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Formulation Lead Time Variability in the Pharmaceutical Industry

Understanding Deviations and Other Causes of Variability

Master's Thesis in Supply Chain Management

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Abstract

The pharmaceutical industry is heavily regulated, with rigorous requirements on manufacturing and the quality of the product. These requirements provide a unique context, making the planning and production of pharmaceutical products challenging. At AstraZeneca, lead time variability in the production of tablets is perceived to be an issue. Therefore, the purpose of this study is to look into the lead time variability, identify causes and suggest improvement opportunities. A mixed methods approach, combining two rounds of interviews with a quantitative analysis of production data, is used to achieve the purpose of the study. The quantitative results show that most batches are produced according to plan, but that outliers, often associated with deviations, cause a great deal of variability. The interviewees give insight into what causes the variability and why deviations happen, and also share ideas on how to work to reduce their occurrence. The most common causes of variability in general are prioritizations that affect the production flow and issues related to staffing. When it comes to deviations, the main driver of the problem is noncompliance with standard operating procedures. Furthermore, the investigations of said deviations are not structured enough and too time consuming. In order to reduce variability, it is suggested that AstraZeneca do an oversight of their standard operating procedures, formalize their deviation handling teams, and invest more resources into their employees.

Keywords: Pharmaceutical industry, lead time variability, deviations, formulation, SOPs, Oral Solid Dosage, Good Manufacturing Practices

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Alexander Grahn and Karin Sjödin, Gothenburg, June 2021

ABBREVIATIONS

Abbreviation	Explanation
API	Active Pharmaceutical Ingredient
BAT	Business Analytics Team
CSM	Current State Map
EMA	European Medicines Agency
FDA	Food and Drug Administration
OSD	Oral Solid Dosage
PET	Process Execution Team
RCA	Root Cause Analysis
VSM	Value Stream Map

DEFINITIONS

Term	Explanation
Brand	A pharmaceutical product that can come in different strengths or formulations
Campaign	A number of batches of the same product that follows immediately after one another in production
Legacy Product	A product that typically entered the market 10-20 years ago, has competitors and low margins

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INTRODUCTION

Pharmaceutical manufacturing differs from most other types of manufacturing and this is in large part due to the fact that the pharmaceutical industry provides a unique context. It is characterized by spending a significant portion of its revenues on research and development and it has throughout time valued high product quality over production efficiency. It is also a strictly regulated industry, which has resulted in companies being reluctant to being first movers. However, some pharmaceutical companies have recently started to look at newer production processes, such as continuous manufacturing and pelletized APIs.

The British-Swedish biopharmaceutical company AstraZeneca is currently experiencing problems at their tablet factory in Södertälje. Varying lead times cause disturbances to surrounding functions and downstream operations, but these issues have not been thoroughly examined. AstraZeneca has now decided to investigate this issue.

1.1 Background

The Pharmaceutical Industry involves "the discovery, development and manufacture of drugs and medications (pharmaceuticals) by public and private organizations" (Dailey, 2018, Introduction). The industry is dominated by a relatively small number of large companies, sometimes referred to as “Big Pharma” (Gibson, 2019). Most large pharmaceutical companies are multi-national and located primarily in North America, Europe, and Japan (Dailey, 2018). On average, pharmaceutical companies invested 17% of their revenue in research and development (R&D) in 2019 (Parrish, 2020), which according to Gibson (2019) is far surpassing other industries. Despite the large investments, only one out of 5 000 potential drug candidates are approved due to strict regulation and high safety requirements (Gibson, 2019). Alex et al. (2015) estimate that pharmaceutical companies invest on average 403 million USD to develop every new drug.

One characteristic of the pharmaceutical industry is the high degree of regulation. According to Dailey (2018), most governments have developed regulatory agencies to respond to concerns regarding drug efficacy and safety. Furthermore, the author argues that most pharmaceutical products entail some adverse health risks, which means that these agencies must consider the risk-benefit trade-off when deciding whether to approve a new product. The manufacturing of pharmaceutical products is also highly regulated, with rigorous quality requirements (Gibson, 2019). According to Lavan et al. (2016), economists argue that government regulation is needed to ensure fair competition and safeguard public interests, which is why the authors believe that regulations will become even stricter in the future.

Another challenge facing the pharmaceutical industry is decreased productivity in terms of fewer products being launched. According to Alex et al. (2015), the number of new drugs approved each year by the US Food and Drug Administration (FDA) has stagnated, even though the R&D spend has increased drastically. This is consistent with Gibson (2019) who adds that new drugs being registered are often modified versions, or combinations, of existing drugs. Another challenge is the limited patent protection. A patent application is submitted when a promising drug has been identified, and if granted, the patent usually last for 20 years (Gibson,

2019). Once patents expire, the profitability typically plunges as generic drug manufacturers enter the market at a lower price point, since they do not carry the cost of R&D (Gibson, 2019). This means that pharmaceutical companies have a limited time to recoup their investment and make a profit.

1.1.1 Pharmaceutical manufacturing

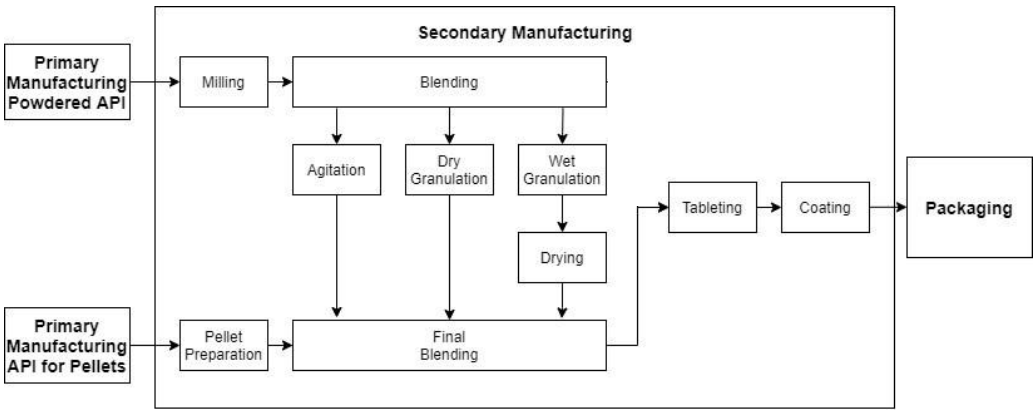
Pharmaceutical products come in many forms, such as tablets, capsules, ointments, liquids, and inhalers. Despite their varying types, Wilson (2016) explains that they all go through the same two phases during manufacturing. According to the author, primary manufacturing comes first and this is when the Active Pharmaceutical Ingredient (API) is produced. The production of APIs is followed by secondary manufacturing, which is when the API is turned into a product that can be administered to patients (Wilson, 2016). Shanley (2017) describes how the same processes have been employed in pharmaceutical manufacturing since the 1950's and that the equipment and quality control procedures are also unchanged at most companies. The author means that a reason for this is that companies are reluctant to being first movers in an industry that is characterized by conservatism and strict regulation. Wilson (2016) argues that pharmaceutical production is inefficient despite its long tradition, and mentions that long and short process times are mixed in the same production lines, causing some of these issues. Significant set-up times are also associated with some of the processes, and quality inspections are mentioned as a main culprit for the inefficiency (Wilson, 2016). Traditionally, these inspection processes have required production to be halted while tests are taken and analyzed, which has caused poor utilization and frequent interruptions (Wilson, 2016).

However, Grangeia et al. (2020) state that because of global competition, the pharmaceutical industry is currently under pressure to improve product quality and operational performance. At the same time, regulatory agencies have started to show a willingness to approve new production methods, given that the safety and quality aspects are not affected. Novel production processes such as automation and continuous manufacturing have started to gain ground within pharmaceutical manufacturing, and in 2017 the EMA (European Medicines Agency) gave its first approval for a continuous production line for tablets (Shanley, 2017). Yu and Kopcha (2017) believe that such emerging technologies within the pharmaceutical industry can result in better product quality, more robust processes, and fewer disruptions. Furthermore, Lopes et al. (2020) have looked at how Industry 4.0 impacts the pharmaceutical industry and especially the quality control procedures. The authors believe that the latest industrial revolution will enable continuous quality monitoring, which will have an immediate positive impact on manufacturing operations. Although the pharmaceutical manufacturing processes have remained essentially the same for the past 70 years, progress has been made. The examples mentioned are indicative of this development, and especially of the increased innovation pace in recent years.

Tablets and capsules that are to be taken orally are referred to as *Oral Solid Dosage*, or OSD, and a schematic illustration of the secondary manufacturing of tablets is shown in Figure 1.1. The processes vary somewhat depending on whether the tablet is based on an API in powdered or pellet form. In pharmaceutical manufacturing, a *pellet* is a very small, spherical mass that contains the API (Pałkowski et al., 2018), and Rajabi-Siahboomi (2017) states that the use of

Figure 1.1

The Processes Included in Secondary Manufacturing of Tablets



Note. A schematic image of the pharmaceutical manufacturing processes for tablets. Particles that are too large need to go through agitation, while those that are too small need to be granulated.

pellets is becoming increasingly prevalent. Certain tablets are based on this type of API, and in those cases, the first part of secondary manufacturing prepares these pellets. Farmoudeh et al. (2020) explain that there are a number of methods used to prepare pellets, including different ways of layering powders, spray drying, and extrusion/spheronization. According to the author, one of the main advantages of using pellets is that their combined surface areas are very large. By using different coatings on the pellets, it is possible to control more exactly where in the patient's body the API is released (Korasa & Vrečer, 2019).

When the API is in powdered form, secondary manufacturing starts with *milling*, which breaks up any lumps in the API (Wilson, 2016). Once this process is complete, the material is combined with other ingredients, *excipients*, in a process called *blending*, which Markarian (2019) deems to be very challenging. The author argues that it is very difficult to achieve a consistent mixture when the ingredients are of disproportionate amounts, and Dailey (2018) points out that the active ingredients only make up a minuscule fraction of the total weight of a tablet. Other challenges stem from the sizes and shapes of the particles (Markarian, 2019). If the particle sizes need to be reduced, the author suggests using a process that is called *agitation*. The size of the particles can also be enlarged using *granulation*, and this can, according to Wilson (2016), be done through either a wet or dry process depending on the properties of the API. Wet granulation is commonly used in pharmaceutical manufacturing and the author argues that it is a process that ensures homogeneous distribution of the API within the mixture. If wet granulation is used, Wilson (2016) explains that the mixture has to be *dried* before proceeding with the manufacturing processes. After the material has been dried it might have to go through a de-lumping process, similar to the one performed on the API at the start of secondary manufacturing (Wilson, 2016).

When producing tablets, the next process entails adding compression agents to the blend (Wilson, 2016), and starting with this step the production looks the same for powdered and pelletized APIs (Rajabi-Siahboomi, 2017). The added excipients are not active ingredients, but Aulton and Taylor (2013) argue that they are all added for a specific reason. For example, lactose can be added to improve the compression properties of the blend, while starches are used to facilitate swelling which aids in breaking up the tablet once ingested, and lubricants are used to ensure that the blend does not stick to the molds (Wilson, 2016). The mixture is then

fed into the compression process, which is called *tableting*. Wilson (2016) explains that the final step in the production of tablets is *coating*, where each tablet is covered with a membrane that makes it durable, visually pleasing, and gives it a uniquely identifiable appearance. According to Wilson (2016), most coatings are applied for cosmetic purposes, but there are also *enteric coatings* that fill a medical purpose, by for example letting the tablet pass further down the intestinal tracts before releasing its active ingredients. Aulton and Taylor (2013) also mention that coatings can disguise unpleasant flavors and make the tablets easier to swallow.

In summary, the steps included in secondary manufacturing differs depending on the form of the API and whether agitation or granulation is needed. A tablet based on powdered API goes through four to seven processes, while pellet-based products go through four main processes. It is, however, worth keeping in mind that this is a simplified explanation of the processes. In reality the steps can include sub-steps that are both numerous and time-consuming.

1.1.2 Explanation of Concepts Used

The terminology used within manufacturing can at times be ambiguous. For example, Jonsson and Mattsson (2009) define *lead time* as the time it takes to either complete a single process or a series of processes. The New Oxford American Dictionary provides a similar definition: "time between the initiation and completion of a production process" (2011). More specifically, Jonsson and Mattsson (2009) refer to the time elapsed between material supply and delivery of finished products as *manufacturing lead time*. The authors distinguish it from the *total throughput time*, which excludes all material supply aspects. The total throughput time can also be referred to as *production lead time*, as done by Rother and Shook (2003). These times include *set-up time*, which is the time that is required to convert a machine from the production of one product to the production of another (Jonsson & Mattsson, 2009).

For the purpose of this report, *formulation lead time* will constitute the time elapsed between the start of secondary manufacturing and the time when a batch is approved for delivery to the packing PET. This is similar to total throughput time, as defined by Jonsson and Mattsson (2009). The time consumed in each process and buffer will be referred to as *operation lead time*. The formulation lead time in this report will therefore be comprised of a number of operation lead times.

The lead time may vary due to a wide range of factors, a concept that will be referred to as *lead time variability*. In spite of this, Bandaly et al. (2016) state that lead times are usually treated as a constant rather than a variable factor. The authors conducted an extensive literature review covering research on lead time variability. The study found that lead time variability impaired supply chain performance, mainly by increasing inventory levels in the supply chain. According to Lödding (2013), lead time variability also affects the reliability of the schedule and delivery targets. These studies are consistent with Heydari et al. (2009), who argue that lead time uncertainty reduces the performance of a supply chain in terms of inventory build-up and that it negatively affects the ability to accurately plan operations. Furthermore, Heydari et al. (2009) suggest employing strategies to reduce lead time variability, arguing that this will lead to increased profitability. This is in agreement with Bendul and Knollmann (2016) who argue that the overall system performance can be improved by reducing lead time variability.

In statistics, data points that are significantly different than the remaining values in a data set are often referred to as *outliers* ("Outlier Analysis," 2017). Aggarwal (2017) states that outliers are often the result of a process behaving abnormally, and that can provide insights into the

process. Some outliers are to be expected in large data sets, but they can also be caused by measurement errors and skewed distributions, among other things ("Outlier Analysis," 2017). There are many ways to detect outliers, with varying complexity, and they are suitable for different use cases, argues Aggarwal (2017). The author says that what constitutes an outlier is often a subjective decision, as the analyst need to decide what data points are sufficiently different from the overall data set, regardless of the method used for outlier detection.

The outliers will not be removed from the data set but rather used to provide more insight into the investigated processes (Aggarwal, 2017). In this report, outliers will refer to the 5% of batches with the largest difference between targeted and actual formulation lead times. This is in accordance with what Aggarwal (2017) calls *extreme value analysis*.

1.1.3 Company Description of AstraZeneca

In 1999, the British Zeneca Group merged with Astra from Sweden to form AstraZeneca, a global biopharmaceutical company headquartered in Cambridge, England (AstraZeneca, 2021a). The subset of the pharmaceutical industry involving biological manufacturing processes is called the biopharmaceutical industry (Jogdand, 2006). So while AstraZeneca refers to themselves as a biopharmaceutical company, they also fall under the pharmaceutical umbrella.

As previously mentioned, research plays an important role for pharmaceutical companies, and AstraZeneca is no exception. The company spent 23% of their revenues on R&D in 2019, which is six percentage points above the industry average (Parrish, 2020). The company has an R&D presence in forty countries, with strategic facilities located in the US, the UK, and Sweden (AstraZeneca, 2021b). AstraZeneca's research is divided into three main focus areas, of which *Oncology*, cancer treatment, is the largest one. The other two are *Cardiovascular, renal, & metabolism*, which focuses on the heart, kidneys and digestive system, and *Respiratory & immunology* (AstraZeneca, 2021a).

AstraZeneca's manufacturing plants are spread across the world, with locations in Europe, Asia, North America, and Australia (AstraZeneca, 2021a). When accounting for local marketing companies owned by AstraZeneca, the company operates in more than 100 countries worldwide (AstraZeneca, 2021a). AstraZeneca produces four different types of products: *Active Pharmaceutical Ingredients (APIs)*, *Oral Solid Dosages (OSDs)*, *Devices*, and *Steriles* (A. Sjögren, personal communication, March 19, 2021). APIs are the substances that actually treat the conditions, and are included in all pharmaceuticals, for example in the tablets and capsules that are administered orally and make up OSDs (Wilson, 2016). Devices are what delivers inhaled medications, while Steriles comprise of solutions for injections (A. Sjögren, personal communication, March 19, 2021). This study covers the OSD segment.

Of the company's 76 100 employees (AstraZeneca, 2021a), 7 200 work in Sweden, with two thirds working at Sweden Operations in Södertälje, and one third at the R&D unit in Gothenburg (AstraZeneca, 2021c). AstraZeneca has two separate locations in Södertälje, and out of the company's total pharmaceutical sales, 35% are manufactured at the production facilities located there (AstraZeneca, 2021c). These two sites comprise of seven individual plants, which are called *PETs* (Process Execution Teams) (A. Sjögren, personal communication, March 19, 2021).

One of the PETs is *OSD Formulation*, which is responsible for manufacturing oral solid dosages. Employing about 600 people, it is one of the largest PETs at the Södertälje production site according to Asset Planner A. Sjögren (personal communication, March 22, 2021). In turn, the PET consists of a number of production units referred to as *sections*. Each pharmaceutical product is manufactured by a specific section. AstraZeneca refers to a pharmaceutical product as a *brand*, which contains all variations of a pharmaceutical product in terms of different strengths, coatings, and administration methods. After the manufacturing process has been completed, the finished products are delivered to another PET in Södertälje for packaging.

1.1.4 Case description

This study intends to solve a problem brought forward by Anders Sjögren, Asset Planner at AstraZeneca Sweden Operations. His role includes production planning at the OSD Formulation PET, and he acts as corporate supervisor for this project.

Because of the nature of the industry, the main focus areas for pharmaceutical companies are R&D and product quality. At AstraZeneca, a consequence of this is that production related KPIs such as lead time variability have not received sufficient attention, and this prioritization seems to be commonplace within the pharmaceutical industry. This is evident in a study by Talluri et al. (2004), who when investigating supply and demand variability at a pharmaceutical company decided to disregard lead time variability stating that it is an inherent problem within the industry. Even though lead time variability has historically been neglected, both in research on the pharmaceutical industry and in practice, AstraZeneca has now decided to look into the issue.

In this study, three large brands making up around 35% of the total production volume at the OSD Formulation PET will be investigated. Lead time data from the past 24 months will be used and the focus will be on the slowest batches, here called *outliers*. The three brands will hereby be referred to as Alpha, Beta, and Gamma and are produced by two different sections within the plant. During secondary manufacturing, both production planners and operators perceive a great deal of lead time variability. This is despite the fact that only a few main processes are involved, which should result in a more stable environment. Furthermore, all products are believed to suffer from lead time variability, regardless of whether they are manufactured on a dedicated or mixed production line. While AstraZeneca collects plenty of data from production, and currently has a strategic goal of reducing lead times, not much has so far been done about the variability. Even though AstraZeneca has not specifically studied the causes of this lead time variability, it is perceived to lead to consequences such as unnecessary inventory and elevated stress levels. Therefore, it is of interest to investigate the lead time variability at the OSD PET more closely.

1.2 Purpose

The purpose of this master’s thesis is to investigate the lead time variability over the past 24 months at AstraZeneca’s OSD Formulation PET in Södertälje. Causes will be identified and suggestions on how to improve the situation will be given.

1.3 Specification of issue under investigation

In order to fulfill the purpose, the study was broken down into four research questions. This study will be based both on interviews with stakeholders from different departments at AstraZeneca's Sweden Operations and on quantitative data. In order to ensure that all discussions and analyses are done based on the same information, it is of the essence to create an understanding of the activities involved in production. This boils down to the following research question:

1. How are the production systems for the brands in question currently organized at the OSD Formulation PET in Södertälje?

Both production planners and operators at the OSD PET have noticed the occurrence of lead time variability. In order to investigate this issue properly, the operation and formulation lead times first need to be computed. This leads to the second research question:

2. What do the operation and formulation lead times look like for the different brands?

All processes have inherent variation, but the lead time variability experienced at the OSD Formulation PET at AstraZeneca is higher than expected. Since the variability is perceived to be problematic, it is of interest to identify its causes in order to develop improvement plans. Therefore, the third research questions is as follows:

3. What are the causes of lead time variability at AstraZeneca's OSD PET in Södertälje?

Once the causes of lead time variability have been identified, improvement suggestions can be made. Therefore it is important to investigate the following question:

4. What can be done to improve lead time variability at the OSD Formulation PET in Södertälje?

1.4 Limitations

The main constraint limiting the reporting of this study was confidentiality. Because of patents, trade secrets, and to maintain competitive advantages, representatives from AstraZeneca needed to approve the text before it was published. Brand names and certain processes were masked to protect confidentiality, and the actual lead were presented after applying a factor, ensuring that patterns and outliers were identifiable without disclosing too much information. However, the company did not have the power to impact the findings, the analysis, or the reporting thereof.

Furthermore, this study was conducted during the spring of 2021, which was heavily impacted by the Covid-19 pandemic. In order to follow guidelines from the public health authorities, the vast majority of work was done remotely. This made direct observations at the production facility impossible, and the study relied on data collected by AstraZeneca. In addition, interviews had to be conducted using video-conferencing software.

2
THEORY

In this section, the theory collected from the literature review is presented. Its purpose is to support the analysis and provide a theoretical perspective. The literature review includes theory on Operations Planning and Control, mainly the different level of planning processes needed to effectively plan and control the production. It is followed by some organizational theory which discusses different ways to structure an organization and some benefits and drawbacks. One of these drawbacks, silo mentality, is discussed in more detail. Standard operating procedures and training of staff discusses standardization and some best practices in the pharmaceutical industry. Regulations includes an overview of some important regulatory aspects. Quality management provides an overview of quality management in the pharmaceutical industry. The following two sections, cleaning and hold time provide some more information about the specific context. Cleaning is a highly regulated topic within the industry, and necessary to bear in mind when planning pharmaceutical manufacturing, and hold time is a related concept that refers to ensuring the quality of materials used. The final section of the chapter explains the handling of deviations from a theoretical perspective.

