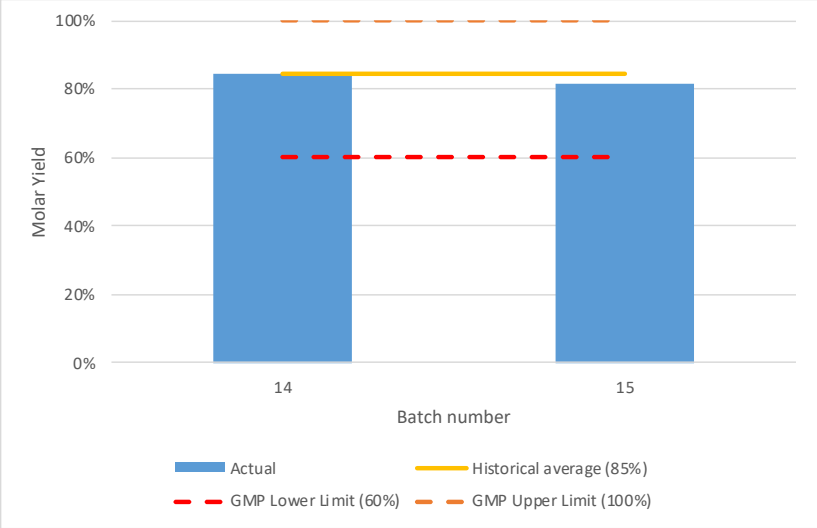


Figure 4.35: Intermediate 4 yield results

Intermediate 4 could not meet the baseline average, but it was within the expected yield value.

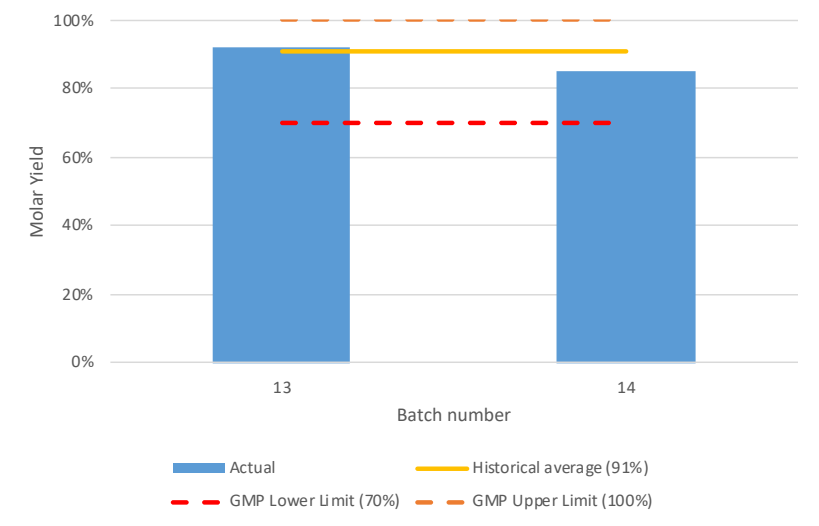


Figure 4.36: Final Product yield results

Finally, the first batch of Final Product set a new yield record, however, due to the low results from the second batch, the average was below the baseline.

Overall, these results indicate the importance of a mass balance study, to maximize the processes yield leading to a higher throughput.

### 4.6.2 Mass Balance

Table 4.11 summarizes the possible chemical and physical losses of product. This analysis was done for each of the processes as indicated by Figures 1.2 to 1.6 of Chapter 1.

Table 4.11: Possible chemical and physical losses of product during the process

| Operation | Possible chemical and physical losses of product |
|---|---|
| **Reactions** | Unconverted SRM as well as secondary reactions that lead to sub-products or impurities |
| **Phase splits** | Product in the aqueous phase and emulsions |
| **Distillations** | Product crystallization or degradation |
| **Crystallization** | Uncrystallized product |
| **Filtration** | Product not retained on the filter |
| **Filter cake washes** | Product dissolution |
| **Drying** | Loss of product in the equipment |

To perform the mass balance a new sampling strategy was designed to identify the steps where yield losses could occur, such as sampling of the aqueous and organic phases, mother liquors, and washing solution. For QC to execute all the samples, it was decided to not perform assay determination of the samples but only quantify the different products by % Area and perform a direct comparison with standards.

- **Intermediate 1**

The mass balance study of Intermediate 1 was not performed since the collected samples were not analysed.

- **Intermediate 2**

The results for the mass balance of Intermediate 2 are available in Table 4.12.

Table 4.12: Mass balance for Intermediate 2

| | Batch 17 | | Batch 18 | | Batch 19 | | Batch 20 | |
|---|---|---|---|---|---|---|---|---|
| | Product loss (kg) | Loss in yield | Product loss (kg) | Loss in yield | Product loss (kg) | Loss in yield | Product loss (kg) | Loss in yield |
| **Reaction 1** | 0.48 | 0.96% | 0.64 | 1.29% | 0.60 | 1.20% | 0.65 | 1.30% |
| **Reaction 2** | 1.98 | 2.67% | 0.16 | 0.22% | 1.37 | 1.85% | 1.01 | 1.37% |
| **PS4** | 0.28 | 0.39% | 0.14 | 0.19% | 0.22 | 0.30% | 0.13 | 0.18% |
| **Filtration** | 3.93 | 5.43% | 4.16 | 5.62% | 5.02 | 6.86% | 4.91 | 6.67% |
| **Washes** | 0.45 | 0.66% | 0.55 | 0.79% | 1.02 | 1.50% | 0.40 | 0.58% |
| **Total** | 7.12 | 10.10% | 5.65 | 8.10% | 8.23 | 11.71% | 7.10 | 10.09% |
| **Batch yield** | | 59.06% | | 68.90% | | 68.99% | | 70.50% |
| **Unaccounted** | | 30.84% | | 23.00% | | 19.30% | | 19.41% |

In each phase split samples were collected, but the results were not available at the end of this study. By analysing Table 4.12, the main concern is the filtration step that accounts for 5.43% to 6.86% of loss in yield; however, reaction 2 has a great variability associated.

For this intermediate, it would be important to study the solubility of the product in the mother liquors, to evaluate if the right solvents are being used; to trial methods to recover product from the mother liquors and evaluate the particle size to make sure that the filter mesh is appropriate.

- **Intermediate 3**

Although four batches of Intermediate 3 were produced, only the last two batches had the new sampling strategy in place, the results are present in Table 4.13. This prevented understanding the yield loss in the first two batches.