2.1 Operations Planning and Control

The *Master Production Scheduling* (MPS) is defined by (Jonsson & Mattsson, 2009, p. 179) as "a process that involves developing and establishing plans for a company's sales and production operations". According to the authors, it involves a greater detail of planning than for example a *delivery plan* which often aggregates demand for different products and has a longer planning horizon. Jacobs et al. (2011) state that the purpose of the MPS process is to translate the delivery plan into a more detailed plan that can be operationalized, containing specific production volumes, capacity requirements and completion dates. Sheldon (2006) argues that the MPS is undervalued in many companies, stating that it is one of the most effective processes to control costs and increase productivity. MPS is an essential part of the *Enterprise Resource Planning* (ERP) system, the author says, and should supported by appropriate IT systems.

The goal of MPS is to balance the available capacity with the production requirements, both known requirements in terms of existing customer orders, but also forecasts (Jonsson & Mattsson, 2009; Sheldon, 2006). For the capacity planning, the information contained within the ERP systems is often used to make a rough-cut capacity plan (Jonsson & Mattsson, 2009).

The more detailed production plans are according to Jonsson and Mattsson (2009) referred to as *material planning* and *capacity requirement planning*, which involves planning the production schedule in detail with regards to material and capacity requirement respectively. The material planning involves planning procurement orders and dimensioning buffers, and the capacity requirement planning involves strategies to match available capacity and the capacity requirements (Jonsson & Mattsson, 2009). The lowest level of planning is according to Jonsson and Mattsson (2009) execution and control, which involves order priority and order reporting. One common order priority rule, the authors state, is *earliest start time first* which ensures that the production progressed as close to the plan as possible.

2.2 Organizational Theory

Organizations can be structured in many different ways, and according to Slack et al. (2016), the aim of formalizing an organizational structure is to divide the company into discrete parts where each part has some autonomy and group resources to allow specialization. One common organizational structure is the functional organization structure which according to Jacobsen and Thorsvik (2014) is based on grouping the resources by their functions. The author states that such a structure allows for a high degree of specialization by creating groups for activities such as purchasing, operations, sales, etcetera. However, a disadvantage with functional organizations is that the different functions tend to develop a separate culture and effectively communicating across functions can be a challenge (Jacobsen & Thorsvik, 2014). There are however organizational structures that attempt to solve this. The matrix structure is a hybrid structure, usually based on both functional and market based grouping of resources (Slack et al., 2016). According to Jacobsen and Thorsvik (2014), matrix structures are complex and difficult to coordinate, among other things because each employee will have two separate managers, which may result in conflicts. Another structure is based on projects, and according to the authors, they can either include a base structure or just consist of temporary project structures. the project organization, which can consist of a base structure in addition to a temporary project structure, or just a collection of temporary project structures. Jacobsen and Thorsvik (2014) also argue that project organizations have drawbacks, for example by requiring more administration.

The separate culture that can emerge in functions, divisions, or teams in organizations can result in *silo mentality* (Jacobsen & Thorsvik, 2014). Jacobsen and Thorsvik (2014) say that silo mentality results in each department being occupied by their own function, which leads to suboptimization and inefficient work. The author argues that silo mentality leads to inefficiencies and often poor product or service quality. Deighton (2016) states that silo mentality results in groups and individual employees not sharing information freely, arguing that it creates a self-destructive and highly inefficient organizational culture. One approach to counteract silo mentality is, according to Jacobsen and Thorsvik (2014), to structure the organization according to business processes, with cross-functional teams managing each process. The authors also argue that the development in information technology and IT systems can help in mitigating silo mentality.

2.3 Standard Operating Procedures & Training

Standard Operating Procedures (SOPs) are "detailed, written instructions to achieve uniformity of the performance of a specific function." (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 2016, p. 7). Jacobsen and Thorsvik (2014) argue that the main objective of SOPs is to ensure that tasks are being performed in the exact same way, time and time again, to create predictability. It is, however, essential to remember that operators are not machines, and Patchong (2012) stresses the importance of developing standards in collaboration "with operators, for operators" (p. 1). The author means that standardization leads to a safer work environment and better product quality.

Even though a SOP is written to document the optimum way of performing a task, Martin and Bell (2011) connect it to the lean concept of continuous improvement. The authors mean that updates and changes to the standardized work descriptions need to be done in small steps, both to minimize risk and to make it easier for operators to implement the new procedures. Gallup

et al. (2008) discuss how employees need to be trained on the standards in order to follow them. The author means that proper training leads to better compliance with regulations and also improved performance. An employee that has gone through the necessary training on the SOPs need to know how to access the documentation and understand their purpose (Gallup et al., 2008). What Gallup et al. (2008) refer to as *qualified personnel*, also need to show that they have read and understood the SOP and that they are able to do the job as described in the material.

Prina (2017) believes that training programs should be taken seriously at all firms. The author argues that investing in employees is vital and that investing through training makes employees more engaged. By exposing employees to new methods and teaching them new things, Prina (2017) means that they can achieve personal growth while avoiding burnouts. The author describes a simulation done on operators manufacturing robots. During the first installment of the simulation, the operators believed that they were understaffed, but after a couple of training sessions they were able to perform the same simulation with fewer operators than during the initial test (Prina, 2017). This, argues Prina (2017), shows that investing in training programs can pay dividends in the long run.

2.4 Regulations

As previously mentioned, the pharmaceutical industry is under strict regulation from agencies tasked with protecting the safety and well-being of those using the drugs. The FDA, for example, regulates quality assurance for each step of the manufacturing process, the purity of the ingredients going into the medicines, the packaging and labeling, the cleanliness of the entire process, the documentation, and of course many other aspects such as the R&D process and the distribution and sales of the finished products (Harris, 2008). Comprehensive documentation is required for all finished pharmaceutical products, and Durivage (2016) states that the specific batch must be identifiable in cases of recall, and that all included ingredients also must be traceable. The documentation for each batch also must list the specific equipment that was used and all employees involved during the manufacturing and testing processes (Durivage, 2016).

2.4.1 Quality Management

The quality of pharmaceutical products is measured when samples are tested against predetermined specifications. Durivage (2016) describes how these specifications are determined. When a drug product is first developed it is the manufacturer that proposes specifications for everything from raw material to the finished, packaged product (Durivage, 2016). Early on in the development process, Durivage (2016) explains that not much is known about the product and the processes included in production, resulting in specifications that focus on safety. As the development progresses, however, more information is collected and the specifications become more detailed, regulating quality, performance, excipients, processes, analytical methodology, compendium, packaging, etcetera (Durivage, 2016). These specifications then need to be approved by regulatory agencies before the drug can be validated and enter the market, and they cannot be changed without going through an extensive process to ensure that the finished product is not negatively impacted by these changes to specifications (Durivage, 2016).

Good Manufacturing Practices (GMP) is a collection of best practices published by the World Health Organization. One fundamental principle specified in the GMP is the separation of the

quality and production departments, and quality control, that ascertains that specifications are met, should be conducted in areas separate from production (World Health Organization [WHO], 2014, Annex 2). Quality Control must test incoming ingredients as well as the finished products (WHO, 2014, Annex 2), and Durivage (2016) explains that the requirements get stricter towards the end of the production process. The GMP also contains specifications on how the samples should be taken (WHO, 2014, Annex 2). Durivage (2016) stresses the importance of proper documentation and labeling throughout all testing processes, both to meet regulatory demands and to limit the risk of mistakes and unnecessary rework. Included in this documentation should be the initials of all employees involved in preparing, taking, and testing the samples, the batch number, the name of the product, and the date (Durivage, 2016).

Quality controls should be performed both on the finished products and during the production process. When the quality is tested without removing the product from the process, it is called *In-Process Control* (IPC) (WHO, 2014, Annex 2). Durivage (2016) states that these controls may inspect product characteristics such as weight and size, disintegration times, dissolution rate, and adequacy of mixture with regards to uniformity. The author suggests integrating IPC in the control of the production flow, by for example mixing until uniform instead of mixing for a given time before stopping to take a sample.

Durivage (2016) also argues that a quality systems approach should be taken, using analytical and statistical methods to monitor and evaluate the operations. Traditional quality management is according to Ranky et al. (2008) difficult to apply to pharmaceutical manufacturing. The authors state that the traditional philosophy allows for mistakes to happen and focuses on correcting them after the fact, and that it also accepts that increases in productivity and volume lead to decreased product quality. The concept of quality management has evolved over the years, originally only involving inspection of finished products, but later focusing on controlling the quality of the individual processes (Cogdill, 2008). Examples of the latter are concepts such as *Zero Defects*, *Total Quality Management*, *ISO certifications*, and *Six Sigma* (Cogdill, 2008). According to the author, all these approaches use systematic methods to identify and manage sources of process variability, with the goal of keeping their effects on product quality at a minimum.

Since the early 2000's, the FDA has had an ongoing initiative aimed at improving the efficiency of the pharmaceutical industry while limiting excessive regulation, and it has resulted in overall improvements to the manufacturing quality (Yu & Kopcha, 2017). Included in this initiative is the *Current Good Manufacturing Practices*, which has borrowed many of its concepts from other industries and was released by the FDA in 2001 (Cogdill, 2008). Even though the overall quality of pharmaceuticals has improved during the past decades, there is a large disparity between new and older products according to Yu and Kopcha (2017). The authors show that poor product quality has resulted in increasing number of recalls of legacy medications, which in turn has led to drug shortages. The recent advances in manufacturing processes and quality control have in other words had a positive impact on new products released to the market, but existing medicines have been left behind.

2.4.2 Cleaning

Regulatory agencies also demand that certain cleaning procedures are undertaken between batches in production, and the type of cleaning that is required depends on a number of aspects. Ghosh and Dey (2010) explain that there are different guidelines for the cleaning of equipment used for primary and secondary manufacturing. The authors list three levels of cleaning required

during the production of APIs, while there are only two levels mandated for drug products. Other parameters affecting the type of cleaning are whether the equipment is dedicated or shared and if the process is in the early or late stages or production (Ghosh & Dey, 2010). Both Wilson (2016) and Ghosh and Dey (2010) explain that a switch from one batch to the next of the same product normally does not require the same thorough cleaning as a switch between two different products does. A simple level 1 cleaning is required when manufacturing two consecutive batches of the same product, while an in-depth level 2 cleaning is mandated when switching between products (Ghosh & Dey, 2010). There is, however, a limit to the number of continuous batches of the same product that can go through a process with only level 1 cleaning taking place. A *campaign* is according to Strohhecker et al. (2014) a number of batches of the same product that follows immediately after one another, and Pacciarelli et al. (2011) define the *campaign size* as the maximum number of such batches that can go through a process before requiring the more thorough level of cleaning.

According to Durivage (2016), an effort should be made to use automated cleaning processes when possible, since repeatability is of the essence. Wilson (2016) mentions that the cleaning taking place between batches is often done automatically by systems that are built into the equipment. The procedures that are required between campaigns and product switches are, however, done manually and require laboratory tests to ensure cleanliness, making them significantly more time consuming (Wilson, 2016). This is in line with Ghosh and Dey (2010), who explain that level 1 cleaning is the least extensive and demand only visual inspection, while level 2 is comprehensive and requires analytical testing to verify cleanliness. Durivage (2016) stresses the importance of ensuring that all cleaning processes are done in consistent manners no matter what operator performs them. A validation program governing cleaning should be in place to ensure that the processes are robust, repeatable, and well-documented (Durivage, 2016).

2.4.3 Hold Time

The World Health Organization regulates the time that a material can be held at a certain temperature and humidity level between processes without it affecting the quality, and this time is referred to as *hold time* (2015, Annex 4). To decide the hold time for a specific material, a sample corresponding to the batch size should be kept in the same type of container as used in production and it should also be held at the same temperature and humidity levels (WHO, 2015, Annex 4). In order to assure that the material meets specifications, the WHO (2015, Annex 4) dictates that Quality Control should analyze samples taken out of the container at different time intervals. The WHO (2015, Annex 4) also mandates the tests that should be performed, and the time intervals that should be used for sampling. These times depend on how far along in the formulation process that the material has come. For example, a solution or suspension meant for coating should be tested when the initial sample is taken and every twelve hours until seven samples have been tested, at hour 70 (WHO, 2015, Annex 4). Granules and blends are to be tested every 15^{th} day until day 45, and uncoated tablets need to be tested initially, and then after 30, 45, 60, and 90 days (WHO, 2015, Annex 4).

2.4.4 Handling of Deviations

A *deviation* is the "departure from an approved instruction or established standard" (ICH, 2000, p. 40) and the FDA (2018) clarifies that not all deviations impact the quality of the product. There are different ways in which deviations can be identified, such as during a laboratory test or a review of the required batch documentation (Durivage, 2016). Kumar et al. (2020) argue

that deviations are a daily occurrence for actors within the pharmaceutical industry and that investigations thereof are an important part of the company's quality management system. The authors list four parts of such an investigation: identifying the deviation, grasping its severity, doing a root cause analysis (RCA), and finally suggesting what can be done to prevent the same deviation from happening again. According to Kumar et al. (2020), all deviations need to be categorized as either *minor*, *major*, or *critical* based on their severity. The authors explain that minor deviations do not affect the quality of the drug product, while critical deviations have a significant quality impact. Major deviations fall in the middle, and may have impacted quality. The root cause analysis, according to Kumar et al. (2020), leads to classifying the deviation as being caused by either *men*, *material*, *machine*, *method*, or *mother nature*.

Durivage (2016) briefly discusses the training required for employees of the *quality unit*. This is the unit that, according to the author, is tasked with releasing approved batches, but also with identifying deviations and rejecting those batches. Durivage (2016) explains that the Good Manufacturing Practice (GMP) Guidelines recommend that employees of the quality unit should be trained to recognize deviations, both during production and the testing processes. Furthermore, they should have good technical and scientific knowledge, an understanding of the products and processes, and be able to assess risk (Durivage, 2016).

3
DEVIATION HANDLING AT ASTRAZENECA

This section is based on an internal document provided by AstraZeneca and an interview with Certified Deviation Coordinator Johan Matti. The handling of deviations at AstraZeneca differs in some ways from theory. The company has a Quality Assurance (QA) unit tasked with releasing and rejecting batches, but they do so after evaluating batch documentation, and are not supposed to identify problems in production or with testing procedures. Instead, the main responsibility for deviation detection lies with the production staff, and it is the First Line Manager of the identifying employee who owns the investigation. This employee is a qualified deviation coordinator. Within a day of detecting a deviation, an investigation team should be in place. This team is always made up of members from Production, Process technology, Maintenance, and QA and is complemented with other departments or experts as needed. Certain deviations might require additional analyses to identify foreign substances or to ascertain no quality impact. In other instances decisions by microbiologists might be needed, or judgements from toxicologists located in England. The fact that many different departments are part of the deviation team makes it difficult to find meeting times that suit everyone. This can delay the handling of deviations, since the members of the team all possess unique skill sets that are needed to move the investigation forward.

When a deviation is identified, the batch is labeled and stopped immediately. The investigation team must decide whether the batch has to stay there or whether it can continue through the rest of formulation. This decision is mainly based on if the batch could affect any subsequent batches by moving on. However, the investigation of the deviation has to be finalized and the batch approved before the product can leave AstraZeneca's internal flows. The deviation team needs specific information from the production staff in order to perform their investigation, and there are standards and check-lists in place to ascertain that the deviation protocols are complete when being sent to the team. The team classifies the deviation as being either Level 1, 2, or 3, and for deviations of the two more serious levels, Level 1 and 2, a Certified Deviation Coordinator is assigned. This is the only member of the investigative team that works with deviations full time. For the others, investigating deviations is only part of their work. The Certified Deviation Coordinator is tasked with arranging meetings and making sure that lab results and judgements are received in a timely manner. There are internal targets dictating the duration of deviation investigations and a Level 3 investigation is to take 5 factor-adjusted days, while Level 1 and 2 have a target of being completed within 18 days. However, these targets are rarely met. The OSD PET has a goal of closing 80% of all deviations within 18 adjusted days, but the actual figure was at 35% last year. A couple of projects have been initiated to look at how the handling of deviations can be sped up, but no changes have been made at this point.

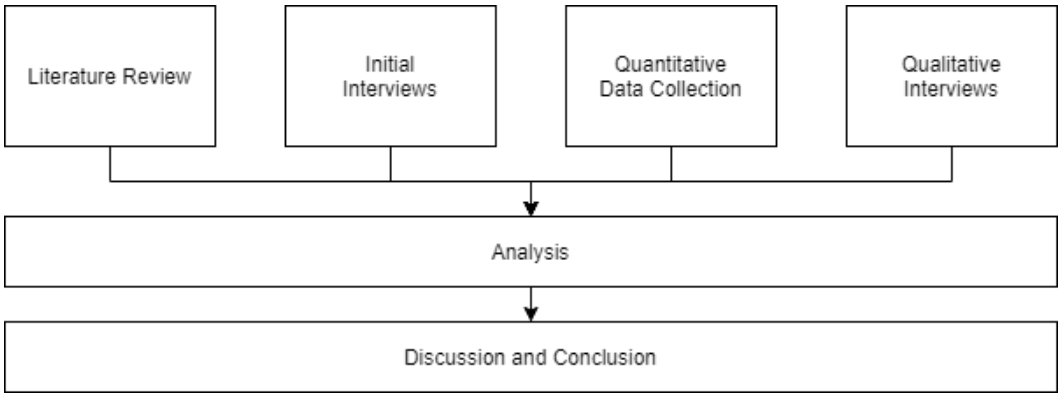
The deviation investigation is not finished when the cause for the deviation has been identified. At that time, suggestions on how to prevent that same problem from happening again are presented, and if needed the SOPs and methods are updated to reflect the change. This is an important part of the process and the investigation progresses at the same intensity until the new procedures are finalized and the deviation report can be closed.

4
METHOD

The lead time variability at AstraZeneca's OSD Formulation PET was investigated by using a number of methods to gather and process both qualitative and quantitative data. The study consisted of a quantitative data analysis and two rounds of interviews, with a literature review that went on throughout the duration of the study. The results of these four phases were analyzed before the conclusion and discussion were written, as outlined in Figure 4.1. The qualitative and quantitative approaches complemented each other by reducing the risk of bias and by offering more than one perspective on the issue at hand. The different types of data were integrated using a mixed methods approach with a qualitative starting point through the initial round of interviews. The information gathered during these interviews was used to prepare a value stream map for each of the three brands under investigation. This resulted in a visual representation of the secondary manufacturing processes, complete with operation lead times. The information presented in the maps was used to gather relevant quantitative data from AstraZeneca's Business Analytics Team (BAT) and this data was processed and analyzed to investigate the lead time variability at the plant. A second round of interviews was conducted in order to gain a broader understanding of the causes of the variability. These interviews were recorded and transcribed before being coded to identify common themes. Analysis of the qualitative data was undertaken both during and after the interview rounds, while the quantitative data was gathered before starting the analysis. In accordance with the mixed methods approach, the results from the three sub-studies were compared and contrasted during analysis.

Figure 4.1

A Schematic Project Outline



4.1 Methodology

The following subsections describe the five methods used for this study. Mixed methods was the overarching methodology, and it was the one used to combine the qualitative and quantitative approaches of the study. Value stream mapping was only used when developing the current state maps illustrating the production flows for Alpha, Beta, and Gamma. Semi-structured interviews were held both during the development of the CSMs and when interviewing representatives from different departments at PET OSD to discuss lead time

variability and its causes. The latter interviews were transcribed and coded in order to analyze the results objectively and being able to present qualitative results in a quantitative manner. The descriptive statistical methods were used to analyze the quantitative data gathered from AstraZeneca's systems. Some method critique and mitigating strategies are discussed throughout the section.

4.1.1 Mixed methods

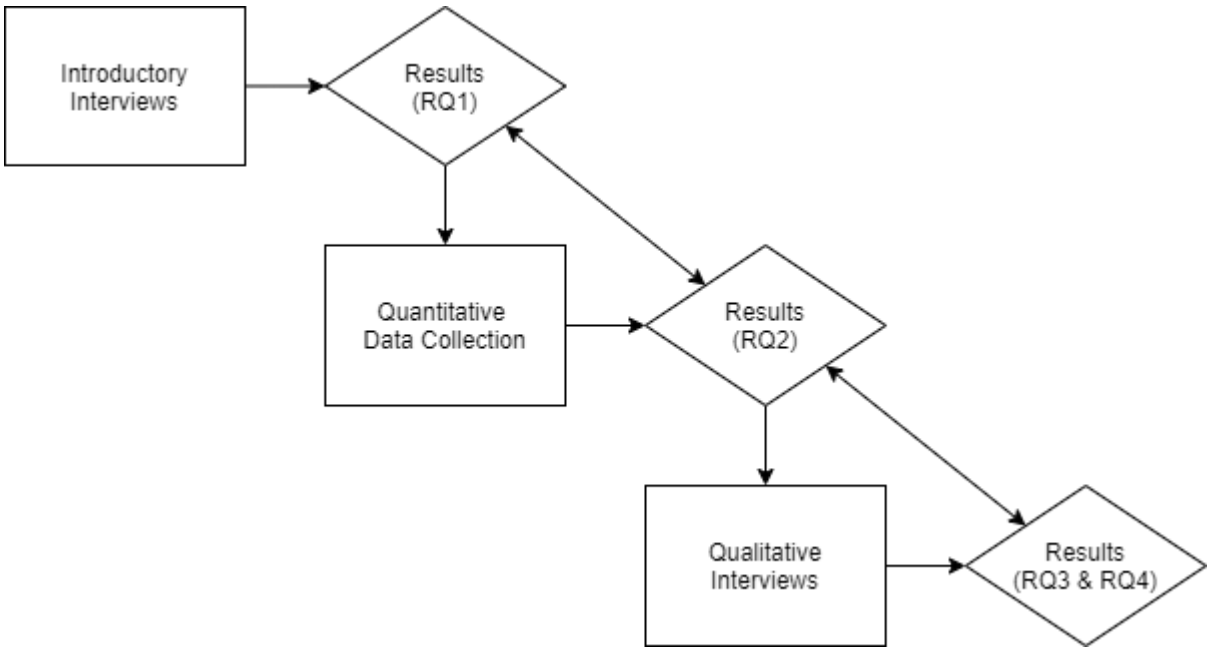
This study mapped out and analyzed the OSD production lines in Södertälje, which are intricate parts of AstraZeneca's supply chain. Golicic and Davis (2012) argue that using *mixed methods*, with both qualitative and quantitative approaches, are suitable when investigating complex systems. The strengths and weaknesses of qualitative and quantitative approaches complement each other and give more than one perspective, thereby reducing the risk of method bias (Bell et al., 2019; Golicic & Davis, 2012). In this case, interviews were used to gain insight into the processes that quantitative data could not provide. On the other hand, all interviews entail bias, where an interviewee might place the blame on a different department for personal gain. That is why both qualitative and quantitative data collection, processing, and analysis were performed. This led to a better and more accurate understanding of both the production processes at AstraZeneca and the problems they experienced with lead time variability.