Table 4.13: Mass balance for Intermediate 3

| Operation | Batch 15 | | Batch 16 | |
|---|---|---|---|---|
| | Product loss (kg) | Loss in yield | Product loss (kg) | Loss in yield |
| **Reaction 1** | 0.03 | 0.06% | 0.003 | 0.01% |
| **Filtration** | 1.13 | 2.71% | 1.148 | 2.83% |
| **1st wash** | 0.32 | 0.78% | 0.948 | 2.41% |
| **Total** | 1.48 | 3.55% | 2.099 | 5.24% |
| **Batch yield** | | 98.23% | | 92.57% |
| **Unaccounted** | | -1.78% | | 2.19% |

The quantities lost during the filtration are within the normal values for this operation and there are no further improvements needed for this intermediate due to the high yield values.

- **Intermediate 4**

The mass balance results for Intermediate 4 are represented in Table 4.14.

Table 4.14: Mass balance for Intermediate 4

| Operation | Batch 14 | | Batch 15 | |
|---|---|---|---|---|
| | Product loss (kg) | Loss in yield | Product loss (kg) | Loss in yield |
| **Reaction 1** | 0.07 | 0.13% | 1.27 | 2.37% |
| **Filtration** | 2.84 | 3.61% | 3.59 | 4.42% |
| **1st wash** | 3.13 | 4.12% | 3.63 | 4.68% |
| **2nd wash** | 3.36 | 4.63% | 5.76 | 7.79% |
| **Total** | 9.40 | 12.49% | 14.25 | 19.26% |
| **Batch yield** | | 84.20% | | 81.67% |
| **Unaccounted** | | 3.32% | | -0.93% |

As assessed previously, this intermediate has the hardest filtration and washes process, as well as a great loss of product associated with it. Once again, it would be important to study the solubility of the product in the mother liquors and washing solution, to evaluate how the process can be improved; to trial methods to recover product from the mother liquors and evaluate the particle size to make sure that the filter mesh is appropriate and study the crystallization step in case it is possible to manipulate the crystal size, easing the filtration and washes procedures.

- **Final Product**

The mass balance results for the Final Product are represented in Table 4.16.

Table 4.15: Mass balance for Final Product

| Operation | Batch 13 | | Batch 14 | |
|---|---|---|---|---|
| | Product loss (kg) | Loss in yield | Product loss (kg) | Loss in yield |
| **PS1** | 0.010 | 0.015% | 0.023 | 0.034% |
| **PS2** | 0.003 | 0.005% | 0.005 | 0.007% |
| **PS3** | 0.005 | 0.008% | 0.002 | 0.003% |
| **PS4** | 0.006 | 0.009% | 0.000 | 0.001% |
| **Filtration** | 0.594 | 0.896% | 0.537 | 0.792% |
| **1st wash** | 0.091 | 0.138% | 0.064 | 0.095% |
| **Total** | 0.69 | 1.043% | 0.60 | 0.888% |
| **Batch yield** | | 91.722% | | 85.205% |
| **Unaccounted** | | 7.235% | | 13.907% |

This mass balance presents the least loss of product during production.

When accessing Tables 4.12 to 4.15, there are intermediates that present a high value for the unaccounted losses in yield or even a negative percentage for unaccounted, such as Intermediate 2 and Final Product. This can be explained either by current samples in place not accounting for the total loss of product or the error associated with the analytical methods. There was no opportunity to study this unaccounted value in further detail, however it is important to do it since its value is higher than the current accounted losses.

The errors associated with each analytical method are present in Appendix G.

## 4.7 Throughput results

With the results from the previous three sub-chapters, it is possible to evaluate the performance of each intermediate in terms of throughput, this is represented in Figure 4.37; Appendix H details the values for this analysis. Note that the values displayed above the bars of Figure 4.37 are the percentual difference between the baseline and actual values.

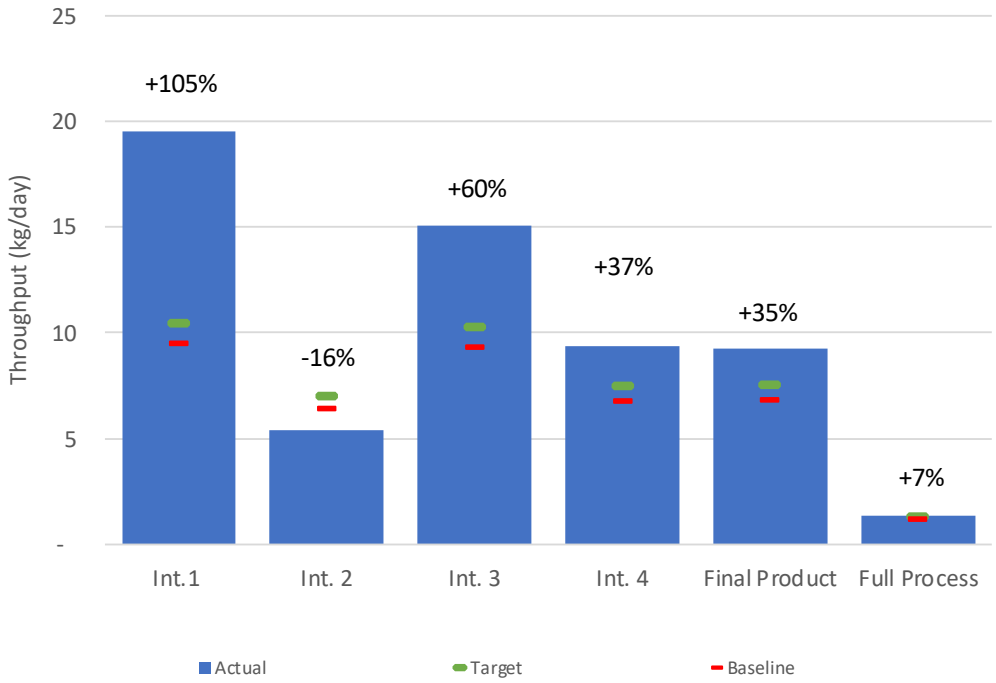


Figure 4.37: Throughput results (manufactured quantity divided by total available time)

To calculate the throughput of the full process, the total production time of all the intermediates was considered (91 days and 12 hours), with the output of Final Product (123.24 kg).

All processes, except for Intermediate 2, had significant improvement and exceeded the target of 10% increase, proving the efficacy of these measures. The result from Intermediate 2 was expected since the mitigation plan prevented the team from implementing any actions related to this improvement plan, aside from recording and analysing downtimes which did help, and the results would have been lower if this did not happen.