Golicic and Davis (2012) and Creswell (2015) stress the importance of integrating the quantitative and qualitative approaches in research using mixed methods. The study also has to have a starting point in one of the two approaches (Golicic & Davis, 2012). Hirschman (1986) suggests starting with a qualitative approach when the subject matter is new and the aim is to understand not just the problem, but also its specific context. Even though varying lead times are commonplace in manufacturing, the specific production lines at AstraZeneca and their context within the pharmaceutical industry have, to the researchers' knowledge, not been studied before. This made a qualitative starting point suitable for this study. Golicic and Davis (2012) mean that gathering qualitative data is necessary in order to clearly describe the problem at hand, and this process can be iterative and ongoing until the problem has been clearly defined. In Figure 4.2, the mixed methods approach used for this project is illustrated, along with the corresponding research questions that were addressed during each phase.

The qualitative and quantitative approaches have to be integrated and this is often done with two parameters in mind: *weight* and *timing*. The weight refers to whether the two approaches should be of equal importance or not, and the timing to whether they should be conducted simultaneously or in sequence (Golicic & Davis, 2012). When putting equal importance on the two approaches and implementing them after one another, it is according to Golicic and Davis (2012) called a *development research purpose*. The authors state that this integration method is employed when the result of the first approach is used to design the second one. The development research purpose suits this project. Initial interviews were used to gain insight into the production processes at the OSD plant. This information was later used to gather relevant quantitative data from AstraZeneca. A second round of interviews was based on these findings and conducted in order to identify the causes and consequences of the lead time variability. The results from the interviews and from the data analysis were finally compared and contrasted, as suggested by Golicic and Davis (2012). Because of new information that was provided in the second round of interviews, some additional quantitative compilations were made.

Figure 4.2

Schematic Diagram over the Used Mixed Methods



Note. Adapted from "Benefits and challenges of conducting multiple methods research in marketing", by D.F. Davis, S.L. Golicic, and C.N. Boerstler, 2011, Journal of the Academy of Marketing Science, 39, 467-479 (https://doi.org/10.1007/s11747-010-0204-7).

Furthermore, when processing data from the second round of interviews, a concept called *data triangulation* was employed. Data triangulation means that a phenomenon is investigated using a range of data sources (Flick, 2018). In this study, the perspectives of individuals at different departments of the case company constituted different data sources. Using multiple sources provided more understanding of the issues at hand, thereby giving the analysis more depth. This is consistent with Flick (2018), who argues that triangulation should be used to gain a deeper understanding of a studied phenomenon.

4.1.2 Value Stream Mapping

In order to ensure an accurate understanding of the production process the production systems were visualized using *Value Stream Mapping* (VSM). VSM is a commonly used tool within lean production, and its purpose is to map the value stream and to identify and remove non-value adding activities, referred to as "waste" (Liker & Hoseus, 2008). A value stream is defined by Martin and Osterling (2013, What is a Value Stream, para. 1) as "...the sequence of activities an organization undertakes to deliver on a customer request". Martin and Osterling (2013) state that companies often lack a holistic understanding of their value streams. The author argues that VSM is especially useful for visualizing how the material and information flows interact, which is often hard to capture with other methods. While not addressing, for example, the design of the individual work stations, the VSM method is suitable for addressing general production and control issues (Baudin, 2002) and it also provides a cross-functional perspective of the production system (King, 2015). This level of detail was adequate for this study, as the purpose of using this approach primarily was to address the first research question, which deals with the overall organization of the relevant production systems.

The first step in VSM is to visualize existing operations in a *current state map* (CSM), which, according to Martin and Osterling (2013), establishes facts and a common understanding of the production system. The CSM can also be used as a basis for improvement work, and a *future state map* is according to the author created to visualize and evaluate possible changes. However, the purpose for using the VSM method in this study was to gain a comprehensive understanding of the production system and to support communication. Therefore, creating only current state maps was deemed sufficient to serve these functions. A CSM contains the processes involved in the production systems, as well as a number of production related metrics for each process. Martin and Osterling (2013) recommend always using the same three performance indicators, while King (2015) presents a comprehensive list of items that can be added to a current state map. King (2015) emphasizes that the chosen metrics should be adapted to the specific situation and the purpose of each current state map. In addition, buffers, information flow, and production control methods can be visualized (Martin & Osterling, 2013).

Martin and Osterling (2013) argue that a current state map should be developed following the lean principle of "going to the Gemba". Within lean, this means being present on the shop floor, observing operations in person (Liker & Hoseus, 2008). However, given the current circumstances, with the ongoing Covid-19 pandemic, this was not possible. It was found that AstraZeneca had previously produced VSMs for the relevant brands and those maps were provided. Although not all VSMs were made recently, initial interviews were conducted with the Industrial Engineers responsible for the respective production flows to ensure their accuracy. Using these maps and the information conveyed during the interviews, new CSMs were made. These were adapted to suit the purpose of this study while also not revealing confidential information. Although this is not the approach recommended in literature, the maps should still be considered valid as they were verified by the responsible Industrial Engineers.

4.1.3 Semi-structured Interviews

This project included two rounds of interviews. The objective of the first one was to gather enough information about the manufacturing processes at AstraZeneca's OSD facility in Södertälje so that a current state map could be developed. The second round of interviews was conducted at a later stage, in conjunction with the quantitative study, with the purpose of investigating what employees believed were the causes of the lead time variability. In both cases, the goal was to access both the explicit and tacit qualitative knowledge possessed by the operators, managers, and planners at the factory, and both Patel and Davidson (2019) and DiCicco-Bloom and Crabtree (2006) suggest using *semi-structured interviews* in such instances. Semi-structured means that the questions asked are open-ended and the person conducting the interview should not try to lead the respondent into specific answers (DiCicco-Bloom & Crabtree, 2006; Warren, 2001). The main questions are decided upon beforehand, but follow-up questions are allowed and the order of the questions is not predetermined (Patel & Davidson, 2019). The authors argue that this approach gives the respondents the ability to freely share their ideas without them being tainted by the hypotheses or beliefs of the interviewer. DiCicco-Bloom and Crabtree (2006) state that the number of interviews to be undertaken should not be predetermined. Instead, the data collection should continue until the interviews do not produce any new information, which is when the study is said to have reached *saturation* (DiCicco-Bloom & Crabtree, 2006).

Semi-structured interview studies come with inherent risks. It is important that the right people are interviewed, since there otherwise would be a risk of the interviewee not being sufficiently familiar with the subject matter. In this case, AstraZeneca helped with identifying and contacting appropriate respondents. In some instances this assistance came from the interviewee's superiors, making it essential to maintain the anonymity of all respondents, as stressed by DiCicco-Bloom and Crabtree (2006). This was done to ensure that the information shared did not result in any negative consequences for the respondents. The respondents were allowed to withdraw from the interview study if they so choose, which is consistent with DiCicco-Bloom and Crabtree (2006).

According to Olsen (2012, Chapter 2.6), *observation bias* exists in almost all settings. The author explains that the researcher might have a pre-existing viewpoint that can taint how interviews are conducted or interpreted. Therefore, it is important to interview employees representing every involved department, to keep an open mind, and to not draw conclusions based on a single, convincing respondent. Furthermore, all questions need to be asked in clear and concise manners to reduce the risk of misunderstandings (Olsen, 2012, Chapter 2.6). For the person conducting the interview, it is important to follow a carefully prepared plan, and by recording and transcribing all interviews the risk of incorrectly interpreting the interviewee is minimized (Olsen, 2012, Chapter 2.1). Because of the Covid-19 pandemic, all interviews were conducted remotely using a videoconferencing software, which might have limited the conveyance of non-spoken communication. While hard to fully mitigate, it was important to be aware of this risk.

Based on this information, semi-structured interviews were deemed to be a suitable approach for both rounds of interviews, as they gave the respondents room to freely share their opinions. Representatives from all relevant departments were interviewed, and saturation was kept in mind.

4.1.4 Coding

The second round of interviews were recorded and transcribed in order to organize the information, which, according to McMillan (2012), is the first step in a thorough analysis of qualitative data. Both Brinkmann and Kvale (2018) and Gibbs (2018, Chapter 1) stress the importance of starting the analysis process during the course of the interview study. This is, according to the authors, a main difference between qualitative and quantitative analysis. By collecting and analyzing data concurrently, the knowledge gained during early interviews can be used during later ones, and Gibbs (2018, Chapter 1) states that the flexibility of qualitative research even allows for new research questions to be developed during the course of the study. In an effort to adhere to the mixed methods approach, where results should be compared and contrasted without having been analyzed, the analytical elements of qualitative processing were kept at a minimum.

The data gathered during the initial interviews was used to create current state maps based on the provided VSMs. Whereas the initial interviews required no further processing methods, the information gathered during the second round of interviews was more extensive and also more ambiguous, resulting in a need for interpretation. The information was also in need of being analyzed in an objective manner and being quantifiable. According to Gibbs (2018, Chapter 1), one of the methods frequently used when analyzing large volumes of qualitative data is *coding*. The author argues that while quantitative analysis often aims at reducing and simplifying data into statistics, qualitative analysis usually enhance and expand the data. Coding means that the

transcribed data is preserved in its original form, but code words are assigned to the text to facilitate interpretation (Gibbs, 2018, Chapter 1). Davies and Hughes (2014) explain that the first step in preparing transcribed material for coding is to separate the touched-upon subject matters by color. After the material has been color coded, the different subjects can be analyzed one at a time by attributing code words to the text (Davies & Hughes, 2014). Gibbs (2018, Chapter 4) discusses that there are a number of terms used for these code words, where some researchers prefer calling them *indices* while others use *categories* or *themes*. There are also methods that combine two or more of these words. For example, McMillan (2012) explains how code words are assigned to text to summarize what is said, while categories are broader and can include many code words.

In this report, the word *code* was chosen to represent the general concepts found in the transcribed material. For the main research area, the reasons behind lead time variability, the code words were numerous and were therefore arranged into broader *categories* that summarized their content. Since the purpose of the interviews was to identify the causes of lead time variability, the code words were deduced from the interviews in what Gibbs (2018, Chapter 4) refer to as *data-driven coding*. The codes and categories were used to find commonality among the respondents, after which the results were analyzed and discussed.

4.1.5 Descriptive Statistical Methods

A mainly *exploratory approach* to data processing was used to gain a deeper understanding of the varying lead times. Byrne (2017) explains that this means that the data is investigated without preconceived hypotheses. The author argues that *descriptive statistical methods* are useful for such an approach. May (2017) says that descriptive statistics is usually the starting point for all data analysis, and the term is used to describe the characteristics of a data set. The author states that descriptive statistics deals with two main characteristics of a data set: the measures of central tendency and the measures of spread. Central tendency is described by dimensions such as *mean*, *median*, and *mode*, while spread is described by measures such *variance*, *range*, and *deviation* (May, 2017). In this study, both central tendency and spread were explored and visualized in various graphs. Brown (2010) states that graphs can be powerful tools for exploratory data analysis, and by using for example *box and whisker plots*, the characteristics of a data set can be shown. Other graphs were also used when appropriate.

4.2 Literature Review

The project was initiated with a literature review in order to gain an understanding of the pharmaceutical industry, the manufacturing processes, and AstraZeneca, the case company. This review was later expanded to include all subjects necessary for a comprehensive analysis of the gathered data. The main sources of information were scientific articles and books found either through recommendations from industry experts or through databases accessed from the Chalmers' Library website. These were complemented with encyclopedias and textbooks from the field of Industrial Engineering. Additionally, the website and annual report of AstraZeneca, as well as communication with Asset Planner Anders Sjögren were the main sources of company specific information. The section explaining AstraZeneca's process for handling deviations was based on an internal document used for training purposes, as well as an interview with Certified Deviation Coordinator Johan Matti.

4.3 Data Collection

The qualitative and quantitative data were collected in different ways. Two separate rounds of semi-structured interviews produced the qualitative information, while access to the quantitative data was provided by AstraZeneca's Business Analytics Team. The initial round of interviews was held with three employees charged with overseeing the production flows of the three brands in question, and with the corporate supervisor for this project. For the second round, the nine interviewees came from the two sections producing Alpha, Beta, and Gamma. Their roles spanned planning, production, process, and quality in order to give different perspectives on the lead time variability affecting the three brands. The researchers dictated what roles were to be interviewed, but the company supervisor, Anders Sjögren, helped in identifying appropriate employees within these functions.

4.3.1 Collection of Qualitative Data

The initial round of interviews were conducted in April of 2021 using Microsoft Teams. Two interviews that lasted between 30 and 90 minutes were held, and they were based on the interview template found in Appendix A. The respondents were responsible for the production flows of their respective section at the OSD Formulation PET, and they all provided and explained VSMs covering their brands.

The first interview was conducted with the Industrial Engineer for Alpha and Beta. The second interview was held with the Industrial Engineer who oversee the production of Gamma. Follow-up questions to complement the interviews were sent to these respondents by email, and the final validation of the CSMs were also done through this channel. Additionally, feedback was continuously given by project supervisor Anders Sjögren.

The second round of interviews was also conducted using Microsoft Teams, and nine interviews were held in May of 2021. The interviewees belonged to either the section producing Alpha and Beta, or the section manufacturing Gamma, and five different roles were covered: planners, process engineers, production staff, quality assurance, and quality control. Even though the interviewees were in many cases able to discuss the concepts in general, the questions asked were geared towards the specific brand to which the employee was attached. The length of the interviews ranged from 24 to 71 minutes, totaling 5 hours and 47 minutes, and each interview resulted in between 2 743 and 8 009 words of transcribed material, as seen in Table 4.1. The concepts covered in the interviews can be found in Appendix B, but the order of the questions and selection of follow-up questions were dictated by what department the interviewee stemmed from and the responses he or she gave.

Table 4.1

The Duration of the Interviews and the Number of Transcribed Words

	Interview								
	1	2	3	4	5	6	7	8	9
Time (mm:ss)	40:23	24:24	71:14	44:33	24:51	40:25	38:19	33:13	30:06
Transcribed Words	4 895	2 743	8 009	4 988	3 320	4 315	4 495	4 511	3 487

4.3.2 Collection of Quantitative data

AstraZeneca has been gathering extensive data on their production systems since 2013. Access to the data was provided by the company through QlikView and QlikSense and relevant data

points were chosen, compiled, and downloaded by the researchers. The selection of data was based on the initial interviews and consultations with BAT analysts. This was done to ensure that the data set provided information that was relevant to the project scope. The OSD Formulation PET underwent a change between two reporting systems during the period of this study, which had a number of implications on the processing of data. The outliers had to be identified using the newer system, which provided formulation lead times that had been "cleaned" from holidays during which the factory was closed. In other words, this data set showed a shorter production lead time, since the Christmas and summer holidays and weekends had been removed from the data. The more detailed data containing all the operations included in the formulation process had to be accessed through the old system, where closures were included in the lead time. By identifying outliers through the newer system, their longer production lead times were assured to be caused by factors other than seasonal closures. Data gathered from the two systems had to be merged, and this was done using relevant batch names and order ID numbers from the older systems. Order numbers that were only present in one of the systems were excluded from the data set.

Because of the ongoing pandemic, no in-person spot-checks could be performed to validate the data. The risk of a biased data collection was however deemed to be minimal since the data had been gathered automatically for years and the collection from the systems was done by the researchers. It was also important to ensure that the years included in the project scope had the same characteristics. For example, if the patent for a pharmaceutical product expired last year, comparing production data from before and after that time is not relevant since the demand is affected by exclusivity.

Data was gathered in April of 2021 and spanned 24 months between April 1, 2019, and March 31, 2021. The three brands under investigation had been produced in different quantities during this period and their production included a different number of subprocesses. This meant that the number of rows of data gathered for each brand differed, spanning from 9 683 for Alpha to 23 928 for Gamma. Table 4.2 in Section 4.4.2 shows detailed information on the number of data rows for each brand.

4.4 Data Processing

For the qualitative data, the second round of interviews was recorded and transcribed to ensure data accuracy. The initial interviews produced information used to map out the production flows within the OSD factory and no further processing methods were required. For the second round of interviews, the transcribed material was coded to identify common themes among the respondents. Descriptive statistical methods were used on the quantitative data in order to produce visual diagrams and statistical measures that explained the production quantitatively.

4.4.1 Processing of Qualitative data

Even though both interview rounds resulted in qualitative data, the information was handled in different ways because of the different purposes of the interviews. The initial interviews aimed at gathering factual information about production processes, while the second round of interviews investigated employees' perceptions and beliefs.

The data gathered during the initial interviews were used to create current state maps based on the given information and the provided VSMs. In order to analyze and compare the different brands, it was necessary to reduce the number of processes from the VSMs. This was done with

some considerations in mind. First, processes that did not impact the lead time or were performed by a different department were removed. Also, as processes were grouped, the largest buffers were kept separate to keep them visible. Finally, some processes were aggregated in order to not disclose confidential information.

All interviews conducted during the second round were recorded and transcribed to ensure accurate representation of the interviewees' responses. The first step in the coding process was to color code the material in accordance with the subject of discussion, for example marking the text in yellow for answers that discussed the reasons for lead time variability. The color coded text from each interview was later transferred to an Excel file. This file was arranged by color, meaning that one sheet was dedicated to all text snippets discussing reasons for the variability, another one for the solutions to the problem, etcetera. The code words were derived from the snippets of text in this Excel file, and an effort was made to do this work on a number of interviews at a time to ensure consistency. The coding was done in two session, each covering four interviews with the final interview being coded separately. The code words covering the reasons for lead time variability were later merged into broader categories based on their contents. For the remaining subject matters, the code words were left as is, and analyzed and discussed without further categorization. All interviews and all coding were performed by both researchers in collaboration to ensure consistent results. The interviews were conducted in Swedish, but selected quotes were translated to English for the purpose of reporting. The translations were done in an effort to maintain both the content and tone of the quote.

4.4.2 Processing of Quantitative data

The quantitative data was accessed through QlikView and QlikSense and processed using Microsoft Excel. Because of confidentiality concerns, all formulation and operation lead times were modified using a factor. The same factor was used across the board for all brands, processes, and buffers.

For Alpha and Beta order numbers were preserved throughout formulation and it was possible to follow a batch through all production steps and buffers. This also enabled the calculation of total formulation lead times. Gamma had more manufacturing steps and it was not possible to connect them all to a single batch. Therefore, this brand was dealt with in a different way. For Gamma, there were two separate pellet processes after which it was possible to follow a batch from tableting to sorting. This had a couple of repercussions: it was not possible to calculate an accurate lead time for a batch of this brand, and outliers were identified within each process instead of on an aggregate level.

All data sets had to be processed in order to enable analysis. This was done in different ways, which is described in more detail below. The total rows of data gathered for each brand is presented in Table 4.2, along with numbers showing how many rows that were removed during each data processing step. For example, the removal of the 5 incomplete variants of Alpha resulted in the loss of 87 rows of data for that brand.

Table 4.2

Overview of Data Processing for Alpha, Beta, and Gamma

	Rows							Batches
Brand	Total Number Collected	Removed Product Type	Removed No Lead Time Impact	Added Buffers	Removed Incorrect Buffers	Final Number for Analysis		Number of Complete Batches
Alpha	9 683	87	6 809	2 084	8	4 863		694
Beta	11 724	0	8 342	2 524	13	5 893		829
Gamma	23 928	0	11 298	0	0	Pellet 1	1 596	798
						Pellet 2	4 831	1 604
						Tab-Sort	6 203	1 217
						Total	12 630	3 619

Alpha and Beta were manufactured in similar ways and the current state maps show the same number of processes for these brands. In order to arrive at this setup, buffers had to be created to fill the time before the ending of one process and the start of the next. This meant that other sub-processes and queues were removed and replaced by these buffers. The time a batch spent in each buffer was calculated based on the same batch's ending time in the preceding process and starting time of the ensuing operation. A handful of times, this resulted in negative times spent in buffers, which was attributed to issues with reporting, and these buffers were removed from the data set. The total number of rows included in the analysis of the two brands came down to around half of the rows of data gathered from AstraZeneca's systems.

The data for Gamma was not organized in accordance with the current state map, which meant that processing of the data was necessary. Operations and sub-processes that did not impact the lead times were excluded, and so were the ones undertaken by other sections. Furthermore, processes had to be combined to form pellet process 1 and 2, which meant that their operation lead times were calculated based on the starting time for the first sub-process and the ending time for the final one. Around half of the gathered rows of data were removed during these processing steps.

When investigating the total formulation lead time for both outliers and the other batches, only complete batches were included. This meant that processes belonging to batches that were started before the beginning of the 24 month window were removed. Similarly, the processes attributed to batches that were not finished before the end of the window were also excluded. All details on the removed and added rows of data can be seen in Table 4.2 above.

Each of the three brands was produced in different variants, with for example different strengths or coatings. Alpha came in 27 different variants, while Beta was only produced in 4. For Gamma, the number ranged between 2 and 4 in the different areas. For Alpha, 10 of these variants did not go through all of the processes and buffers included in the formulation of that brand. In those cases, the batches being produced of such a product variant were removed from the data set to ensure comparability. This resulted in only 17 variants of Alpha being included in the analysis.

The number of outliers identified for each brand, or process in the case of the first two processes for Gamma, corresponded to the total number of batches included in the collected data set. The batches making up the slowest 5% of production lead times were chosen as outliers for each brand. These batches were investigated in two ways: the operation lead times and total formulation lead times were analyzed, and deviation protocols were gathered and studied. However, not all outliers had a corresponding deviation protocol, which can be seen in Table

4.3, below. Also, some batches had been flagged multiple times resulting in more than one deviation protocol. The causes for the deviations were listed in detail in the reports. These causes were grouped into larger categories, such as *Material*, *Man*, and *Machine*. The different brands had different categories, which can be seen in the results for each brand. For the lead time investigation, data was not available for all identified outlier batches. Additionally, only batches that were both started and completed within the 24 month period were included. This meant that not all identified outliers were part of the investigation of lead times, but they were included when looking at deviation reports.

Table 4.3

Overview of Outliers

		Outliers		
Brand		Total Number	Complete Batches	With Deviation Protocol
Alpha		36	34	24
Beta		43	36	36
Gamma	Pellet 1	40	40	18
	Pellet 2	81	81	27
	Tab-Sort	69	60	9

4.5 Discussion of Methods

Section 4.1 contains descriptions of the methods used for this study, and risks associated with each method are discussed there. However, there are some topics worth elaborating on, and the selection of interviewees is one of them. The selection was made by the project supervisor in collaboration with the superiors of the interviewees. This entails risks, for example that the interviewees are pre-selected based on sharing opinions with the superior. Since the researchers had no prior connections within the company, they were dependent on the supervisor for this help. Therefore it was a risk that had to be accepted.

The Covid-19 pandemic was also something that needed to be accepted. Not being able to observe the production flow in person and having to rely on videoconferencing software were two repercussions of the pandemic. Another, less obvious, effect was that the perspectives of the interviewees might have been influenced as well. The frequent discussions of staffing levels, for example, could have been affected by increased sick leave as a result of the ongoing situation.

During the second round of interviews, deviations became a focal point of the discussion, and singled out as the main driver of lead time variability. If this was known at the beginning of the study, it would have changed the research design. More emphasis would have been placed on the interviews, and less focus would have been put on operation lead times. In addition, more data on deviations and prioritizations would have been collected. However, the study still fulfills its purpose, but it could have been even more informative by narrowing the scope. This would be a suggestion for further research.

5
RESULTS

The initial interviews resulted in current state maps for each of the three brands, and these CSMs are presented in the first section of this chapter. Two of the products, Alpha and Beta, were manufactured using powdered APIs in the same section of AstraZeneca's OSD Formulation PET, while Gamma was a pellet-based product manufactured in a different section of the PET. Quantitative data was gathered and processed during the second phase of the study. Total formulation lead times and individual operation lead times for Alpha and Beta are presented, and deviation protocols for the brands are compiled and presented in tables. Operation lead times and deviation protocols are presented for Gamma as well, but because of its different manufacturing process, the computation of a total formulation lead time was unfeasible. For all three brands, the lead times are split into the slowest 5% of the batches, the so called *outliers*, and the rest of the data. The third part of the study, the qualitative interviews, is presented next. Transcriptions from the second round of interviews were coded and categorized, and the compiled data is shown in tables together with exemplifying quotes. An overarching theme that emerged from all interviews was that deviations was the main cause of lead time variability, leading to a separate section presenting the respondents' views on deviations. The categories found to best describe the causes of lead time variability at AstraZeneca's PET OSD were *Investment Requirements*, *Structural/Organizational*, *Ways of Working*, and *Contextual factors*. These qualitative interviews also gave rise to additional quantitative compilations. Adherence to a different queueing policy and the share of batches without deviations were compiled.

5.1 Current State Maps

The process for developing the current state maps for Alpha, Beta, and Gamma started with interviews with three people involved in the production of the three brands, as explained in Section 4.3.1. AstraZeneca provided value stream maps for the brands, which were modified to protect confidential information, resulting in the current state maps presented in this section. Even though the interviews were focused mostly on the processes, it emerged that buffers are present between the processing steps and that the *first-in, first-out* (FIFO) principle should be used when withdrawing material from them. The current state maps were verified by the project supervisor and other representatives from the two sections during the second round of interviews. This was done to ensure a valid representation of reality.

5.1.1 Current State Maps for Alpha & Beta

Two of the brands under investigation, Alpha and Beta, were manufactured at the same section of the OSD Formulation PET, they went through the same main processing steps, and they shared the same production staff. Therefore, they were presented jointly with similarities and differences clearly pointed out and explained in more detail.

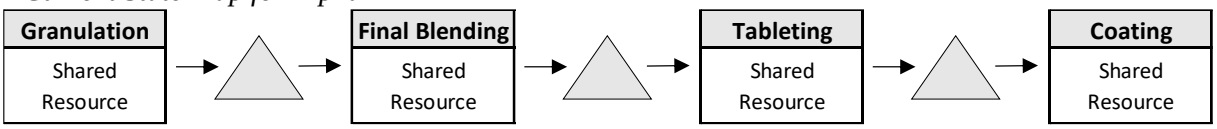
Alpha and Beta were manufactured in the traditional way, using an API in powdered form. Both products went through wet granulation, meaning that the main production processes were blending, granulation, drying, final blending, tableting, and coating. In addition to producing a number of variants of Alpha and Beta, the section also manufactured a number of other AstraZeneca brands, with some processes being shared and others dedicated to a single brand.

The operators moved between the different brands, and they followed predetermined prioritization rules if attention was needed at multiple places at once.

The value stream map AstraZeneca provided for Alpha encompassed five main processes, of which granulation also included the mixing and drying processes. Additionally, the initial interview with the Industrial Engineer at the section, gave that a number of subprocesses took place as well. It was however clear that not all operations had a significant impact on the production lead time. The subprocesses were excluded from the current state map due to them being very short in duration and being handled by a different department. One of the main processes from the original VSM was found to take place entirely in parallel with other operations, meaning that it did not affect the lead time. It was therefore also left out of the current state map. This resulted in a CSM consisting of four main processes and three buffers, as shown in Figure 5.1.

Figure 5.1

Current State Map for Alpha

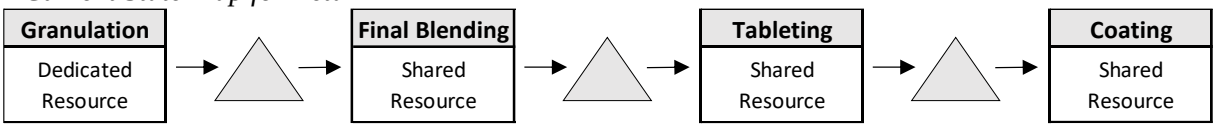


Granulation was a shared process for Alpha, meaning that both the staff and the equipment was used by other brands as well. For final blending and tableting, the staff was still a shared resource but the equipment was dedicated to each brand, which limited the need for thorough sanitation between batches. At coating, which was the final production process, both machinery and staff were shared by all brands being produced within the section.

The manufacturing steps for Beta were very similar to those of Alpha. The existing VSM provided by AstraZeneca showed that one additional process was needed for the production of Beta. However, the initial interview gave that the output of this process was treated as an ingredient to the first main process and it did not affect the formulation lead time. Other subprocesses were also present in the formulation of Beta, but they could once again be removed from the CSM for the same reasons as listed for Alpha. The current state map can be seen in Figure 5.2.

Figure 5.2

Current State Map for Beta



Beta had a dedicated granulation process with a separate staff that was not shared with other brands. This process has historically been a bottleneck for the production of Beta, but the ability to implement an additional shift to meet demand alleviated this problem. For final blending and tableting, the brand had dedicated equipment at the facility, but the staff was shared with the other products. And for coating, the final production step, both equipment and staff were shared with all brands within the section.

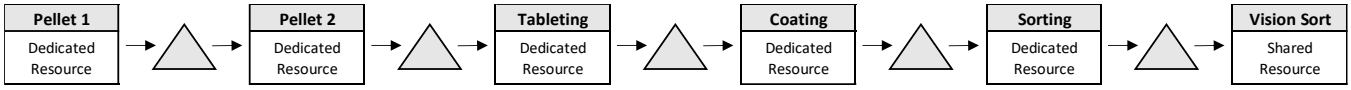
Alpha and Beta were produced at the same section of the OSD PET at AstraZeneca, using wet granulation. Neither brand had dedicated resources for the final three steps of production, but they had the same number of days as their planned lead time for formulation. The main difference between the two brands was that Beta had dedicated staff and equipment for the granulation process, enabling them to add shifts when needed. Another difference was that the demand for Beta was very high. Therefore, that brand was to be prioritized by production personnel if disturbances caused deviations from the production plan.

5.1.2 Current State Map for Gamma

In contrast to Alpha and Beta, Gamma was a pellet based product. An initial interview was conducted with the Industrial Engineer overseeing the section producing this brand. The production processes for Gamma were aggregated into five processes, with the first two processes consisting of multiple sub-processes. These two processes, pellet 1 and pellet 2, prepared the pellets by, among other things, spraying the API and excipients onto a core. The next process was tableting, which for Gamma also included the final blending step when pelletized API and excipients were mixed. The tablets were then coated and finally sorted. The sorting process was automatic and fast, but could be more extensive if issues were identified. In such instances a process called vision sort was used. This was fairly uncommon and therefore not a part of the standard manufacturing process for Gamma. After sorting, the products were sent to storage and packaging. The production flow for Gamma is illustrated in Figure 5.3.

Figure 5.3

Current State Map for Gamma



The entire production process was dedicated to the Gamma tablet brand, although it came in varying strengths and market adaptations, such as different coatings. The two pellet preparation processes belonged to a single production unit, while the tableting process was handled by another unit. The final production unit was responsible for the coating and sorting processes. All production units were located in the same building, within close proximity of each other. In addition, another section was able to provide additional capacity for the first pellet process if needed.

5.2 Quantitative Data Compilation

The result from the quantitative data compilation is presented in this section, after being processed as described in Section 4.4.1. The three brands, Alpha, Beta, and Gamma, are presented individually. First, the data was used to complete the current state maps shown in Section 5.1, and the operation lead times are presented for the processes and buffers in finalized CSMs. Then follows a comparison between the outliers and the general data set, and deviation reports are also compiled for the outliers. The different product variants were also examined, and the result from this is presented. Finally, the buffers are examined in detail.

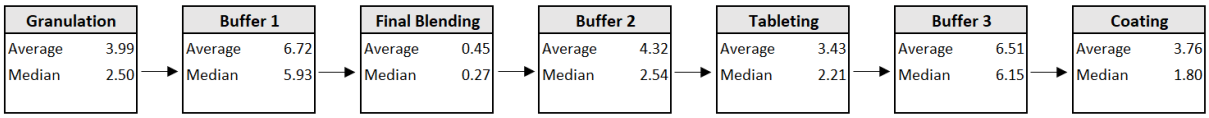
5.2.1 Alpha

The production system for Alpha consists of four main processes, as displayed in the CSM, as seen in Figure 5.4. These are granulation, final blending, tableting, and coating. Buffers are

present between these processes. The quantitative data compilation was also used to complete the CSM. Before the exploratory data analysis, the data was cleaned and prepared as described in Section 4.4.2. This results in a difference in the number of batches for each process. These range from 694 batches for the granulation process to 702 for the coating process.

Figure 5.4

Completed Current State Map for Alpha

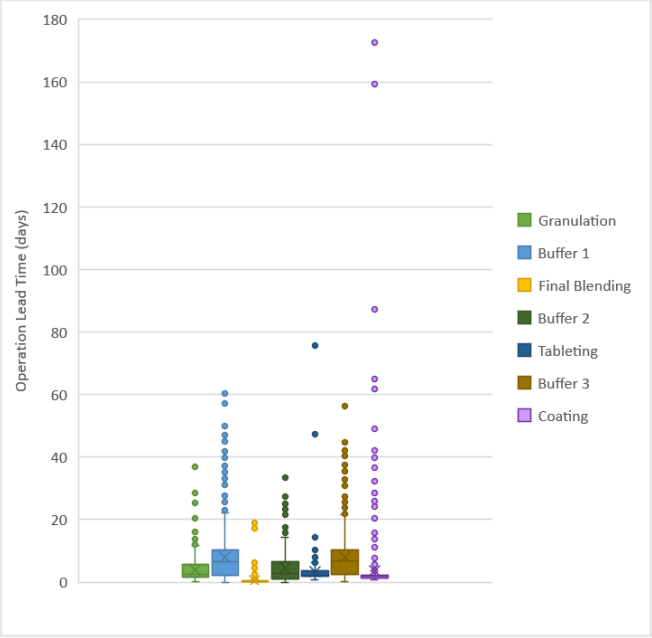


Note. The numbers represent operation lead times

The operation lead times of the individual processes and buffers are shown in Figure 5.5. All buffers have a higher lead time average than the processes. Among the processes, the average operation lead time for the final blending process is significantly lower than the others, being only about 11% of the corresponding value for the longest process, granulation. The average is higher than the median value for all operations, meaning that the distribution of operation lead time is positively skewed. The processes also have a tighter spread than the buffers, meaning that more values are close to the median.

Figure 5.5

Box and Whisker Plot over the Operation Lead Times of Alpha's Processes



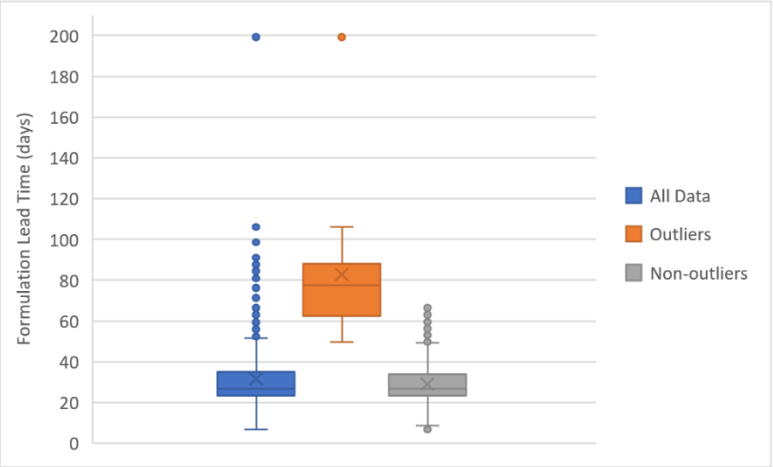
5.2.1.1 Alpha's Outliers

As shown in Figure 5.6, there is a large spread of formulation lead time. To see what differentiates the more extreme values from the normal values in the data set, a selection of outliers were studied in more detail. For Alpha, 5% of the batches produced during the investigated time period amounted to 36 batches. Out of these outliers, 34 completed the

formulation process in the time interval and will be used to compare the outliers to the general data set. For the outliers, both the average and median formulation lead time was about 3 times longer than the remaining 95% of batches.

Figure 5.6

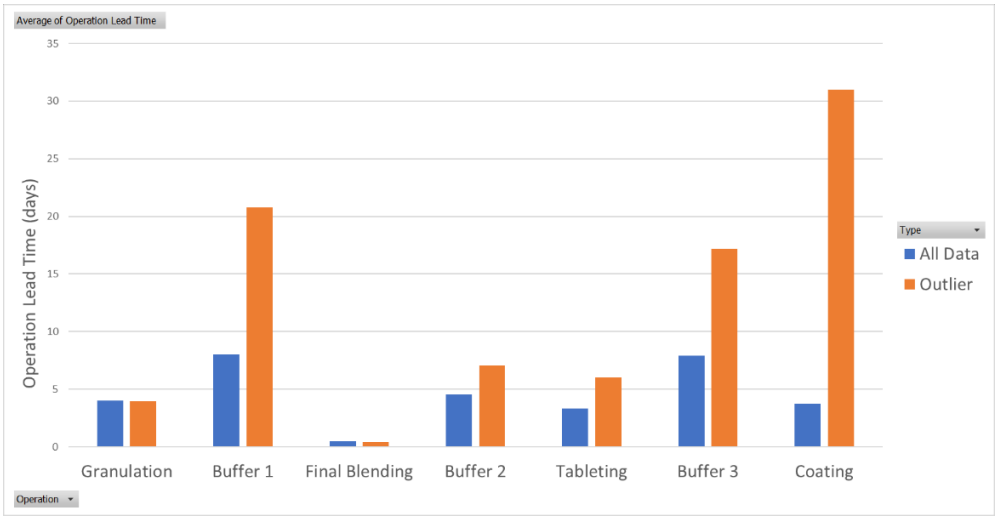
Box and Whisker Plot over the Formulation Lead Time of Alpha



Comparing the operation lead times between the outliers and the general data set containing all data, outliers spend more time in buffers, as seen in Figure 5.7. However, the largest difference in operation lead time between the outliers and the general data set can be found in the coating process. The factor-adjusted operation lead time in that process was almost 4 days for all data and 29 days for outliers, meaning that the average value for all data is only about 13% of the average for the outliers in that process. Two processes have similar averages for both the outliers and the general data set. In the granulation process, all data and the outliers both have 4 days operations lead time on average. In the final blending processes, both data sets have an average of approximately 0.5 days. Outliers spend more time in buffers on average than all data. The largest difference is found in buffer 1 where outliers on average spend more than twice as much time. Buffer 3 is similar to buffer 1 both in terms of average lead time and the difference between outliers and all data. Buffer 2 has the shortest average operation lead time for both data sets.

Figure 5.7

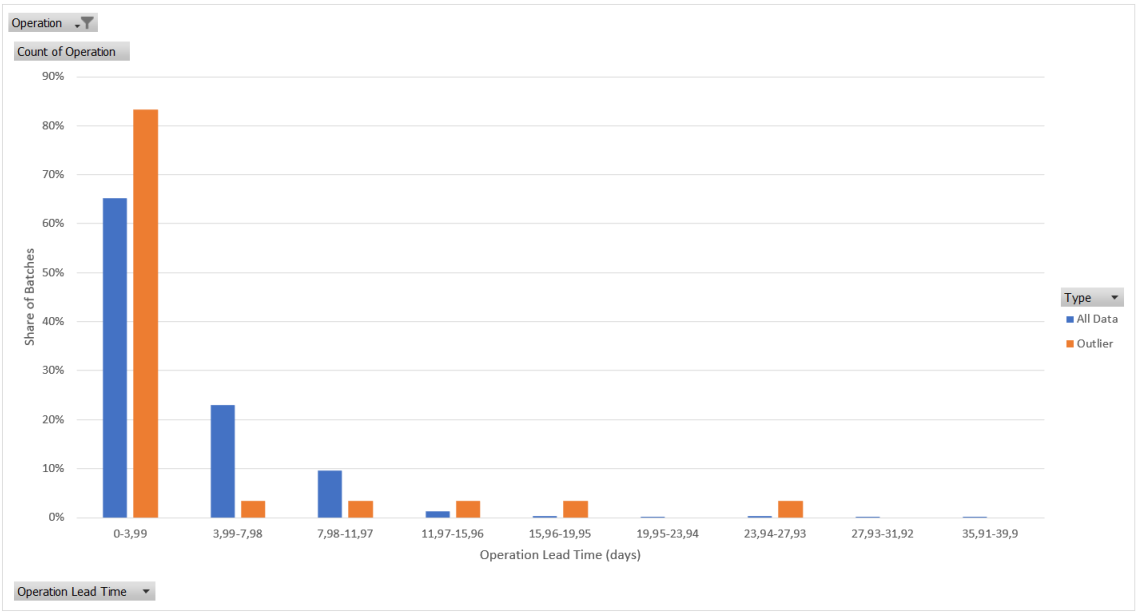
Operation Lead Times for Alpha



The distribution of lead times in the granulation process is fairly similar between all data and the outliers, as shown in Figure 5.8. For all data, 65% of the batches have an operation lead time that is shorter than the process average of about 4 days, and 88% of all batches have a lead time that is less than 8 days. For the outliers, the corresponding values are 83% and 87%.

Figure 5.8

Histogram of the Operation Lead Time for Alpha's Granulation Process



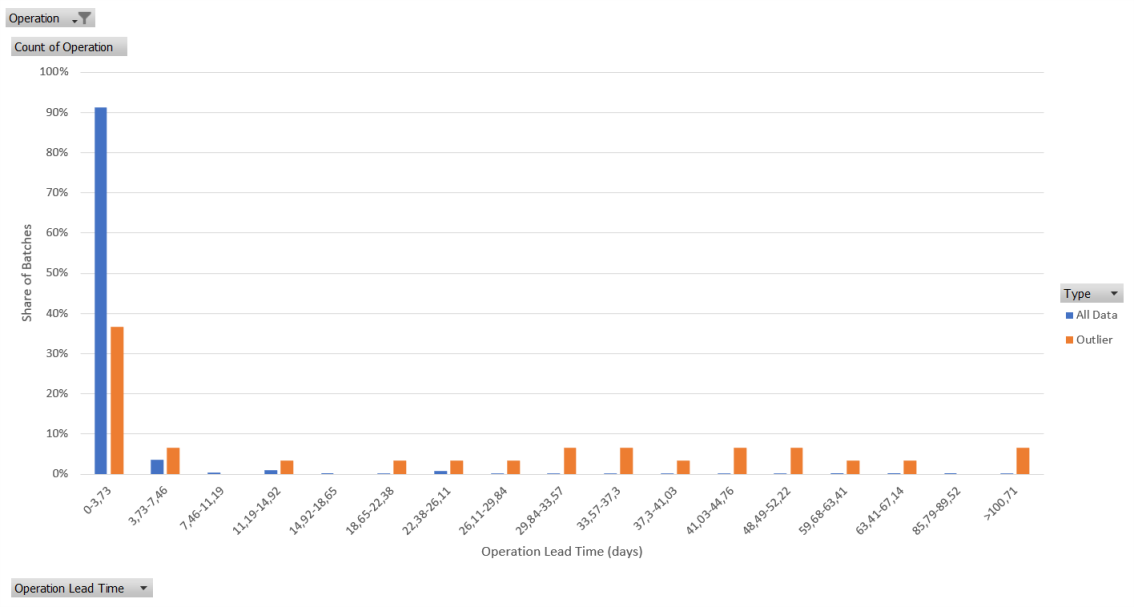
Note. The groupings along the X axis correspond to the factor-adjusted average operation lead time of 3.99 days.

On the other hand, the process with the least similar distribution of lead times between the outliers and the general data set is coating, shown in Figure 5.9. For all batches, 91% have an operation lead time less than the process average for all data. For outliers, only 37% of the

batches have an operation lead time less than the process average. In addition, 53% of the outliers have more than five times the average lead time.

Figure 5.9

Histogram of the Operation Lead Time for Alpha's Coating Process



Note. The groupings along the X axis correspond to the factor-adjusted average operation lead time of 3.73 days.