Regarding the full process, it had a throughput value of 1.35 kg/day, revealing an increase of 7%, not meeting the target of 1.38 kg/day. This target was set with four Final Product batches planned, so there was Intermediate 1 and Intermediate 3 left in stock, which led to a higher total available time but less manufactured API. Based on the previous execution, if the production continued as planned, the four remaining batches lasted the average of the previous ones, and considering the average output of Final Product, the total available time would be 123 days and 12 hours and the manufactured quantity would be 246.48 kg, leading to a throughput of 2 kg/day, proving an increase of 59% from the baseline.

When evaluating the individual values for each intermediate, it can be expected that the API throughput would reach the set target however four reasons prevented this:

1. Only two batches of Final Product were manufactured (there were four batches planned for this target);
2. Two batches of Intermediate 3 and one batch of Intermediate 1 were left in stock, since only two batches of Final Product were manufactured; this led to a higher total production time;
3. This project focused mainly on the execution of each intermediate. To improve the API throughput result, the team would have to focus more on the changeover between them, to ensure the bottleneck was always running with no idle time;
4. The yield results were lower than the baseline, therefore performing a complete mass balance results and implementing corrective actions would lead to a higher throughput.

# 5. Conclusions and future perspective

This dissertation aimed to increase the throughput of an Active Pharmaceutical Ingredient (API) process by 10%, focusing on three fronts: golden Cycle Time reduction, downtime reduction, and yield improvement.

The API is chemically synthesized in batch production mode with four intermediates and a final product. Eight batches were previously manufactured with an average throughput of 1.26 kg/day; therefore, the target was to increase it to 1.38 kg/day.

This dissertation showed how a Continuous Improvement approach can enhance the productivity. These projects are very important in the pharmaceutical industry since it reveals inefficiencies at an operational level that can and should be improved with Lean initiatives, to make processes more efficient and robust in terms of time and yield.

In this study, the identification of the bottleneck played an important role in the campaign planning, to ensure the reduction of Cycle Time by optimizing the batch overlap allowing the manufactured quantity to increase in a set period.

The established target of 10% increase in throughput had planned for four batches of Final Product, however due to an unexpected quality issue, only two batches were manufactured.

In Table 5.1 the throughput increase for each process is presented.

Table 5.1: Throughput increase of the processes

| | Intermediate 1 | Intermediate 2 | Intermediate 3 | Intermediate 4 | Final Product | Full process |
|---|---|---|---|---|---|---|
| **Throughput increase** | +105% | -16% | +60% | +37% | +35% | +7% |

The throughput of the full process was 1.35 kg/day, revealing an increase of 7%, not meeting the target of 10%. Based on previous execution, if the production continued as planned, the two remaining batches lasted the average of the previous ones, and considering the average output of

Final Product, the total available time would be 123 days and 12 hours and the manufactured quantity would be 246.48 kg, leading to a throughput of 2 kg/day, proving an increase of 59% from the baseline.

When evaluating the individual values for each intermediate, it can be expected that the API throughput would reach the set target however four reasons prevented this:

1. Only two batches of Final Product were manufactured (there were four batches planned for this target);
2. Two batches of Intermediate 3 and one batch of Intermediate 1 were left in stock, since only two batches of Final Product were manufactured; this led to a higher total production time;
3. This project focused mainly on the execution of each intermediate. To improve the API throughput result, the team would have to focus more on the changeover between them, to ensure the bottleneck was always running with no idle time;
4. The yield results were lower than the baseline, therefore performing a complete mass balance results and implementing corrective actions would lead to a higher throughput.

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# Appendix A:

## Bottleneck identification

In the figures bellow the total occupancy time of each equipment is analysed for every intermediate allowing the identification of the bottleneck.

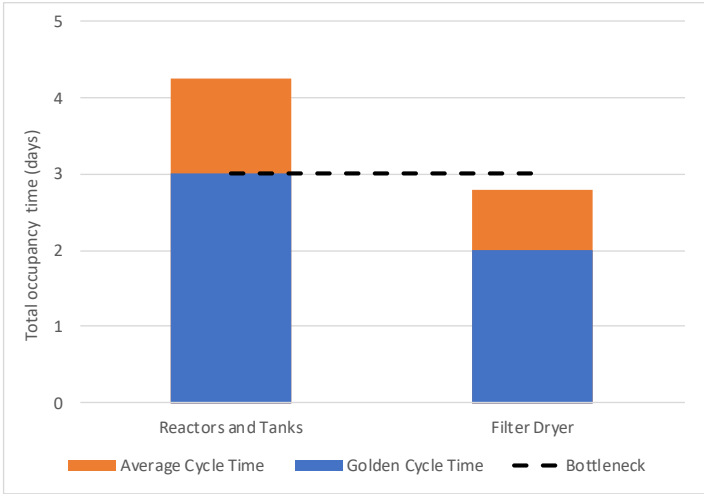



Figure A.1: Intermediate 1 Bottleneck identification (batch of 50kg)

Analysing Figure A.1, it can be determined that the reactors and tanks are the bottleneck of Intermediate 1, both when considering average and Golden Cycle Time.

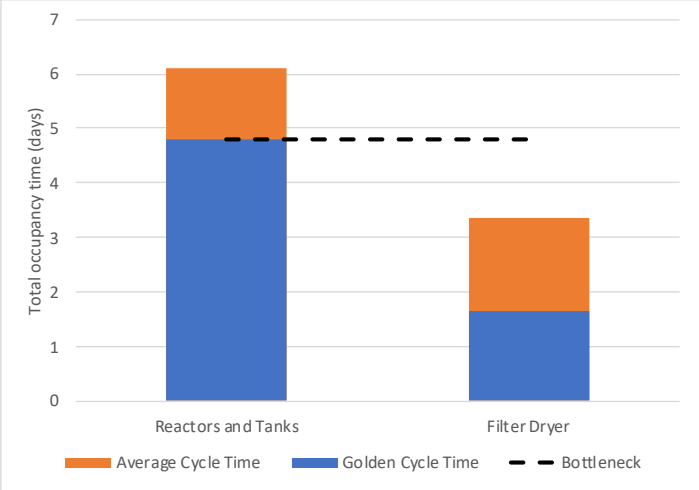



Figure A.2: Intermediate 2 Bottleneck identification

Analysing Figure A.2, it can be determined that the reactors and tanks are the bottleneck of Intermediate 2, both when considering average and Golden Cycle Time.

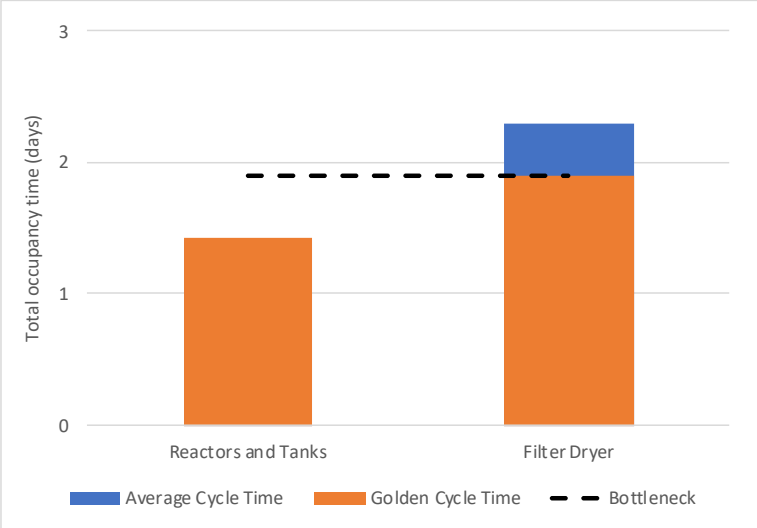



Figure A.3: Intermediate 3 Bottleneck identification

Analysing Figure A.3, it can be determined that the filter dryer is the bottleneck of Intermediate 3, both when considering average and Golden Cycle Time; note that for this intermediate the average Cycle Time is aligned with the Golden Cycle Time.

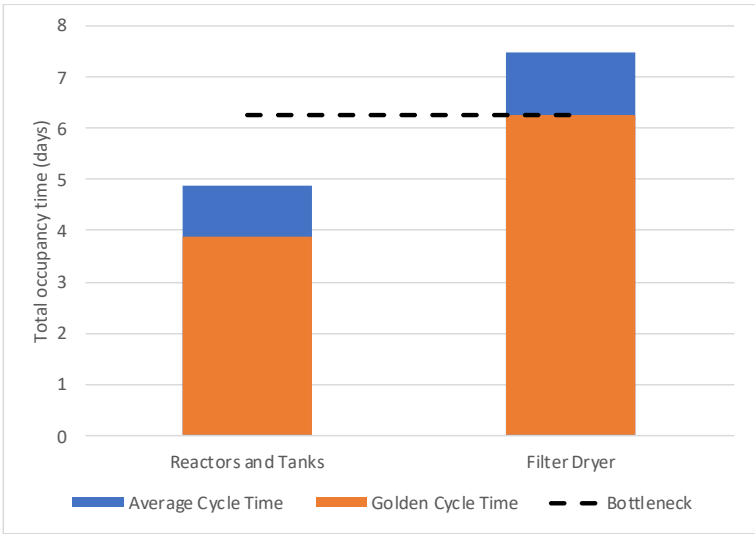



Figure A.4: Intermediate 4 Bottleneck identification

Analysing Figure A.4, it can be determined that the filter dryer is the bottleneck of Intermediate 4, both when considering average and Golden Cycle Time.

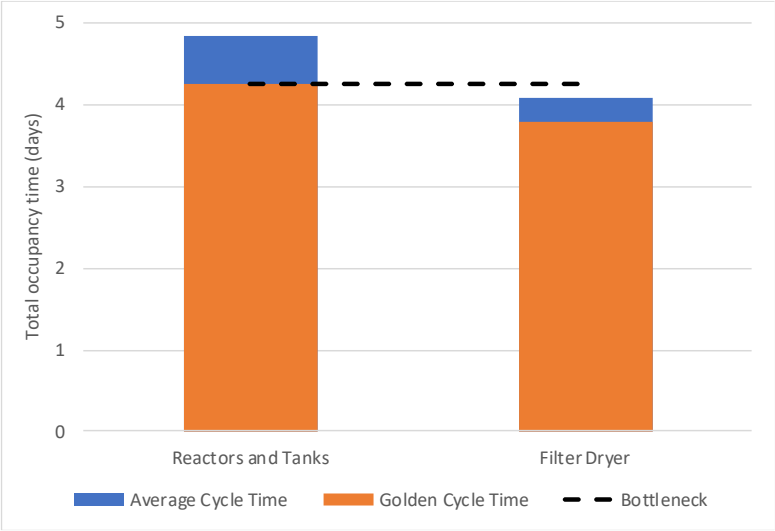



Figure A.5: Final Product Bottleneck identification

Analysing Figure A.4, it can be determined that the reactors and tanks are the bottleneck of the Final Product process, both when considering average and Golden Cycle Time. Here it is important to note that the difference between average and golden Cycle Time in the filter dryer is reduced, and so is the difference between the average Cycle Time of the reactors and tanks and filter dryer; this means that delays above 11 hours will change the bottleneck of this process to the filter dryer. This should be avoided by careful scheduling of the reactors and tanks operations, as well as close monitorization of the filter dryer operations.

# Appendix B:

## Defining potential effort of the improvement opportunities

Table B.1 describes in detail the necessary actions to implement the improvement opportunities aforementioned for each intermediate; this will allow to estimate the potential effort. The times considered in the potential effort column are an estimate based on the current process engineers' team and the area that the API is manufactured.

Table B.1: Implementation actions and potential effort for the intermediate improvement actions (1/2)

| Intermediate_Action | Implementation actions | Potential effort (h) |
|---|---|---|
| **Int1_1** | Alert QC<br>Create new procedure document<br>Provide training | 15 |
| **Int1_2** | Study the conditions and *DeltaV*™ data<br>Change indications on the operational manual | 8 |
| **Int1_3** | Create an action plan and have client approval<br>Change indications on the operational manual<br>Alert QC | 19 |
| **Int1_4** | Alert QC<br>Create new procedure document<br>Provide training | 15 |
| **Int2_1** | Create action plan and have client approval<br>Change indications on the operational manual | 18 |
| **Int2_2** | Study the conditions and *DeltaV*™ data | 6 |
| **Int3_1** | Create action plan and have client approval<br>Change indications on the operational manual | 18 |
| **Int3_2** | Evaluate the *DeltaV*™ data and set the standard<br>Change indications on the operational manual | 8 |
| **Int3_3** | Evaluate the *DeltaV*™ data and set the standard<br>Change indications on the operational manual | 8 |