Deviation reports were studied for the outliers, as shown in Table 5.1. It was found that 24 out of the 36 batches had one or more deviations. Using the information available in the reports, the deviations were categorized as being caused by Man, Machine, Material, Method or Other. Some deviations were also linked to other PETs or functions than PET OSD Formulation. The most common deviations were classified as Man and Machine with 9 and 8 deviations respectively. If a deviation did not conform to these categories, it was classified as other, which happened in one case. Deviations were connected to activities by other departments, which was the case 3 times.

Table 5.1

Compilation of the Deviation Reports for the Outliers of Alpha

Category	Major	Minor	Total deviations
Man	4	5	9
Machine	3	5	8
Material	5	1	6
Method	3	2	5
Other	0	1	1
Other department	2	1	3

The connection between where the deviation occurred in the production system and the operation lead time for each operation was also investigated. Deviations concerning the coating

process, resulted in the batch spending a considerable amount of time in that process. For most deviations discovered at other operations, there was no similar correlation, but batches would often be halted at either a buffer or the coating process instead. For Alpha, the average time spent handling a deviation was factor-adjusted to 46 days.

5.2.1.2 Alpha's Product Variants

During the studied time period, 17 variants of Alpha were produced to completion. An overview of the product variants of Alpha is shown in Appendix C. Seven variants each accounted for 1% or less of the batches produced. The five most common variants amount to 83% of the produced batches, and can be seen in Table 5.2. The most common variant, type A, accounts for 25% of all batches but only 19 of the outliers. Type B and D are the most common variants in the outlier data, with 22% each. Type B accounts for almost the same percentage, 23% of the general data set. Type D is only present in 13% of the batches in the general data and it has the largest difference between the two data sets in percentage points.

Table 5.2

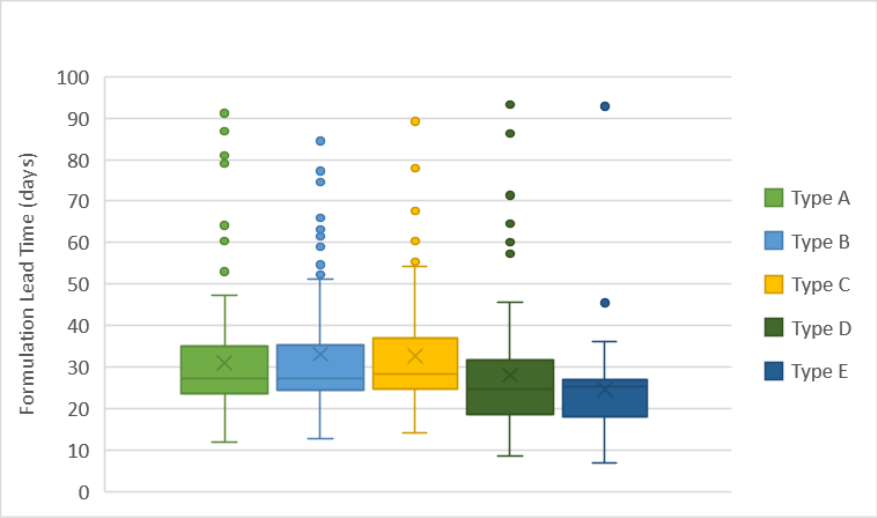
Overview of the Product Variants of Alpha

	All Data		Outliers	
Product Type	Number of Batches	Rate	Number of Batches	Rate
Type A	173	24.5%	7	19.4%
Type B	159	22.5%	8	22.2%
Type C	95	13.5%	4	11.1%
Type D	91	12.9%	8	22.2%
Type E	70	9.9%	1	2.8%

Looking closer at the five most common variants and the individual operations, as shown in Figure 5.10, types A, B, and C have similar median formulation lead time, while type D and E have shorter medians. Type C has the highest average formulation lead time, and type E has an average that is shorter than the median. This indicates that for type E, the distribution is negatively skewed. As shown in Figure 5.11. Type E has the shortest average operation lead time in all buffers and the shortest in all processes, except for in final blending, where it has the highest average operation lead time. In buffer 1, type B has the longest average operation lead time and type C has the longest operation lead time in buffer 3. Overall, the average time spent in processes is similar between all the types, while the time spent in buffers varies more between the variants.

Figure 5.10

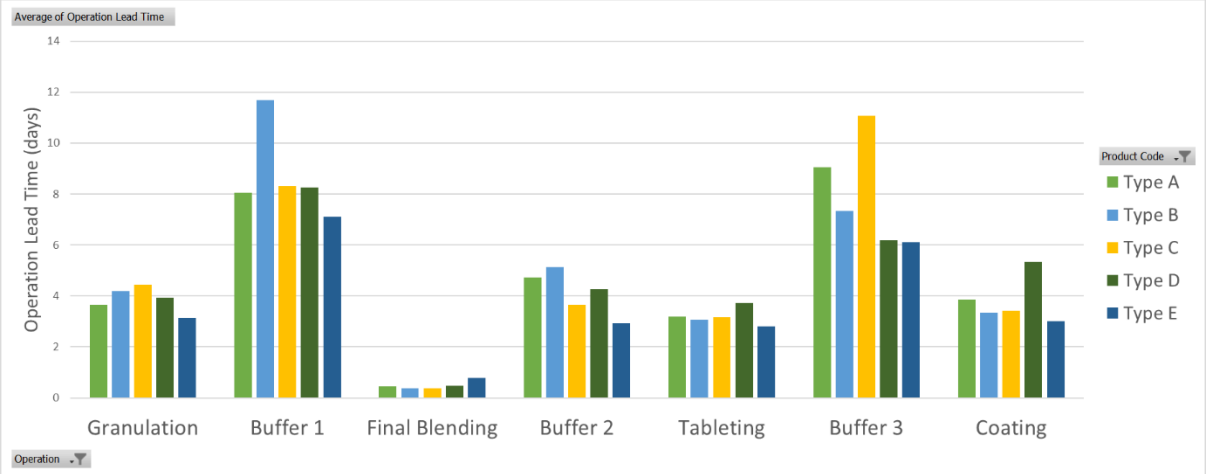
The Formulation Lead Time for the Five Most Common Variants of Alpha



Note. The number of batches differ between the different product types.

Figure 5.11

Operation Lead Times for the Five Most Common Variants of Alpha

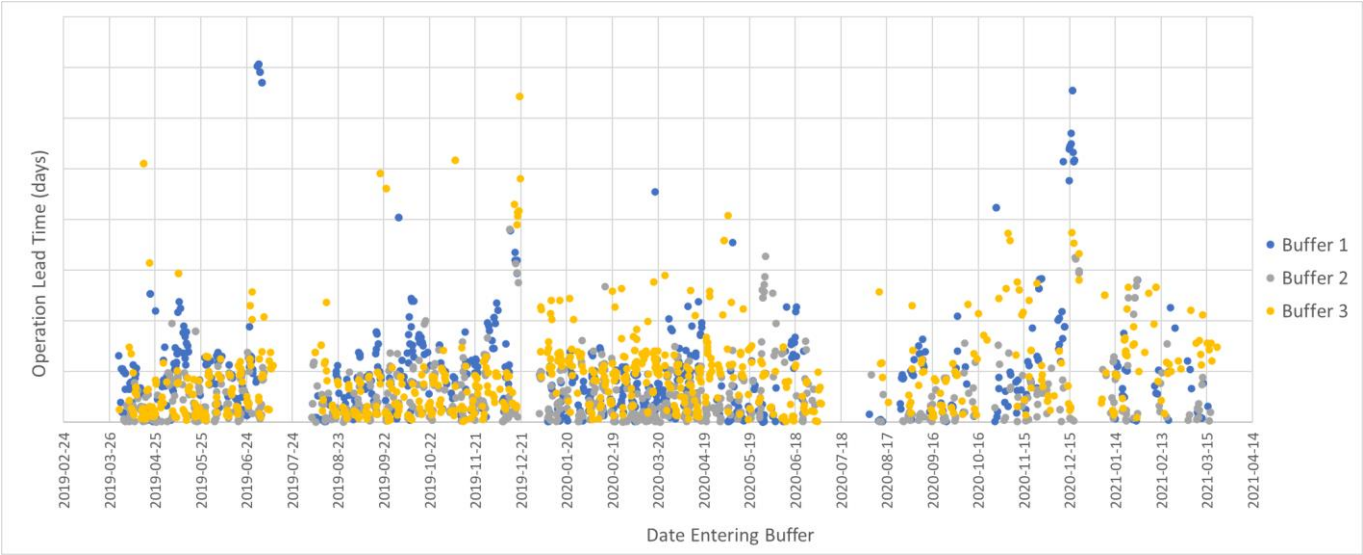


5.2.1.3 Alpha's Buffers

The OSD Formulation PET closes down during summer and Christmas holidays, which was discovered in the initial interviews. By plotting the lead time and start date of the buffers, this can be observed in the data, as shown in Figure 5.12. For example, in 2019 no batches entered any buffers between July 10 and August 5.

Figure 5.12

A Chronological Illustration of the Buffers of Alpha



Note. The numbers on the vertical axis were removed to protect confidentiality.

In the initial interviews, it was said that operators should adhere to the rule of FIFO when choosing batches to go into the next process. However, as summarized in Table 5.3, it was found that this rule was broken 182 times in buffer 1, 149 times in buffer 2 and 216 times in buffer 3. This means that the FIFO rule was broken between 21% and 31% of the time in the three buffers. The FIFO principle was also departed from for batches without any deviation reports. This happened in 148, 130 and 134 instances for buffers 1, 2 and 3 respectively. This means that the rule was broken in between 19% and 22% of the time for batches without deviations. In 2021, the principle was only departed from 7% of the time in buffer 1.

Table 5.3

Adherence to the FIFO Principle for Alpha

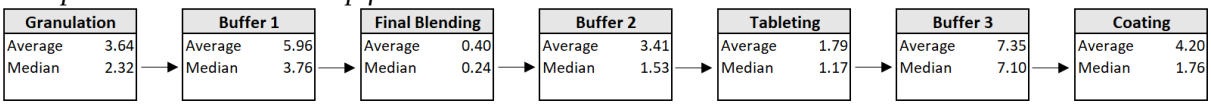
		Buffer 1		Buffer 2		Buffer 3	
		Number	Rate	Number	Rate	Number	Rate
Total number of withdrawals		686		695		695	
Departures from FIFO		182	26.5%	149	21.4%	216	31.1%
Departures from FIFO without reported deviation	Total	148	21.6%	130	18.7%	134	19.3%
	2019	66	21.1%	57	18.4%	41	13.4%
	2020	80	23.4%	64	18.7%	83	24.3%
	2021	2	6.9%	9	23.1%	10	23.3%

5.2.2 Beta

The production process for Beta consists of four main processes and three buffers and the number of batches going through the different operations ranged between 829 and 858. The quantitative data was used to complete the current state map, as can be seen in Figure 5.13.

Figure 5.13

Completed Current State Map for Beta

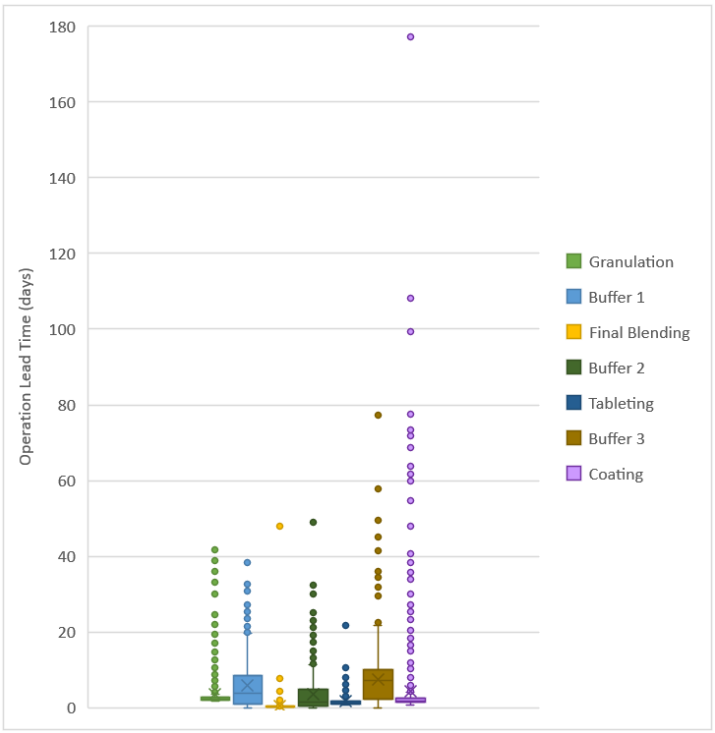


Note. The numbers represent operation lead times

Continuing to investigate the processes and buffers in more detail, the box and whisker plot in Figure 5.14 shows that the values for operational lead time are more dispersed for the final two operations than the others. The fact that the boxes are much smaller for the processes compared to the buffers shows that their distribution is significantly tighter. Similarly, the longer whiskers on the buffers show that there is a larger overall spread in these operations. Amongst the processes, it is clear that granulation and coating have longer tails, while final blending and tableting have tighter distributions.

Figure 5.14

Box and Whisker Plot over the Operation Lead Times of Beta's Processes

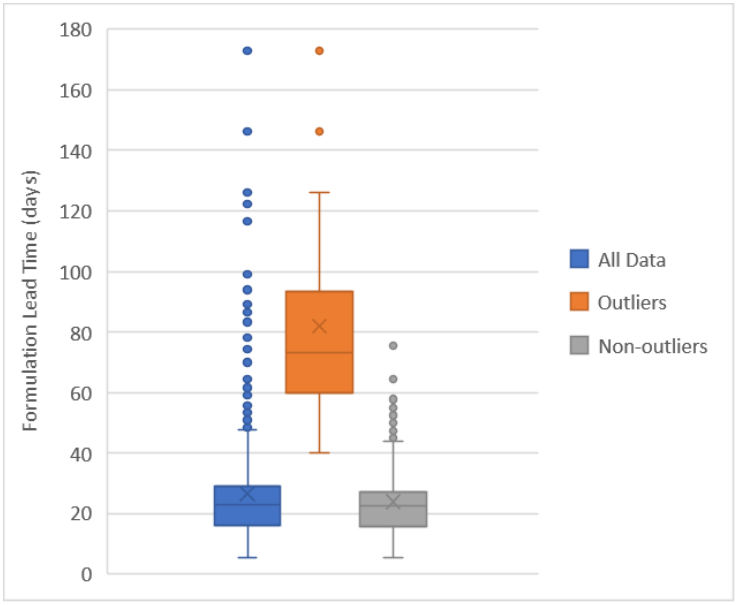


5.2.2.1 Beta's Outliers

Outliers for Beta were deemed to be the batches making up the slowest five percent of total formulation lead times for that brand. For Beta, there is a large disparity between the average time for the worst 5% of the batches and the other 95%, as seen in Figure 5.15. The outliers have a total lead time that on average is more than 3 times that of the other batches.

Figure 5.15

Box and Whisker Plot over the Formulation Lead Time of Beta

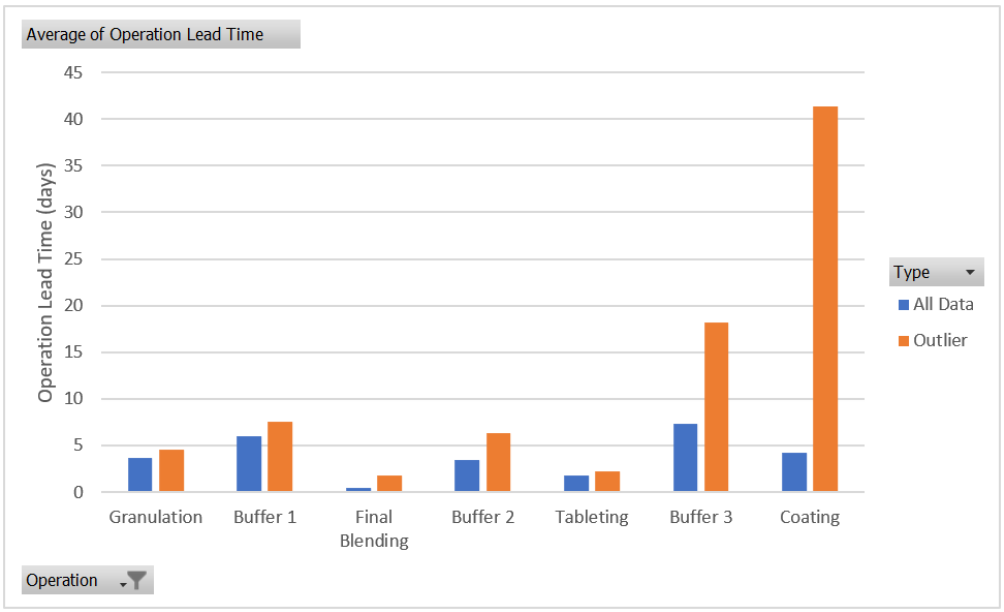


Note. A value of 221 was omitted from both All Data and Outliers in order to improve readability.

A comparison between the outliers and all data for each operation can be seen in Figure 5.16. It shows that the average operation lead times are higher for the outliers in all processes and buffers. It is also clear that the disparity is considerably larger for the final two operations: buffer 3 and coating. For tableting, an outlier only spends slightly longer in the process compared to the average batch, while the number for coating is almost 10 times the average. Even though there are three buffers and four processes, the average batch spends more time in the buffers than it does being processed. More than 60% of the total formulation lead time is spent in buffers. The figure also shows that the average time spent in each buffer is higher for outliers than for all batches combined. The disparity between the two groups increases as formulation progresses, with an outlier spending 2.5 times the average in buffer 3.

Figure 5.16

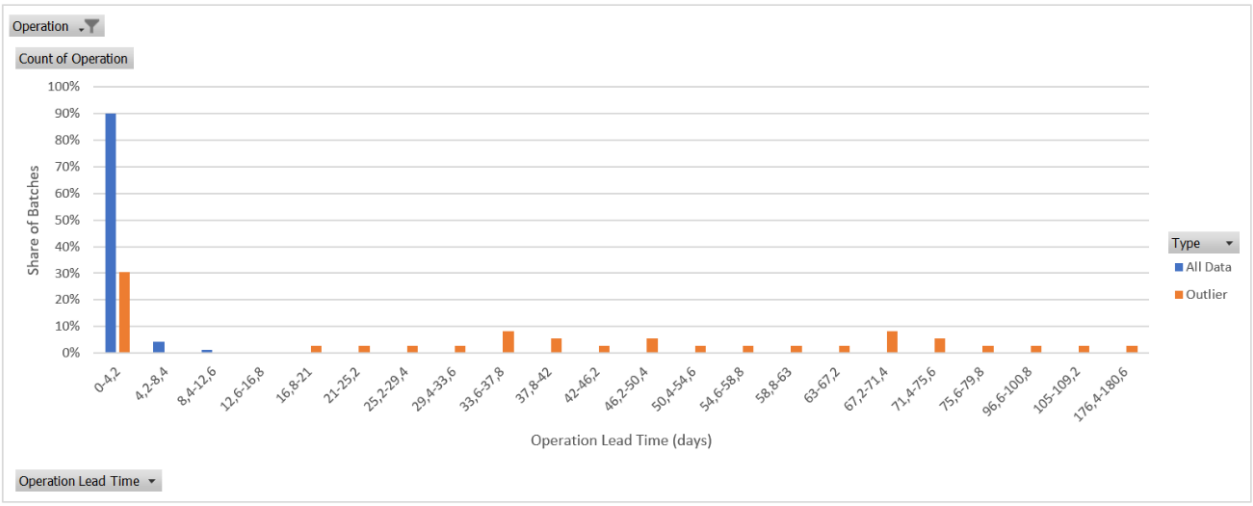
Operation Lead Times for Beta



As shown in Figure 5.17, around 90% of all batches pass through the coating process in less than the average operational lead time. For outliers, only 30% of the batches go through the process in the same amount of time, while a quarter of the batches use more than 16 times the average lead time. For comparison, the share of batches going through tableting in the average operational lead time are considerably more similar, which can be seen in Figure 5.18. 77% of the total number of batches and 75% of the outliers are processed within this time.

Figure 5.17

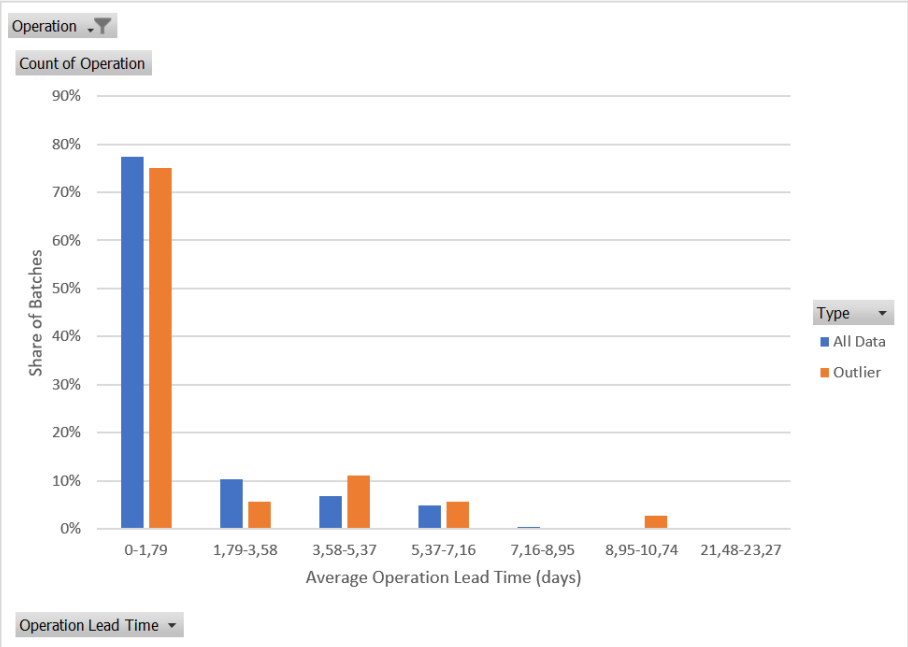
Histogram of the Operation Lead Time for Beta's Coating Process



Note. The groupings along the X axis correspond to the factor-adjusted average operation lead time of 4.2 days.