Table B.2: Implementation actions and potential effort for the intermediate improvement actions (2/2)

| Intermediate_Action | Implementation actions | Potential effort (h) |
|---|---|---|
| **Int4_1** | Evaluate *DeltaV*™ data<br>Change indications on the operational manual<br>Create new document for the operators | 10 |
| **Int4_2** | Evaluate *DeltaV*™ data | 6 |
| **Int4_3** | Change indications on the operational manual<br>Create new document for the operators | 4 |
| **Int4_4** | Change indications on the operational manual<br>Evaluate *DeltaV*™ data | 8 |
| **Int4_5** | Evaluate the *DeltaV*™ data and set the standard<br>Change indications on the operational manual | 8 |
| **Int4_6** | Evaluate the *DeltaV*™ data and set the standard<br>Change indications on the operational manual | 8 |
| **Int4_7** | Create an action plan and have client approval<br>Change indications on the operational manual | 18 |
| **Int4_8** | Discuss with chemists | 8 |
| **FP_1** | Evaluate previous sample results<br>Change indications on the BPR | 20 |
| **FP_2** | Discuss with chemists<br>Identify Constraints<br>Model with appropriate software | 32 |
| **FP_3** | Discuss with chemists<br>Change indications on the operational manual<br>Alert QC | 11 |
| **FP_4** | Discuss with chemists<br>Change indications on the operational manual<br>Alert QC | 11 |

# Appendix C:

## Reduction to the Golden duration of operations

In the following tables the saved time, in critical path operations, compared to the previous establish records is represented for each intermediate.

Table C.1: Reduction to the Golden duration of Intermediate 2 operations

| Step description | Batch 17 | Batch 18 | Batch 19 | Batch 20 |
|---|---|---|---|---|
| **Sample Reaction 1.1** | 1:33 | 0:47 | 1:25 | |
| **Charge solvents** | 4:55 | 4:35 | 5:45 | |
| **Reaction 2** | 2:50 | 2:42 | 4:54 | |
| **Equipment preparations (RH4001)** | | 1:33 | 0:15 | 0:45 |
| **Filtration + Charge + Rinse** | 4:07 | 5:14 | 5:39 | |
| **Drying + VI** | 0:42 | 0:46 | 1:02 | |
| **Sample Reaction 2.2** | 0:50 | 0:57 | | |
| **Reaction 1** | 0:12 | | 0:13 | |
| **Sample Reaction 2.1** | 0:50 | 0:45 | | |
| **Sample KF water search** | 5:29 | 6:49 | | |
| **Remove product + Drying + VI** | | 0:20 | | |
| **Rinse with process solvent + Drying + VI** | 2:30 | | | |
| **Distillation 1 + Charge Solvents + Cooling** | | 2:47 | | |
| **Transfer Solvent + Heating + Charge and transfer solvent** | | | 0:20 | |
| **Sample Drying** | | 1:00 | | |

Table C.2: Reduction to the Golden duration of Intermediate 1 operations (1/2)

| Step description | Batch 14 | Batch 15 |
|---|---|---|
| **Reaction 1** | 1:25 | 3:00 |
| **Cooling** | 1:17 | 1:29 |
| **Crystallization** | 1:18 | 0:23 |
| **Heating** | 0:15 | 0:08 |
| **Equipment preparations (RV4011)** | 0:20 | |
| **Sample Reaction 1.1** | 0:42 | |
| **Sample Reaction 1.2** | 0:43 | |

Table C.3: Reduction to the Golden duration of Intermediate 1 operations (2/2)

| Step description | Batch 14 | Batch 15 |
|---|---|---|
| **Charge solvents** | 0:14 | |
| **Sample Reaction 2.1** | 1:36 | |
| **Sample Reaction 2.3** | 0:14 | |
| **Remove Solvent (CBB) RV4011** | 0:06 | |

Table C.4: Reduction to the Golden duration of Intermediate 3 operations

| Step description | Batch 14 | Batch 14 | Batch 15 | Batch 16 |
|---|---|---|---|---|
| **Filtration** | 0:23 | 0:14 | 3:51 | 0:15 |
| **Equipment preparations** | 0:35 | | 1:02 | 0:47 |
| **Reaction 1** | | 0:43 | | 1:20 |
| **FSEC Cleaning** | | | 8:53 | 6:43 |
| **Sample Reaction 1** | | 0:43 | | 1:20 |
| **Cake wash** | | 0:38 | | 0:26 |
| **Drying** | | 3:22 | | |
| **Packaging** | | | 0:04 | |

Table C.5: Reduction to the Golden duration of Intermediate 4 operations

| Step description | Batch 14 | Batch 15 |
|---|---|---|
| **Prepare RM solution** | 0:18 | 1:27 |
| **Cooling and Charge Solvents** | 0:27 | |
| **Heating and distillation** | 0:04 | |
| **Drying** | 0:21 | |

Table C.6: Reduction to the Golden duration of Final Product operations

| Step description | Batch 13 | Batch 14 |
|---|---|---|
| **FSEC Cleaning** | 0:15 | |
| **Cooling** | 0:45 | |
| **Temperature adjustment, Filtration, Rinse with Solvent, Filtration** | 0:31 | 0:42 |
| **KF IPC Sample** | 1:00 | 0:18 |
| **Charge Seed, Heating, and Stirring** | 0:20 | 0:02 |
| **Charge SRM and solvents** | | 4:27 |
| **Transfer + Charge water for PS3 + Phase Split 3** | 1:07 | |
| **Distillation 1 e charge solvents** | 0:55 | |
| **Crystallization** | | 0:10 |
| **Packaging** | | 4:30 |

PROJECT: **API**

TEAM: API Production Team, OPX Member, Catarina Martins

START DATE: 01.06.2021

# DEFINE

## 1. Define the problem and write a problem statement

**5W2H**

- What is the problem? KF result of the RH4001 failed on batch 17
- Who did / has detected the problem? The QC technicians
- Where did it occur / was it observed? KF Analysis in the QC laboratory
- When did it occur / was it detect? During the KF analysis of the RH4001 CBB
- Why is it a problem? Criteria: ≤0.05%(w/w) Result: 0.06%(w/w)
- How many times has the problem occur? One time
- How was it detected? As a result of the analytical verification, the criteria was not met

**Problem Statement:** The problem at (object) which caused by (defect) originated (impact):

In the ***KF analysis of the RH4001 CBB*** it was observed the ***presence of water above the criteria of 0.05%(w/w)*** , impacting the ***start of the next batch***.

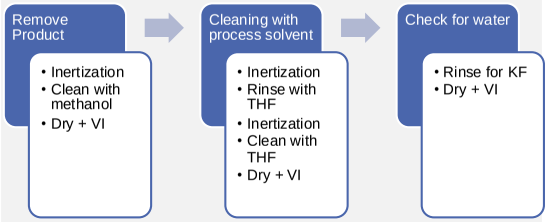
## 2. Define a success metric

Select a success metric to measure improvement and define how you will track it

# of OOS KF analysis in RH4001 CBB

# MEASURE

## 3. Map the process




## 4. Record relevant data

- List and collect any relevant data that might be needed to solve the problem

The CBB of RH4001 is the last one to be executed, since the RV4011 and the TC2401 are cleaned with water and the solvents charging line is the same for all equipment.

The condensers don't have a specific cleaning procedure, therefore there might be water in the equipment

- Identify the main contributors for impact or occurrence
- List the symptoms of the failure

## 5. Record known changes

List any known changes that might have occurred prior to shift in performance that reasonably explains the shift in performance.

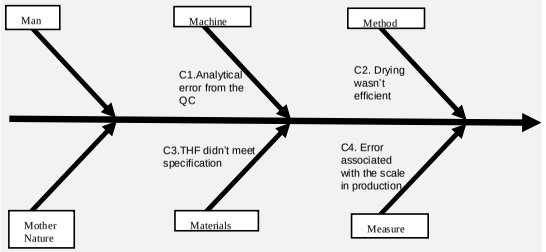
There were no changes in the cleaning procedures since the last campaign

## 6. Record distinctions

- List any object or place or time that you might expect to see the problem.
- List the differences or distinctions between where or when or who has the problem compared to where or when or who does not have the problem when it does not exist

# ANALYZE

## 7. Record possible causes




## 8. Test hypothesis and select most probable causes

| Cause | Sub-Cluster | Supporting Facts | Contradicting Facts | Classification (Proven, Excluded, Unlikely, Likely) |
|---|---|---|---|---|
| C1. Analytical error from QC | Machine | | The blank value was 0.003% (w/w) | Unlikely |
| C2. Drying wasn't efficient | Method | Water residue found in the sample | | Likely |
| C3. THF didn't meet criteria | Material | Residue on evaporation and peroxides is lower in the THF used in batch 11 (passed the KF analysis) than the one used in batch 17 | Water level was the same | Unlikely |
| C4. Error associated with the scale in production | Measure | | BPR confirmed the scale's calibration before charges | Unlikely |

## 9. Develop & Select possible corrective actions

| Counter Measure | Impact (1_3_5) | Implementation Effort (1_3_5) | Sustainability (1_3_5) | Priorization # (I+S+E) |
|---|---|---|---|---|
| C2-Increase drying period (from 30 min to 90 min) | 5 | 5 | 5 | 15 |

## 10. Test the best solution

All countermeasures above where tested.

# IMPLEMENT

## 11. Implement solution

All countermeasures were implemented in the following batches.

# CONTROL

## 12. Implement controls

- Define and implement controls to prevent a recurrence of the problem and continue to monitor for compliance
- Create a monitoring plan

# EVALUATE

## 13. Document your success

Batches 18 and 19 CBB passed the KF analysis.

**<<<<<<<<<< CELEBRATE >>>>>>>>>>**

**Appendix D:**

**Root-cause analysis template**

# Appendix E:

## Baseline yield results

In the figures bellow the baseline (batches from the validation campaign and two commercial campaigns) yield results are displayed for each intermediate.

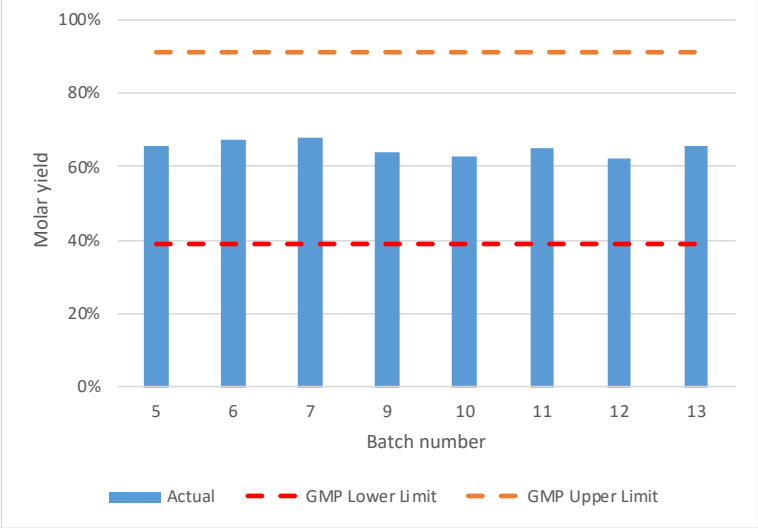



Figure E.1: Baseline yield values for Intermediate 1

Intermediate 1 revealed an average yield of 65.1% and the best observed value was 68%; this intermediate shows a low variability in yield throughout the different campaigns.

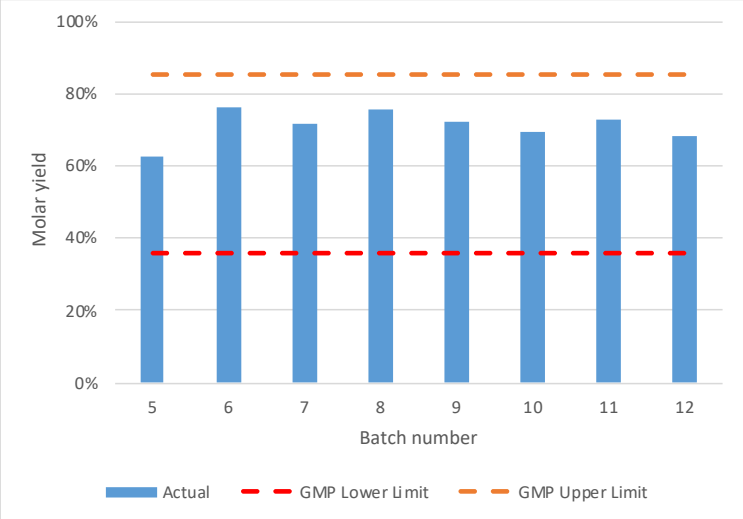



Figure E.2: Baseline yield values for Intermediate 2

Intermediate 2 revealed an average yield of 69.7% and the best observed value was 76%; this intermediate shows the highest variability in yield throughout the different campaigns.