Figure 5.18

Histogram of the Operation Lead Time for Beta's Tableting Process



Note. The groupings along the X axis correspond to the factor-adjusted average operation lead time of 1.79 days.

Out of the 43 outlier batches identified for Beta, 36 were accompanied with one or more deviation reports. The causes of the deviations were categorized, as seen in Table 5.4, and showed that 20 out of 52 deviations were caused by Man. This category was quite broad, including skills, training, lack of attention to detail, and other humancentric causes. 12 problems were attributed to Machine, and 9 each to Method and Material. Out of the 52 deviations, 22 were deemed to be of Major criticality, while 30 were Minor. Out of the major deviations, eight were related to procedures and attributed to the Method category. The majority of the minor deviations were caused by Man.

Table 5.4

Compilation of the Deviation Reports for Beta's Outliers

Category	Major	Minor	Total deviations
Man	4	16	20
Machine	5	7	12
Material	5	4	9
Method	8	1	9
Process	0	2	2

The correlation between where deviations happened and where they caused longer operation lead times was also investigated. In general, deviations happening during the first three processes did not lead to longer operation lead times in those specific operations. In most cases, such batches were instead delayed in buffer 3 or granulation. The only process that showed a close correlation between attributed deviations and long operation lead times was granulation,

the last step of formulation. Out of the examined deviation protocols, the average factor-adjusted time spent investigating a deviation was 37 days.

5.2.2.2 Beta's Product Variants

Beta is produced in four different variants, as seen in Table 5.5, with type A making up 61% of the total production, but representing 74% of the outliers. Type B makes up 26% of the production but is slightly underrepresented among the outliers, accounting for 23%. Product type C and D each make up 6% of the production, but only 0% and 2% respectively of the outliers.

Table 5.5

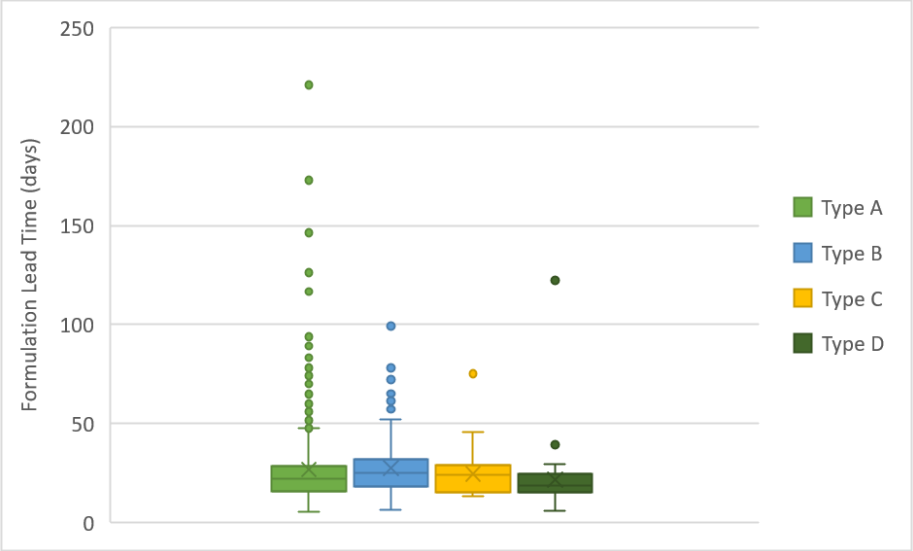
Beta's Product Variants

	All Data		Outliers	
Product Type	Number of Batches	Rate	Number of Batches	Rate
Type A	527	61.4%	32	74.4%
Type B	224	26.1%	10	23.3%
Type C	55	6.4%	0	0%
Type D	52	6.1%	1	2.3%

The formulation lead times for the four types of Beta that are shown in Figure 5.19 are fairly similar. Type D is slightly faster than the others, and it is also skewed downward, while the others are skewed towards the longer lead times. Type C also stands out, having no fast batches in its data set.

Figure 5.19

The Formulation Lead Times for the Different Product Types of Beta



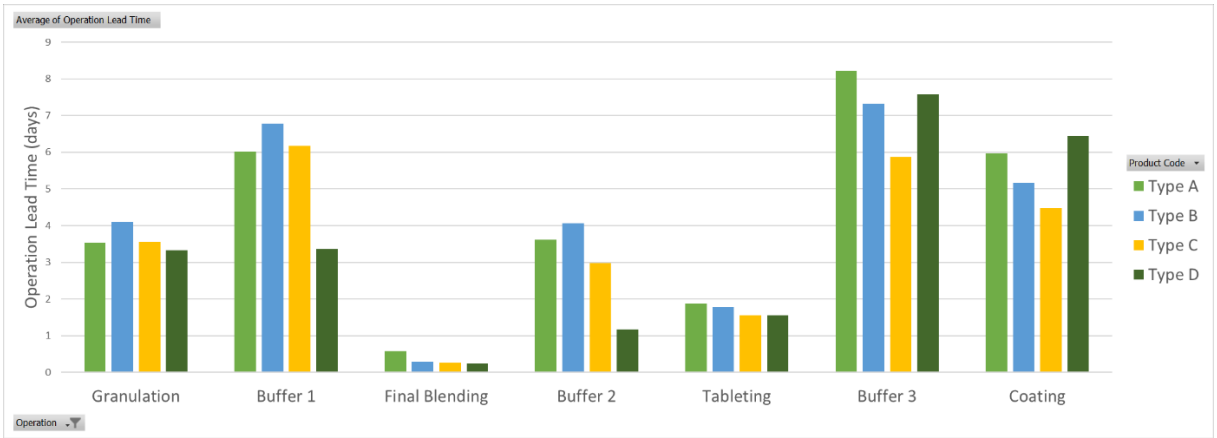
Note. There are five times more batches of A than C and D, meaning that the number of points above the whiskers will differ too.

Breaking the formulation lead times into the different processes, as shown in Figure 5.20, it is evident that the operation lead times are fairly similar for each variant. The time spent in buffers

show more dispersion, with product type D spending significantly less time than the others in buffer 1 and 2, and type C moving faster through the final buffer.

Figure 5.20

Operation Lead Times for Beta's Product Types

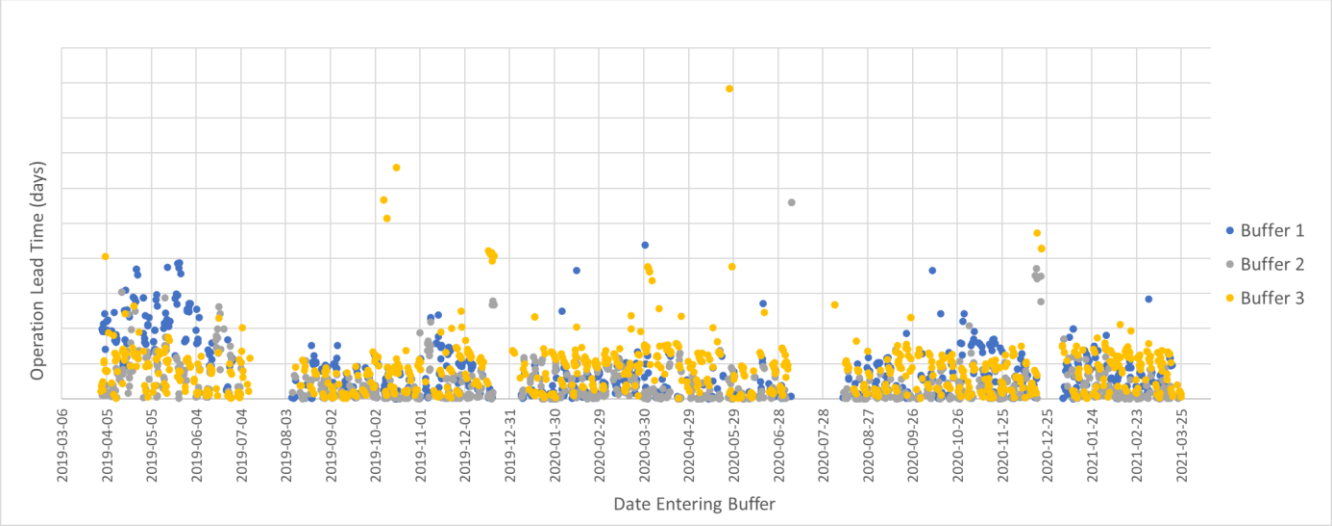


5.2.2.3 Beta's Buffers

During the interviews it was disclosed that production halts during the summer and Christmas holidays. The quantitative data illustrated that these breaks also had effects on the buffers, which can be seen in Figure 5.21. Buffer 1 empties before each extended break and does not have any batches getting stuck over the holidays. Buffer 2 and 3 also show signs of emptying before breaks, but these two buffers have a few batches that stay over some holidays, especially during Christmas.

Figure 5.21

A Chronological Illustration of the Buffers of Beta



Note. The numbers on the vertical axis were removed to protect confidentiality.

It was also found during the development of the current state map that the FIFO principle should be used in the three buffers separating the processing steps. The quantitative data showed that this principle was not always followed, which can be seen in Table 5.6. In buffer 1, operators

departed from the FIFO principle a total of 279 times, and 127 batches were skipped despite not being listed in any deviation reports. In total, 16% of the batches going through buffer 1 spent longer than necessary in the buffer, and this could not be explained by any reported deviations. For buffer 2 and 3, the share of batches departing from the FIFO principle despite not having any listed deviations were 11 and 18% respectively. The share of departures from the FIFO principle declined in all buffers from 2019 to 2020, and again from 2020 to 2021. Buffer 1 went from 23% to 11% over the two years, while buffer 2 went from 17% to 7%, and buffer 3 from 20% to 12%.

Table 5.6

Adherence to the FIFO Principle for Beta

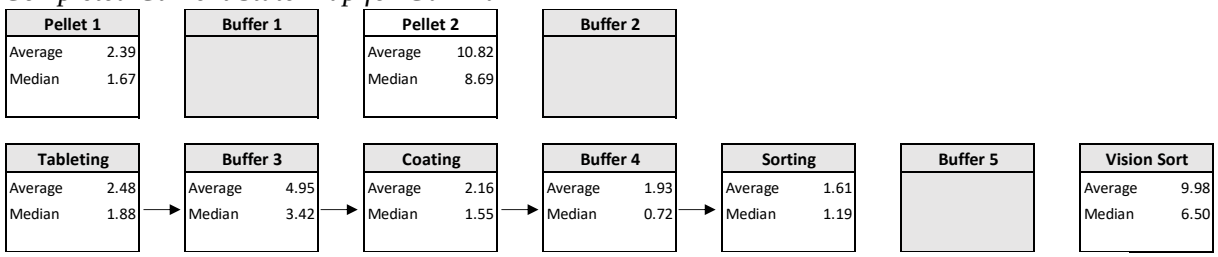
		Buffer 1		Buffer 2		Buffer 3	
		Number	Rate	Number	Rate	Number	Rate
Total number of withdrawals		822		838		851	
Departures from FIFO		279	33.9%	165	19.7%	324	38.1%
Departures from FIFO without reported deviation	Total	127	15.5%	94	11.2%	149	17.5%
	2019	63	22.5%	50	17.1%	61	20.3%
	2020	51	12.1%	36	8.5%	73	17.3%
	2021	13	10.7%	8	6.6%	15	11.7%

5.2.3 Gamma

The first two production steps for Gamma are quite different from those of Alpha and Beta, and the available data reflected this difference. As previously stated, subprocess were aggregated to form pellet process 1 and 2, and vision sort only took place in rare occasions. Because of how Gamma is manufactured and how the data is reported, it was not feasible to follow one batch through the entire formulation process. It was, however, possible to connect the tableting, coating, and sorting steps, which meant that the buffers in this segment could also be analyzed. 1 375 batches went through that final segment, but only 77 out of those went through vision sort. Therefore, that process is not included in most compilations. The average and median operation lead times for each process can be seen in Figure 5.22.

Figure 5.22

Completed Current State Map for Gamma



Note. The numbers represent operation lead times

5.2.3.1 Gamma's Product Variants and Outliers

The fact that it was not possible to follow a batch from start to finish also meant that outliers had to be identified for each segment individually. This resulted in 40 outlier batches for pellet process 1, 81 for the second pellet process, and 69 batches for the final three steps, as explained in Section 4.4.2. The split between the different processes, product types, and outliers can be seen in Table 5.7. The first pellet process manufactured two different product variants, with

type A making up 94% of total production and 88% of outliers. Two other product types were produced in pellet 2 and their numbers were fairly similar to those in the first pellet process. Type C made up 94% of production and 86% of outliers. For the final three processes, four different product variants were manufactured. Type E made up 88% of production and 84% of outlier batches and type F accounted for 6% of production and 9% of outliers. The other two variants made up less than 4% of both total production and outliers.

Table 5.7

The Product Variants of Gamma Split into All Data and Outliers

	All Data						Outliers					
	Number of batches			Rate			Number of batches			Rate		
Product Type	**Pellet 1**	**Pellet 2**	**Tab-Sort**	**Pellet 1**	**Pellet 2**	**Tab-Sort**	**Pellet 1**	**Pellet 2**	**Tab-Sort**	**Pellet 1**	**Pellet 2**	**Tab-Sort**
Type A	752			94.0%			35			87.5%		
Type B	48			6.0%			5			12.5%		
Type C		1516			93.9%			70			86.4%	
Type D		99			6.1%			11			13.6%	
Type E			1158			88.4%			58			84.1%
Type F			73			5.6%			6			8.7%
Type G			47			3.6%			2			2.9%
Type H			32			2.4%			3			4.3%

In pellet process 1, type A has a shorter lead time than type B for all data, but this relation is the opposite for outliers, as seen in Figure 5.23. For the second pellet process, type C has a shorter operation lead time than type D does for both all data and outliers, but there is a larger difference between the two types for outliers. All product variants going through the final three processes can be seen in Figure 5.24. Type E spends more time in buffers than the other three types do, and type G spends less time than the others. Product type E shows the biggest disparity between average time and outlier time in the tableting process, with almost double the amount of time spent in the process for an outlier batch. An outlier for type F spends twice the average amount of time in the coating process, but is also twice as fast as the average of all batches through the sorting process. The coating process for type G is the one showing the largest overall discrepancy. An outlier batch takes almost five times as long as an average batch through that process. In buffer 3, an outlier of type E, F, and H spends significantly longer than the average batch time. Type F shows the same tendency in buffer 4 as well, while an outlier batch of type G spends less time than the average batch in both buffers.

Figure 5.23

Operation Lead Times for the Product Types of Pellet Process 1 (A & B) and 2 (C & D)

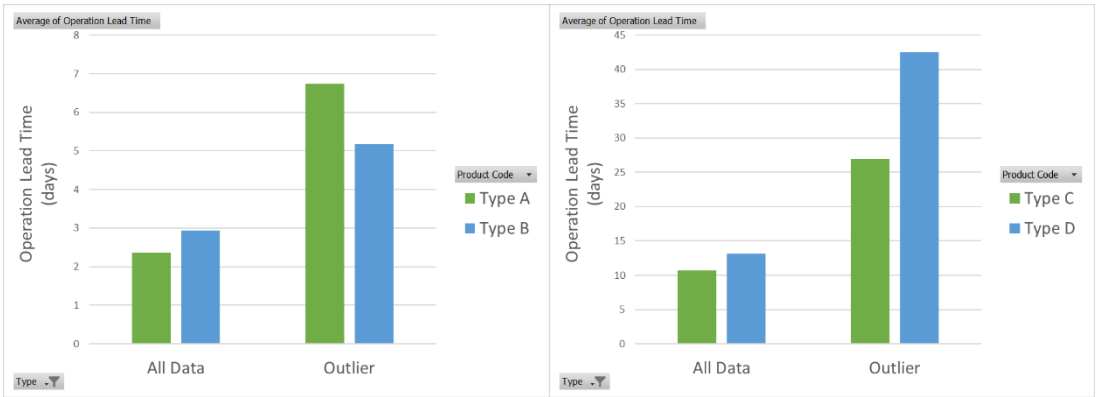


Figure 5.24

Operation Lead Times for the Product Types of the Final Three Processes

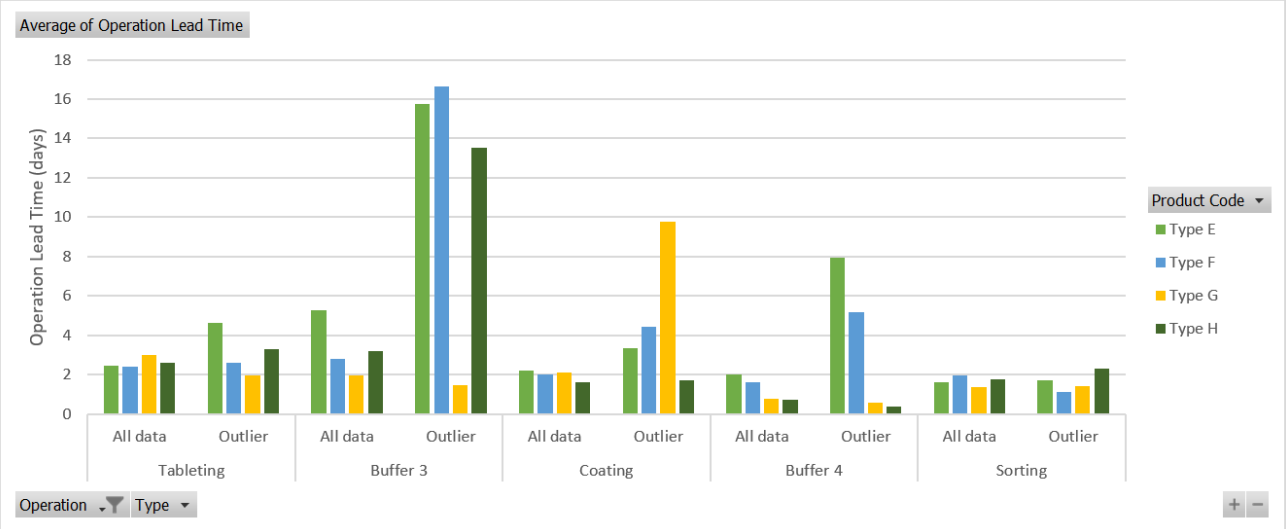
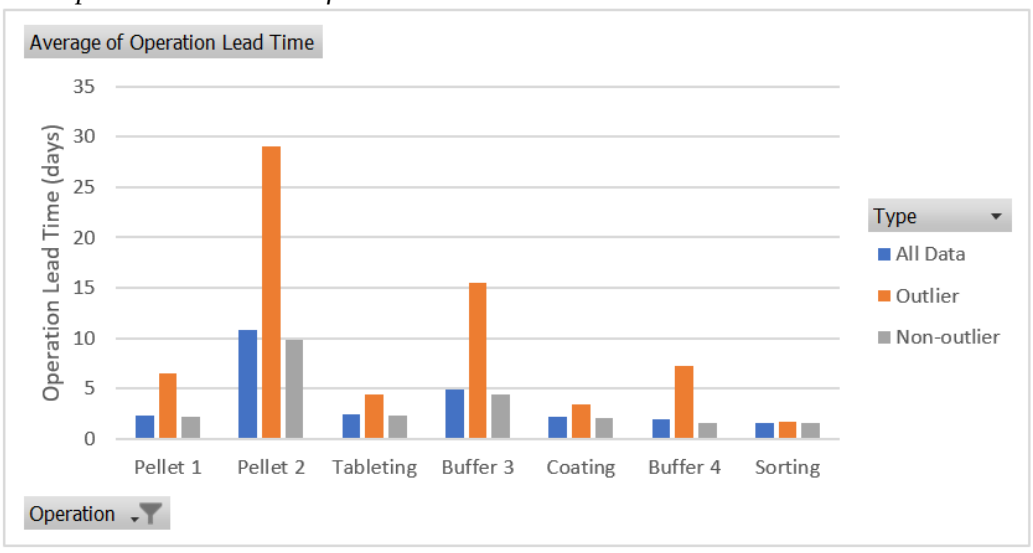


Figure 5.25 shows the average operation lead times for the six processes and two buffers, but as previously stated, the first two processes cannot be connected on a batch by batch basis with the rest of the operations. The pellet 2 process dominates, with an average operation lead time that is larger than the other four operations combined. This is true both for an outlier and for all data. It is also clear that outliers spend more time than the average batch in all processes and buffers. The sorting process is the one showing the least correlation to what makes a batch an outlier. That is, the operation lead time for an outlier is not too different from any other batch in that process. Starting with tableting, it was possible to follow batches through the end of the formulation process. When singling out the three processes and two buffers being part of that segment, it is evident that the buffers show the largest disparity between an outlier and a non-outlier.

Figure 5.25

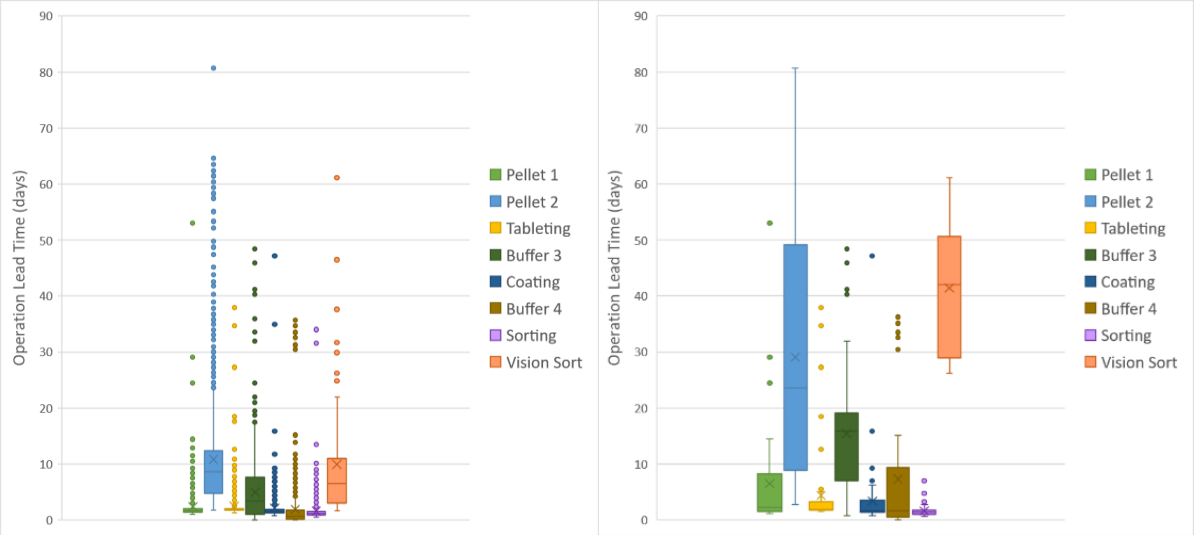
The Operation Lead Times for Gamma



The box and whisker plots in Figure 5.26 also include the vision sort process. The figure shows that outliers not only have higher operation lead times in all process, but also that the dispersion is larger for those batches. This is especially clear for the two pellet processes and the buffers. Vision sort also stands out, with an average lead time that is more than 4 times higher for outliers than other batches.

Figure 5.26

Box and Whisker Plots over All Processes of Gamma

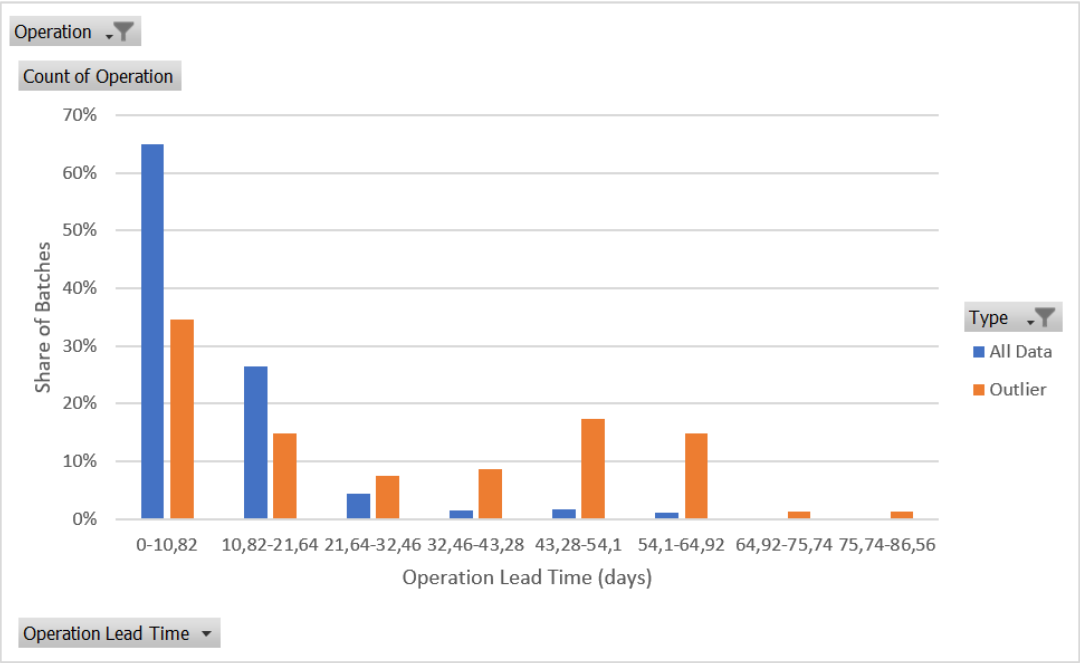


Note. All data is presented in the plot to the left, and outliers in the one on the right

As seen in Figure 5.27, around 65% of the batches go through the second pellet process in less than the average operation lead time. If looking at the first two intervals, around 90% of all batches are processed in twice the average lead time. For outliers, the figures are 35% and 49%, respectively. On the other end of the spectrum is the sorting process, which can be seen in Figure 5.28. In this process, the share of outliers spending less than twice the average operation lead time slightly exceeds the share for all data. If looking at only the batches being processed within the average operational lead time, the relationship changes, with a higher share of all batches making it through in that time.

Figure 5.27

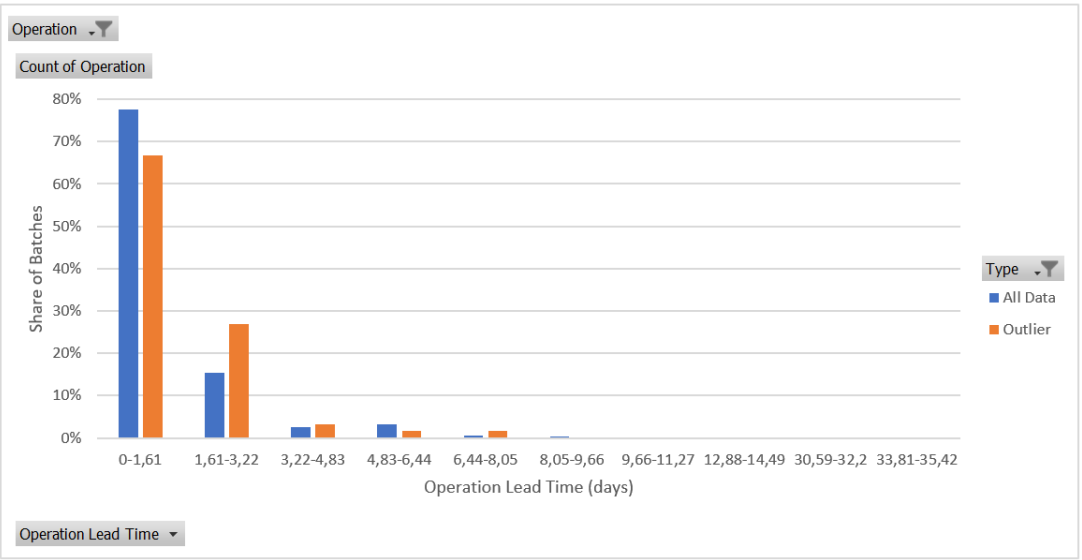
Histogram of the Operation Lead Time for Gamma's Pellet 2 Process



Note. The groupings along the X axis correspond to the factor-adjusted average operation lead time

Figure 5.28

Histogram of the Operation Lead Time for Gamma's Sorting Process



Note. The groupings along the X axis correspond to the factor-adjusted average operation lead time

Deviation protocols were processed for Gamma as well. The category deemed to have caused most deviations in each segment was Man, but Machine, Method, and Material were close behind, as seen in Table 5.8. Section 4.4.2 gave that out of 40 batches of outliers for the pellet process 1, 18 were accompanied with deviation reports. The same numbers were 27 out of 81 batches for pellet 2, and 9 out of 69 for the final three processes. Since such a large share of

outliers did not come with deviation reports, the operation times for subprocesses and -buffers were looked into as well, as shown in Table 5.9. For pellet 1, 22 batches lacked reported deviations and lead time data for half of these did not explain why the batch had been slow through the process. The average time spent investigating a deviation for an outlier of Gamma in the first pellet process was factor-adjusted to 37 days. Out of the 54 batches lacking reports for pellet process 2, 29 could not be explained by looking at lead time data, while the buffer before the second subprocess had extended lead times for 22 batches. It took an average of 43 factor-adjusted days to investigate an outlier with a deviation in that process. For the segment making up the final three processes and two buffers, 59 outlier batches lacked deviation reports, and 38 of these showed unusually long lead times in buffer 3. The average outlier with a deviation was closed in 39 factor-adjusted days in for this segment.

Table 5.8

Compilation of the Deviation Reports for the Outliers of Gamma

	Pellet 1			Pellet 2			Tableting - Sorting		
Category	**Major**	**Minor**	**Total Deviations**	**Major**	**Minor**	**Total Deviations**	**Major**	**Minor**	**Total Deviations**
Man	0	8	8	0	12	12	1	4	5
Machine	0	6	6	5	5	10	1	2	3
Method	0	3	3	9	2	11	1	2	3
Material	1	2	3	0	0	0	1	2	3

Table 5.9

Reasons for Extended Lead Times of Outliers Lacking Deviation Reports

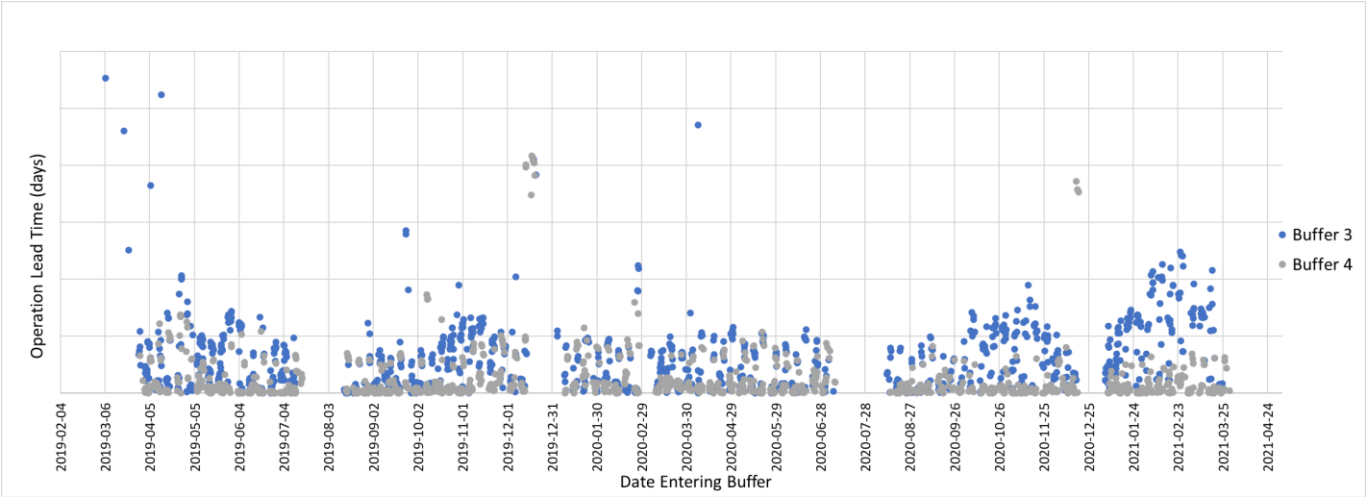
	Pellet 1		Pellet 2		Tableting - Sorting	
Total number of outliers without deviation reports	22		54		59	
Lead time data does not indicate where the problem is located	11		29		0	
Most common problem	Buffer before final subprocess	5	Buffer before second subprocess	22	Buffer 3 (before coating)	38

5.2.3.2 Gamma's Buffers

The buffers belonging to the final segment, buffer 3 between tableting and coating and buffer 4 between coating and sorting, were looked into in more detail. Just like for Alpha and Beta, the initial interviews gave that the factory closed down during the summer and Christmas holidays. Plotting the quantitative data in chronological order showed that no batches stayed in the buffers over the summer holidays during the years under investigation, as seen in Figure 5.29. However, a handful of batches were left in buffer 4 over Christmas each year. It was also clear that the time spent in buffer 3 increased over the final 6 months of collected data.

Figure 5.29

A Chronological Illustration of Gamma's Buffers



Calculations were performed to investigate adherence to the FIFO policy, and the results are shown in Table 5.10. In buffer 3, operators departed from the principle 40% of the time. When accounting for batches possibly being stopped to investigate deviations, the departure rate was 26%. The numbers for buffer 4 were 20% and 10% respectively. When looking at the rate of departure for each of the three years under investigation, buffer 3 went from a 28% departure rate without a recorded deviation in 2019 to 20% in 2020 and 41% in 2021. Buffer 4 was more stable, going from 10% to 11% between 2019 and 2020 and sitting at 6% in 2021.

Table 5.10

Adherence to the FIFO Principle for Gamma

		Buffer 3		Buffer 4	
		Number	Rate	Number	Rate
Total number of withdrawals		1 224		1 222	
Departures from FIFO		495	40.4%	243	19.9%
Departures from FIFO without reported deviation	Total	321	26.2%	117	9.6%
	2019	156	28.2%	54	9.7%
	2020	108	20.4%	55	10.5%
	2021	57	40.7%	8	5.7%

5.3 Qualitative Interviews

In this section, the results from the second round of interviews are presented. The data was processed as described in Section 4.4.1, including coding the transcribed interviews. The reasons given for lead time variability are presented, and the code words deduced from the interviews were divided into four categories: *Investment requirements*, *Organizational/ Structural*, *Ways of working*, and *Contextual factors*. The categories and the code words that they encompass are presented in an informative table completed with representative quotations. The interviewees also discussed ideas that could potentially decrease the lead time variability. These statements were also coded and are presented in a table along with exemplifying quotes. Deviations and deviation handling emerged as a theme in the interviews. When discussing lead time variability, all interviewees talked about deviations as a significant cause. Therefore, the interviewees' views about deviations are presented in along with some illustrative quotes.

5.3.1 Reasons Given for Lead Time Variability

During the interviews it was clear that all respondents believed that deviations were the main culprit for lead time variability, and the causes of lead time variability became intertwined with the causes for deviations. Because of this, a decision was made to code the reasons for deviations and reasons for variability in the same way in this section, and to present the common views on deviations in general in Section 5.3.3.

A total of 21 code words were deduced from the transcribed material relating to reasons for lead time variability. They were later grouped into four broader categories, each holding between four and eight code words. Table 5.11 presents these code words and categories, and shows the number of interviewees that have discussed each topic. Each code word is also exemplified with a quote from the interviews. Only code words that were discussed in four interviews or more are presented in the table below, with a complete listing found in Appendix D. All code words are, however, mentioned and explained in the following sections.

Table 5.11

Summary of the Reasons Given for Lead Time Variability

Exemplifying Quote	Code Word	Category
It all boils down to the number of operators. With sufficient staffing it would be possible to handle the prioritized batches and still be able to run the others.	Resources: Employees (8)	Investment Requirements (5.3)
There might be things happening that are related to machinery and affect the entire flow. That results in one deviation, for example, but it has a large impact on many batches.	Equipment Failures (7)	
And each piece of equipment has a flaw, either related to how it's operated, the machine itself, or both. The machine could be designed in a way that requires continuous manual attention.	Resources: Equipment (4)	
	Others (2)	
There are many things that can be prioritized, but the laboratory lead time… It takes time to analyze things. It's hard to force that.	Waiting for Results (7)	Organizational/ Structural (5.3)
Our main problem is that there is no room. We cannot work in a way where one process is running at full speed and the next one has batches for weeks. There is no physical room for that.	Production Design (6)	
…because the choice is to prioritize the production and to not look outside of one's own silo. Or past one's own silo, and that affects the next node.	Silo Mindset (5)	
	Others (3)	
I believe that the saying is that one prioritized batch delays three other batches, or something like that.	Planning Prioritization (9)	Ways of Working (4.3)
Vertically, we can spit out quite a bit in a day, without really releasing any batches. So yes, we want to put out batches each and every day, which we don't do right now.	Working Methods (6)	
We have identified that good routines are lacking for these critical processes.	Standards (5)	
Yeah, I believe so. I believe that [Section X] tends to play it safe and stops batches that could have been moved along.	Process while Investigating (4)	
	Others (10)	
The third thing driving variability is that we are a multi-section manufacturing many different products.	Product Mix (8)	Contextual Factors (4.4)
…some products are fairly new and might cause more deviations than more established products do.	Experience: Product (5)	
Sometimes you can see that there are more deviations when new people start working, because some things are just not that selfexplanatory.	Experience: Staff (5)	
	Others (4)	

Note. The numbers in parentheses following each code word show the number of interviewees that discussed the topic. The numbers that follow the categories show the average number of interviewees that discussed the code words included in that category. Code words that were mentioned in less than four interviews are aggregated under *Others*.

5.3.1.1 Investment Requirements

The category *Investment requirements* included four code words that all related to causes for lead time variability that could be traced to investments: *Resources: employees*, *Equipment failure*, *Resources: equipment*, and *IT system*. This category was discussed by an average of more than 5 out of the 9 respondents.

When interviewees made statements that were coded as *Resources: employees* the discussions related to how deviations and prolonged lead times were cause by either insufficient staffing levels or the lack of properly certified employees. *Equipment failure* was a more narrow code word, only dealing with how malfunctions caused issues during the formulation process. These two code words were the most commonly talked about within this category, being discussed by 8 and 7 respondents, respectively. *Resources: equipment* was next at 4 mentions, and includes discussions on how newer and older equipment can lead to different problems and how some machines require more manual work than other. The final code word, *IT system* gathered those respondents discussing how flaws with the current IT systems lead to unnecessary problems during formulation. This topic was only brought up by 2 interviewees.

5.3.1.2 Organizational/Structural

Code words that related to the organizational or structural causes for lead time variability were categorized as *Organizational/Structural*. On average, the code words in this category were mentioned in just over 5 out of 9 interviews.

This category encompassed four code words. *Waiting for results* related to statements that mentioned waiting for either the input from other departments or the result from analyses, and it was mentioned in 7 interviews. Statements relating to the design of the production system and shop floor, such as buffer levels, storage areas, resource utilization and, the flow of products gave the code word *Production design*, which was the case in 6 interviews. 5 respondents made statements about lack of communication or insight between departments that could cause lead time variability, they gave the code word *Silo mindset*. Finally, *Wasteful use of resources* was discussed in 3 different interviews.

5.3.1.3 Ways of Working

Ways of Working was the category that included the most code words, aggregating 8 code words that related to the way work was being done at AstraZeneca's PET OSD. The category was on average discussed by slightly more than 4 interviewees and the included code words were in order of magnitude *Planning prioritization*, *Working methods*, *Standards*, *Process while investigating*, *Process variation*, *Planning freeze*, *Human errors*, and *Inconsistent reporting*.

Two of the code words related to the planning process, with *Planning prioritization* being discussed by all interviewees and encompassing statements regarding how prioritized batches affect the production flow. *Planning freeze* compiled answers relating to how the production plan was frozen a number of weeks before the start of formulation. It was only brough up by 3 respondents. *Working methods* was discussed in 6 interviews and included answers discussing how the certain ways of working could cause lead time variability at different departments. For example, one department could prioritize performing tasks benefitting that department alone during staffing shortages, instead of dealing with paper work that could benefit the entire formulation PET. It could also be about a department doing lots of work on multiple batches at once, but not finishing any of them. *Standards* encompassed any answer relating to either the

need for or adherence to clearly defined standardized instructions and routines. It was brought up by 5 interviewees. The remaining three code words were all related to the production floor. *Process while investigating* was discussed by 4 respondents and related to how some batches were stopped during deviation investigations while others continued on while being investigated. *Process variation* gathered answers related to how certain process were designed in ways that led to variation and was discussed by 3 interviewees. *Inconsistent reporting* was used for 2 answers: one discussed how it was not always possible to see where a batch was located in the flow depending on how and when operators reported the batch, and the other related to how data could be changed in the systems at different points in time. *Human errors* gathered the 2 answers that discussed how human mistakes led to lead time variability.

5.3.1.4 Contextual Factors

The category *Contextual factors* contains 5 code words relating to the pharmaceutical production context or aspects that lie beyond the immediate short term influence of AstraZeneca. On average, these codes were discussed by more than 4 out of 8 interviewees. *Product mix* was mentioned as a cause for lead time variability in 8 interviews. Two code words in this category related to experience. Both the code words *Experience: staff* and *Experience product* were discussed in 5 interviews. *Experience product* related to the fact that some products are more established than others and *Experience staff* related to the experience of the individual employees. *Supply issues* were brought up in 3 interviews and related to the ingoing material and supplies not meeting specifications. The final code word, *Insufficient methods*, was discussed by 1 interviewee and related to the need for methods that currently are not available.

5.3.2 Proposed Solutions to Limit Lead Time Variability

The interviewees also mentioned what they believed could lead to decreased lead time variability. These statements were coded but not grouped into larger categories. From the statements made, 10 code words were deduced. The code words discussed by more than 4 interviewees can be seen in Table 5.12, while the remaining code words are shown in Appendix D. The code word for the most common topic was *Resources: employees*, which was discussed by 6 interviewees. These expressed that it was beneficial when operators could move between stations and when they had the necessary competence and certifications to do so. They also believed that more operators would help to decrease variability.

The code word discussed by the second most interviewees was *Standards*. It was deduced from statements from 5 different interviews. Some answers related to the importance of updating the standard operating procedures, and creating new ones where none currently exists. Other answers discussed how previously updated standards have improved production. One such improvement that was commonly mentioned was the introduction of batch-specific production schedules. The same amount of interviewees discussed topics coded as *Cross-functional*. These answers related to the need for collaboration and communication between departments, and how that for example cross functional meetings could be beneficial.

Two code words were deduced from 4 interviewees, *Ways of working* and *IT system*. *Ways of working* related to statements about creating a more even work and product flow, as well as work processes such as visual boards. *IT Systems* was deduced from statements that suggested that the use of existing or new IT systems could be beneficial.

Table 5.12

Summary of the Solutions to Lead Time Variability

Exemplifying Quote	Code Word
We cannot handle it by implementing four shifts in the short term, but in the long haul it could be a possibility if needed. At the moment it is dealt with by working overtime.	Resources: Employees (6)
All operators need to understand how the deviation process is handled, why we have it, and what is asked of them…	Standards (5)
Yes, that is an opportunity for improvement, to have a closer cooperation… …That would save us an awful lot of time.	Cross-Functional (5)
They are fairly good at trying to solve the problem by moving staff. Even though someone is working in coating today, they might have worked with tableting in the past, and they make sure to stay certified in both so that they can be moved around.	Ways of Working (4)
There is a an improvement project going on now, when everything will be handled digitally… …a computer program will stop you from moving on to the next step if something is missing. And the software will react if mistakes are made in reporting. The majority of our deviations are due to things like that...	IT System (4)

Two interviews discussed *Process while investigating*. These both argued that the formulation lead time could be shortened if batches were not stopped in production but allowed to be processed during the handling of the deviations. One of these interviewees thought that this should be done to a greater extent, and that the production department was a little bit too cautious. Two interviewees also discussed *Planning freeze* as a way to reduce the lead time variability. By not changing the production plan late, the production can be planned more effectively, considering for example campaign lengths and cleaning routines. One interviewee also emphasized the importance of giving the production staff some peace of mind.

The final code words, *Experience: product* and *Planning prioritization* were deduced from 1 interviewee each. *Experience: product* relates to more established products benefiting from previously gained knowledge to handle deviations more effectively. One interviewee discussed *Planning prioritization* and said that prioritized batches had shorter and more stable lead times. In addition, it was important that the batches were being prioritized throughout the value stream, not only in production. See Appendix D for a complete compilation of the code words assigned to improvement ideas.