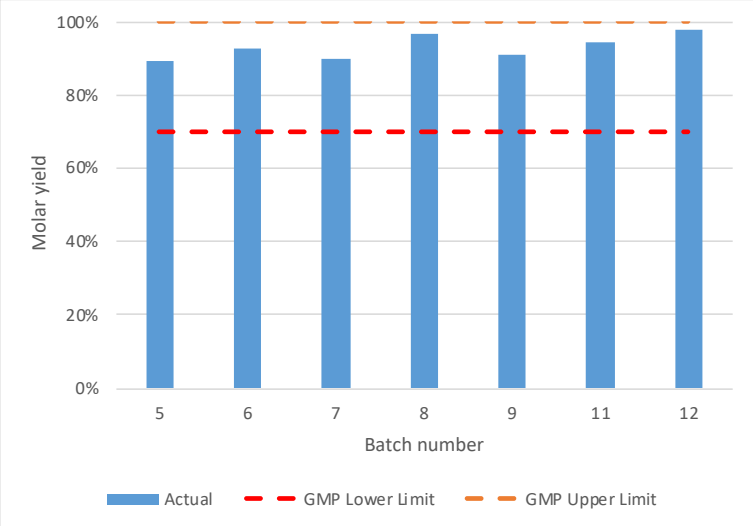



Figure E.3: Baseline yield values for Intermediate 3

Intermediate 2 revealed an average yield of 93% and the best observed value was 98%.

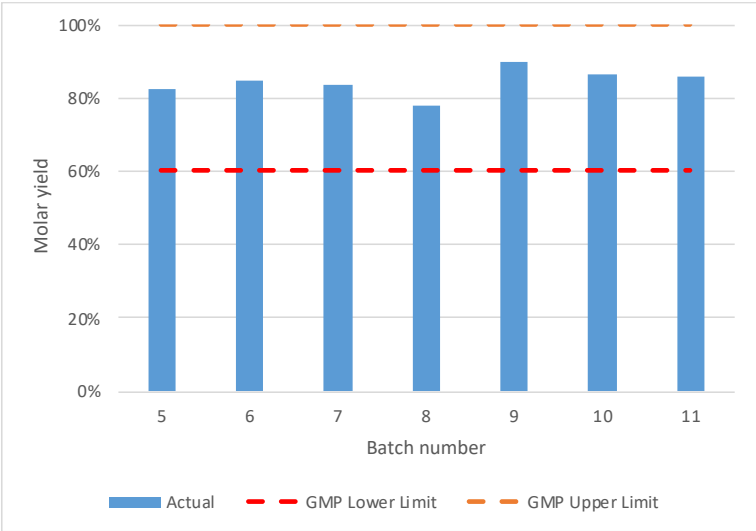



Figure E.4: Baseline yield values for Intermediate 4

Intermediate 4 revealed an average yield of 84.5% and the best observed value was 90.1%.

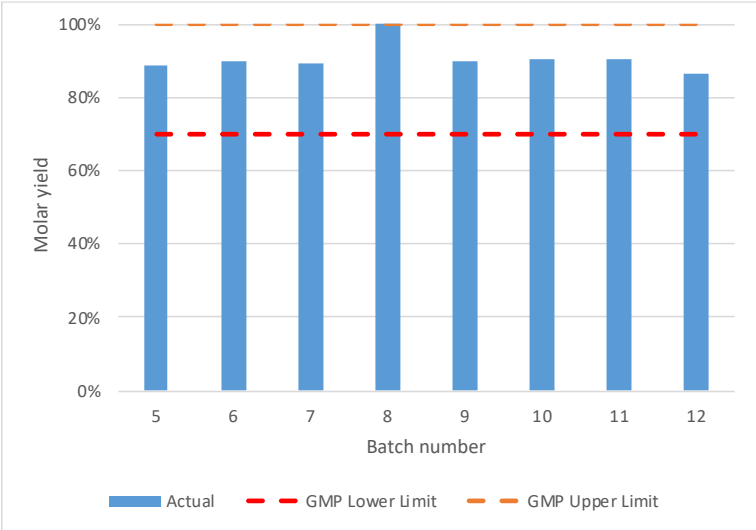



Figure E.5: Baseline yield values for Final Product

The Final Product process revealed an average yield of 90.9% and the best observed value was 100%; this intermediate shows the lowest variability in yield throughout the different campaigns.

# Appendix F:

## Baseline and actual yield results

Table F.1 compares the molar yield results from the previous campaigns and this campaign.

Table F. 1: Baseline and actual molar yield values (average and best observed)

| Molar yield | | Intermediate 1 | Intermediate 2 | Intermediate 3 | Intermediate 4 | Final Product |
|---|---|---|---|---|---|---|
| **Baseline** | **Average** | 65.1% | 69.7% | 93.0% | 84.5% | 90.6% |
| | **Best Observed** | 68.0% | 76.0% | 98.0% | 90.1% | 100% |
| **3rd commercial campaign** | **Average** | 65.8% | 66.9% | 84.2% | 82.9% | 88.5% |
| | **Best Observed** | 67.1% | 70.5% | 98.2% | 84.2% | 91.7% |

# Appendix G:

## Mass Balance Errors

Table G.1: Mass Balance errors associated with the analytical methods [32, 33].

| Intermediate | Step | Precision | Repeatability for assay | Accuracy for assay |
|---|---|---|---|---|
| **Intermediate 1** | Reaction 3, filtration, and washes | 0.10% | 0.60% | 100% |
| **Intermediate 2** | Reaction 1 | | | |
| **Intermediate 2** | Reaction 2, phase splits, filtration, and washes | 0.87% | $3.25 \times 10^{-5}$ % | 99.04% |
| **Intermediate 3** | Reaction, filtration, and washes | 0.89% | 0.24% | 100% |
| **Intermediate 4** | Reaction, filtration and washes | 0.13% | 0.04% | 100% |
| **Final Product** | Phase Splits, filtration, and washes | | 1.30% | 100% |

# Appendix H:

## Throughput values

In Table H.1, the baseline and target values for throughput are displayed; the total available time and manufactured quantity relate to the 3rd commercial campaign (that was the focus of this dissertation) and allow to calculate the throughput; comparing the baseline throughput with the throughput of this campaign it is possible to estimate the throughput increase for each of the processes.

Table H.1: Baseline, target and achieved throughput

| Intermediate | Baseline Throughput (kg/day) | Target Throughput (kg/day) | Total available time (h) | Manufactured quantity (kg) | Throughput (kg/day) | Throughput increase |
|---|---|---|---|---|---|---|
| **Intermediate 1** | 9.52 | 20.51 | 291 | 236.76 | 19.53 | 105% |
| **Intermediate 2** | 6.44 | 7.08 | 898 | 202.58 | 5.41 | -16% |
| **Intermediate 3** | 9.38 | 10.32 | 238 | 149.14 | 15.04 | 60% |
| **Intermediate 4** | 6.82 | 7.50 | 448.5 | 174.88 | 9.35 | 37% |
| **Final Product** | 6.88 | 7.57 | 319.5 | 123.24 | 9.26 | 35% |
| **API** | 1.26 | 1.38 | 2 196 | 123.24 | 1.35 | 7% |

# Annex I:

## Meeting guidelines for TOP15 and TOP60

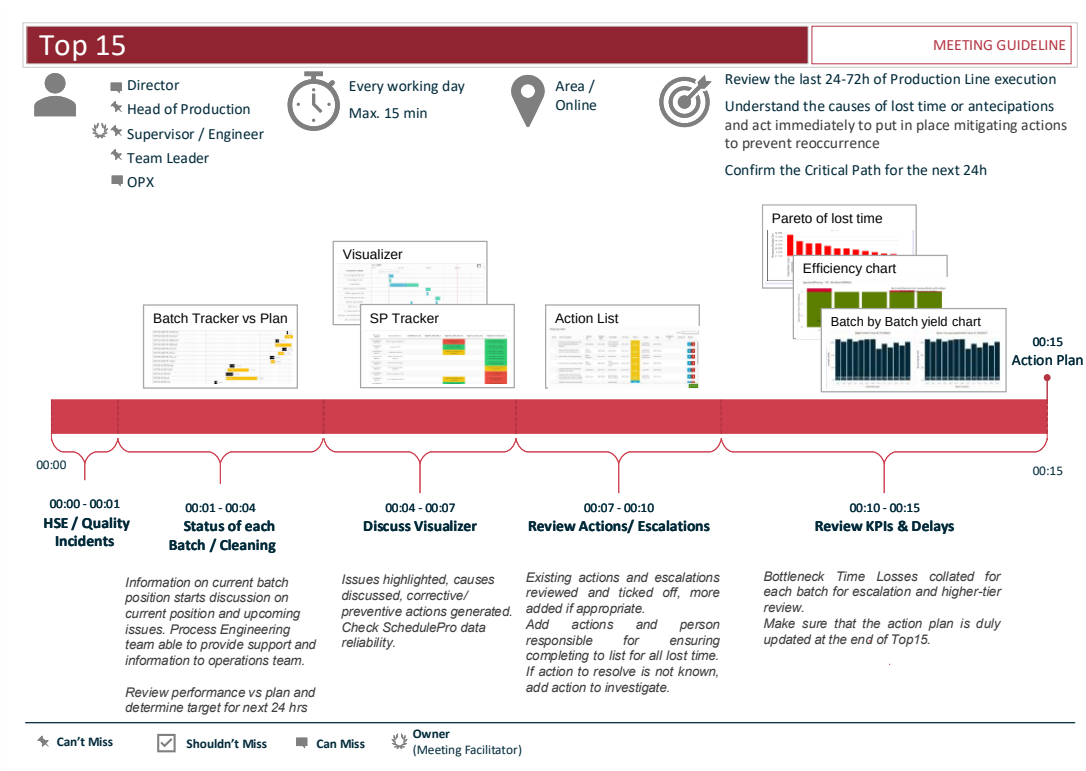



Figure I.1: Meeting guideline for TOP15

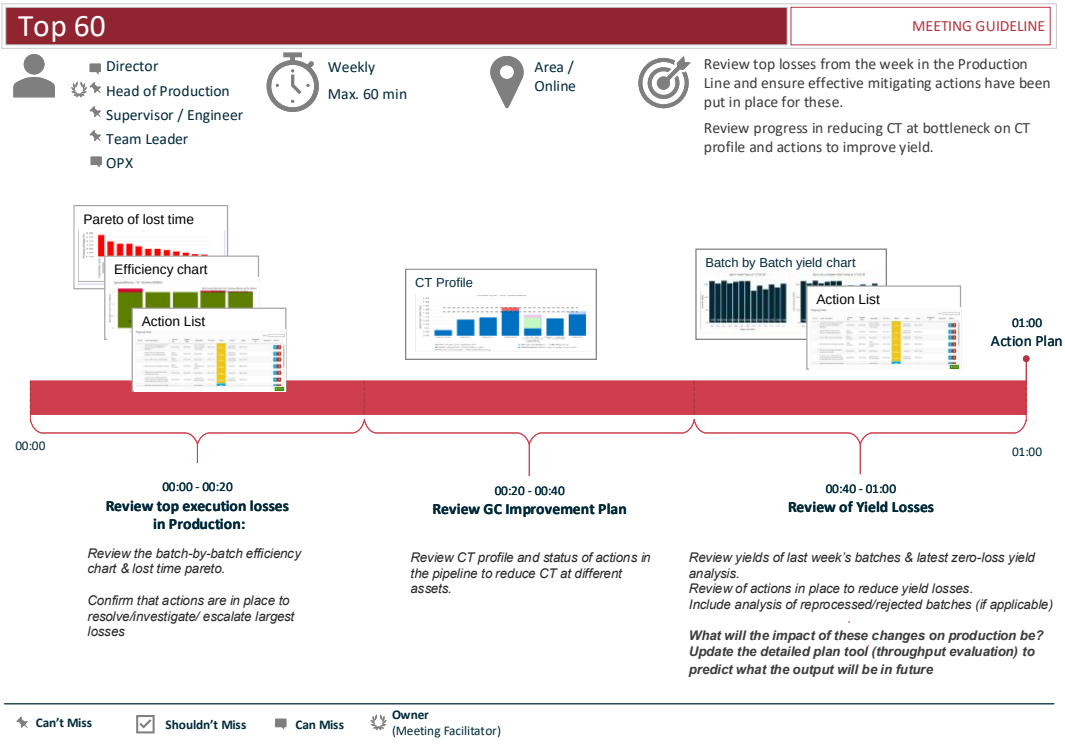



Figure I.2: Meeting guideline for TOP60