5.3.3 Deviations

All employees brought up deviations during the interviews. Some discussed the process of handling them in detail while others mentioned them in broader terms. The majority of the interviewees believed that the production processes involved in the formulation of their brand in question were fairly stable, but that deviations were a problem. One interviewee called these batches *"bad eggs"* while another complained that there are batches that are stuck in production for over a year. These descriptions are exemplified with the following quote:

Quote 1

"…but what drives up the average are a few batches that are stopped. They can stay in place for a long time waiting for the deviation investigation."

- Interviewee I

There were certain processes that were more susceptible to deviations than others, which some of the interviewees mentioned. Reasons for that could be that the process was unusually complicated or had a combination of ingredients that made it difficult to replicate. It was, however, clear that most interviewees saw deviations as something that could happen to any process and any operator. The following quote is an example of that viewpoint:

Quote 2

"It's hard to say... I believe that deviations happen haphazardly, at different segments. But yeah, we do have some deviations that are more common than others, I would say that."

- Interviewee VI

Most of the respondents brought up that deviation investigations are undertaken by cross-functional teams, consisting of representatives from many different departments at AstraZeneca's PET OSD. In exceptional cases, experts from outside of the PET can be called upon as well. The interviews gave that different departments were involved since they possess different kinds of knowledge and expertise. The following quote is an example of that viewpoint:

Quote 3

"A lot of different functions are involved too… …[Process Technology] needs to figure out what [the unknown solution] consists of. They need to contact other groups who can analyze the solution. Where it originated from and how it got there is up to Maintenance to work out."

- Interviewee VI

It was also clear from the interviews that the handling of deviations can be a complex and time consuming task. The interviewees discussed how the reports from the operators are not always complete, with necessary information about the deviations missing. As the previous quote stated, the deviation can be caused by an unknown substance that needs to be analyzed. There are many variables that need to be taken into account, as illustrated by the following quote:

Quote 4

"Getting a grip of the extent [of the deviation] can take a while, and one has to search through systems, flip through papers, turn the equipment inside out, open it up… …And sometimes it's hard to find what one's looking for immediately, so one might have to look around for a bit. It takes a while."

- Interviewee III

The interviewees who worked directly with quality related tasks, and those that had previous experience from such departments, made clear that a deviation does not have to be complicated to be serious. Even if it is obvious what caused the deviation, the reasons behind it need to be investigated so that they can be prevented moving forward. An example of a simple, but serious deviation is discussed here:

Quote 5

”But for us, one missed signature is a significant deviation. That is our only way to let Läkemedelsverket [The Swedish Medical Products Agency] know that we manufacture according to our pledge... …So a missed signature is a lost piece of evidence that could have proved that we have manufactured according to the agreement.”

- Interviewee II

A deviation can affect a single batch or a number of batches. Many of the interviewees described that if a deviation is noticed and it is certain that the problem did not affect other batches, only the batch in question will be stopped and investigated. In other cases, the problem could be caused by a foreign substance in the incoming material or faulty equipment. Such deviations affect many batches, as explained by the following quote:

Quote 6

”…and it could be a deviation on a solution for example, and things like that can stop a lot of batches without the deviation being connected to any of them… …and in those cases, all 12 batches will be halted because of a common ingredient…

- Interviewee VII

None of the interviewed employees were solely tasked with the handling of deviations. It was clear from the interviews that it can be a challenge to both find sufficient time to investigate deviations in a timely manner. At the same time, the handling of deviations take a significant amount of time out of their regular schedules, making it difficult to keep up with their daily tasks. The following quote illustrates this dilemma:

Quote 7

”Unfortunately, [process development] is something I believe isn’t emphasized enough. But it’s a bit hard when most of the working hours are spent investigating deviations. And there are other projects that need to be finished. So it is understandable that other things are prioritized…”

- Interviewee VI

5.4 Additional Quantitative Compilation

The second round of interviews gave that the FIFO queueing principle discussed in Section 5.1 was not used by operators on the production floor. Instead, they are told to always pick the batch with the oldest batch ID, which is the batch that started the entire formulation process first. In order to investigate adherence to this principle, the quantitative data was compiled to reflect this. Furthermore, calculations were done to assess the impact of deviations on the formulation lead times. This results is also presented in this section.

5.4.1 Additional Queueing Principle Tables

This principle described above was departed from in all the buffers in the production of Alpha. Buffer 3 had the highest rate of departure, with 21% compared to 18% and 14% in buffer 1 and buffer 2 respectively, as seen in Table 5.13. When taking deviation reports into account, the rate of departure decreased in all buffers. Buffer 2 skipped the most batches despite not having a deviation protocol related to them, 89 batches or 13%. In buffer 1, 83 batches were skipped, or 9% and 69 batches without deviations were skipped in buffer 3, or 10%. For buffer 1, the

rate of departure from the principle decreased in 2021, from 13% the year before to 3%. The rate of departure for buffer 2 has increased over the investigated period, from 12% in 2019 to 14% in 2021.

Table 5.13

Adherence to the Queueing Principle for Alpha

		Buffer 1		Buffer 2		Buffer 3	
		Number	Rate	Number	Rate	Number	Rate
Total number of withdrawals		686		695		695	
Departures from Batch ID		123	17.9%	98	14.1%	149	21.4%
Departures from Batch ID without reported deviation	Total	83	9.3%	89	12.8%	69	9.9%
	2019	37	11.8%	38	12.2%	26	8.5%
	2020	45	13.2%	45	13.2%	38	11.1%
	2021	1	3.1%	6	14.0%	5	10.6%

For Beta's first buffer, operators departed from the given principle 26% of the time, as seen in Table 5.14. When adjusting the numbers to reflect those batches accompanied by a deviation report, the departure rate declined to 9%. The numbers for buffer 2 were 11% departure rate from the principle of always taking the oldest batch, but 5% when accounting for reported deviations. Buffer three had a departure rate of 28% but only in 9% of the cases were those batches not affected by deviation reports. All three buffers have in common that the departure rates decline over the three years under investigation. For the first buffer, 14% of the batches had no deviation reports and departed from the queueing principle in 2019. In 2020 and 2021 the departure rate was at 7%. In buffer 2, the rate went from 7% in 2019, to 3% in 2021, and in buffer 3 the rate improved from 11% to 5%.

Table 5.14

Adherence to the Queueing Principle for Beta

		Buffer 1		Buffer 2		Buffer 3	
		Number	Rate	Number	Rate	Number	Rate
Total number of withdrawals		822		838		851	
Departures from Batch ID		211	25.7%	88	10.5%	239	28.1%
Departures from Batch ID without reported deviation	Total	75	9.1%	44	5.3%	78	9.2%
	2019	39	13.9%	21	7.2%	35	11.2%
	2020	28	6.7%	20	4.7%	37	9.2%
	2021	8	6.6%	3	2.5%	6	4.6%

Table 5.15 shows the results for Gamma. In buffer 3, operators departed from the principle of always taking the oldest batch first 35% of the time, a number that went down to 19% when taking reported deviations into account. Even though the average departure rate was 19% over the 24 months under investigation, the 3 months of 2021 showed a departure rate of 37% in buffer 3. In buffer 4, the departure rate was 15%, but only 5% when accounting for deviation reports. The figures for 2019, 2020, and 2021 were fairly steady going from 6% in 2019 to 4% in 2021.

Table 5.15

Adherence to the Queueing Principle for Gamma

		Buffer 3		Buffer 4	
		Number	Rate	Number	Rate
Total number of withdrawals		1 224		1 222	
Departures from Batch ID		430	35.1%	177	14.5%
Departures from Batch ID without reported deviation	Total	238	19.4%	66	5.4%
	2019	101	18.2%	32	5.8%
	2020	85	16.0%	29	5.5%
	2021	52	37.1%	5	3.5%

5.4.2 Assessment of the Impact of Deviations

To provide more insight into the lead time variability, deviation reports were collected for all data, not just the outliers, which can be seen in Table 5.16. By removing all batches with deviations, the average formulation lead time for Alpha and Beta, decreased by three days. In total, the formulation lead time for Gamma was also reduced, but to a smaller extent. If removing all outliers, similar reductions in lead times were seen for Alpha and Beta. For Gamma, the total formulation lead time was reduced by two days when removing outliers, which was significantly more than by removing deviations.

Table 5.16

Formulation Lead Times when Removing Deviations and Outliers

		Number of complete batches	All data (days)	Number of batches with deviations	Without deviations (days)	Number of outliers	Without outliers (days)
Alpha		694	31.6	141	29.4	34	29.0
Beta		829	26.6	290	23.6	36	24.0
Gamma	Pellet 1	798	2.4	60	2.2	40	2.2
	Pellet 2	1 604	10.8	272	10.5	81	9.9
	Tab-Sort	1 217	13.0	34	13.0	60	12.1
	Total		26.2		25.7		24.2

6
ANALYSIS

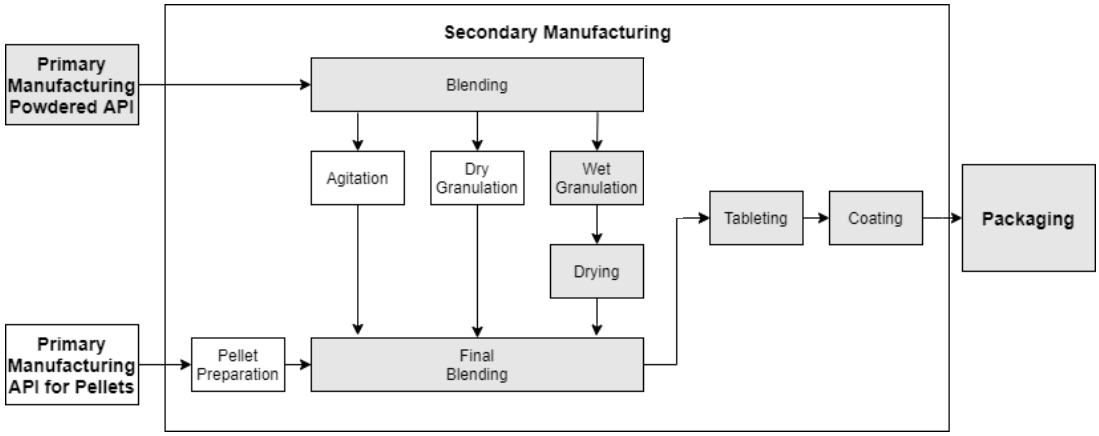
This section starts with a comparison of the theory on pharmaceutical manufacturing and the processes observed at AstraZeneca. In general, the company follows theory, but in some cases two or more theoretical processes were combined into one, as done with blending, wet granulation, and drying for Alpha and Beta. In other instances, what theory described as one process was split into a number of processes and subprocesses. An example of this was the two pellet preparation processes for Gamma, that contained two and three subprocesses, respectively. In the next two subsections, the results from the quantitative analysis and the qualitative interviews are compared and contrasted and connected to relevant theory. One section is devoted causes of lead time variability, while another one focuses on possible solutions to the problem. The analysis showed that many of the causes suggested by the interviewees were in fact supported by theory, and in many cases connections could be drawn between both qualitative and quantitative data and theory. An example of such a phenomenon would be prolonged lead times in the coating process of both Alpha and Beta. They were discussed in an interview, quantitative data clearly showed their existence, and theory explained how those lead times came about. There were, however, other instances when the quantitative data could not confirm the statements made during interviews, or when theory disagreed with the findings. An example of the latter would be the fact that many interviewees believed that their older brands had fewer deviations, while theory pointed to the opposite. In these sections, results and theory are combined to form the analysis and the text is built up around exemplifying quotes that convey the beliefs of the interviewees.

6.1 The Production Flows of Alpha, Beta & Gamma

At the studied PET at AstraZeneca, OSD Formulation, drug products in the form of oral solid doses were produced from API. The company refers to this process as the formulation process, which corresponds to secondary manufacturing as described by Wilson (2016). There are however some differences. The current state maps for the two brands using API in powdered form, Alpha and Beta, only contain four main processes. The first process, granulation, encompasses the processes referred to by Wilson (2016) as blending, wet granulation, and drying. Despite encompassing three of the six processes described by Wilson (2016), granulation only accounts for about a third of the total operation lead time for the processes. At AstraZeneca, the formulation processes for Alpha and Beta start with blending, meaning that what Wilson (2016) refers to as the milling process is not included. The secondary manufacturing processes are presented as a framework in Figure 1.1. In Figure 6.1, AstraZeneca's formulation process for Alpha and Beta is illustrated in the framework for comparison.

Figure 6.1

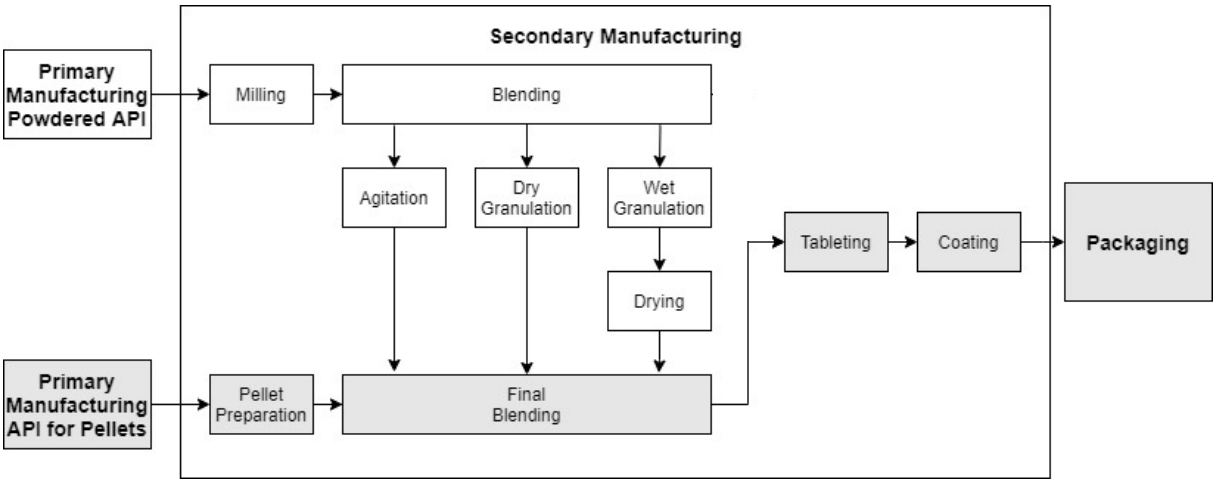
The Formulation Process of Alpha and Beta



Gamma is the only brand in this study based on pellet technology. Farmoudeh et al. (2020) describe several production methods for pellets, one of which corresponds to AstraZeneca's processes where the API is sprayed onto a core. Pellet preparation is very complex and consists of two separate processes in Gamma's CSM. The total operational lead times for these two pellet processes are about the same as for the remaining processes combined. After pellet preparation, Gamma goes through the same processes as Alpha and Beta, in accordance with Wilson (2016), but the final blending process is included in the tableting process for Gamma. The production process for the brand and how it relates to the theory presented in Section 1.1.1 can be seen in Figure 6.2.

Figure 6.2

The Formulation Process of Gamma



According to Wilson (2016) pharmaceutical production contains a mixture of short and long processes, which is consistent with the findings in this study. For both Alpha and Beta, the process with the shortest operation lead time was final blending. They had factor-adjusted lead times of less than 0.5 days, while the longest operation lead times were more than eight times longer. For Alpha, this was the granulation process and for Beta coating. Making the same comparisons for Gamma was difficult, since the two pellet preparation processes also include buffers.

6.2 Analysis of the Reasons for Lead Time Variability

The quantitative results showed that there was a significant difference between outliers and all batches when it came to almost all processes and buffers. For Alpha and Beta, it was also clear that almost all outliers were affected by deviations. The frequent occurrence of deviations at the OSD PET at AstraZeneca is in line with Kumar et al. (2020), who state that deviations happen daily within the pharmaceutical industry. This somewhat contradicts Ranky et al. (2008), who argue that traditional quality management is not suitable for pharmaceutical manufacturing, simply because it allows for mistakes to happen. Theory does, however, support using systematic methods for managing sources of process variability (Cogdill, 2008), and Kumar et al. (2020) specifically bring up root cause analysis (RCA) as an example of a method used when handling deviations. This corresponds well with the process used at AstraZeneca, where all deviations are attributed to either *man*, *machine*, *material*, *method*, or *process* during the RCA. A majority of the examined deviation protocols at PET OSD gave *man* as the cause of the deviation, and a number of interviewees elaborated on this categorization:

Quote 8

"I have observed the operators at work, and I feel like they're in a tough spot. There is a lot of paperwork and lots of signatures. Many of our deviations are what we call "handling errors". The wrong signature somewhere, or a missing signature, or some other administrative error. It's super easy to understand those when you see the piles of paperwork that the operators are dealing with."

- Interviewee VI

The paperwork referenced in the quote is part of the strict regulations levied on the pharmaceutical industry by regulatory organizations such as the WHO, ICH, and the FDA. Durivage (2016) discusses the importance of proper documentation, and mentions for example that signatures, initials, dates, and batch numbers need to be included in the batch documentation. The author also explains that this is done to minimize the risk of mistakes and to meet regulatory requirements. This rhymes well with the quote presented in Table 5.11, explaining how a missing signature is a serious deviation. Another interviewee discussed that deviations categorized as *man* may in fact be caused by missing or lacking standard operating procedures:

Quote 9

"But the people shouldn't be blamed for the deviations. They're caused by the lack of a structured system for the people to follow."

- Interviewee III

Quote 8 and 9 show that the interviewees have understood the importance of both having standards, and of keeping the human aspect of the operators in mind. This is in line with Patchong (2012), who has a humancentric perspective on standardized work, emphasizing that standards are created for, and with, the operators. Quote 9 clearly stated that deviations can be caused by insufficient standards, and the following quote puts it in a broader perspective:

Quote 10

"The training of the staff isn't good enough, and the routines are not clear enough. There should be rules dictating how to act as an employee, and clear and easy-to-follow instructions. If so, there wouldn't be as many deviations. But we update our routines very frequently, usually to improve them, which puts

additional demands on for example operators to stay up to date on all of them…"
- Interviewee III

In Quote 10, the interviewee says that existing standards are insufficient and updated too frequently, making it hard for employees to stay up to date. According to Jacobsen and Thorsvik (2014), the purpose of the SOPs is to create predictability by dictating exactly how tasks should be performed, and Martin and Bell (2011) underscores that the procedures should be incrementally updated on a continuous basis in order to simplify adoption among the operators. Even though updated SOPs are part of the deviation handling at AstraZeneca, it is clear that some employees believe that there is more to be done on that front. Gallup et al. (2008) argue for training programs aimed at improving employee compliance with the SOPs, but the interviewee in Quote 10 states that the training offered at PET OSD is deficient. Another aspect of training is offered in the following quote:

Quote 11
"Training people, for example operators, takes time… …initially it would take capacity away from the existing work force. But it might have a positive impact further down the road, more in the long run than the short."
- Interviewee IX

The interviewee brings up the trade-off between producing today and focusing on the long term, by increasing the capacity through training. This belief was also present in discussions regarding standards, when employees were said to not be properly trained on the SOPs. One interviewee explained that it is up to the operator to study the standards, but that there is no formal test done to ensure that he or she has internalized the knowledge. Prina (2017) argues that investing in training can pay dividends in the long run, but the interviews did not reflect that this was part of the ways of working at AstraZeneca. Another aspect related to the resources dedicated to employees is the general staffing levels, as discussed in Quote 12:

Quote 12
"The best thing would be to have four people, maybe. Starting both [machines] at once and always having two people at hand. But it's fairly expensive, from a payroll perspective, to have twice the number of employees… …So I think it's a strategic decision. A choice has been made to man the machines with the fewest number of operators possible."
- Interviewee III

A number of other interviewees were less direct in bringing up the fact that they believed that staffing was an issue. For example, it was said that deviations could be handled faster if more employees were dedicated to the investigations. Quality Assurance and Quality Control were said to be undermanned, and the production staff did not appear to have enough time for both their production related and administrative tasks. Additionally, one interviewee made clear that the process engineers spent too much time handling deviations, and too little time on actually improving the processes. To summarize, the interviewees gave input suggesting that not enough resources were invested into the employees, both when it came to training and proper staffing.

In the case of Alpha and Beta, it was clear that many of the outlier batches had deviation protocols attached to them. 66% of Alpha's outliers had one or more deviations, and the corresponding number for Beta was 84%. For Gamma, the number of outliers with deviation reports ranged between 13% and 45% in the two pellet processes and the final segment of three

processes and two buffers. However, the interviews gave that batches can be affected by deviations even though no deviation report is attached to their batch number. For example, batches can be stopped while awaiting the result of a deviation investigation belonging to another batch. Quote 13 illustrates this as the interviewee uses a cinnamon bun production line as an analogy:

Quote 13

"If I were to pour cayenne into the mixer [instead of cinnamon], that will lead to a deviation on that batch of cinnamon rolls. But we might not notice the mistake until testing… …At that point we might have produced another 5-6 batches of rolls on the same equipment. Those batches might taste like cayenne too, so we have to hold those batches too in order to ensure that they aren't affected by this cayenne deviation."

- Interviewee III

It is not always clear how many batches were affected by a deviation, since other batches may be stopped pending the original investigation. During the interviews, it was also explained that machine failures were relatively common. These might cause prolonged lead times without deviation protocols being attached to specific batches. Another example was given by an interviewee regarding Gamma. In the second pellet process, a solution solidified easily and became difficult to handle. In that case, the machine needed to be emptied and cleaned before continuing the process, creating delays and longer operation lead times. This was believed to be a contributing factor to the relatively large share of outlier batches that have issues in that process without being connected to deviation protocols.

Kumar et al. (2020) state that grasping the severity of a deviation is an important step of the deviation handling process, and Quote 13 exemplifies some of the difficulties that this step entails. Durivage (2016) states that the employees in the quality unit need a very comprehensive skill set. At AstraZeneca, the deviation team corresponds to that quality unit. According to the description on how AstraZeneca handles deviations, this team consist of a group of individuals representing different departments, each contributing a different skill set. It was also clear that the members of the investigative team were the ones deciding what happens to a batch affected by a deviation. It was either stopped immediately, or moved on through formulation. In the latter case, the batch could not move past the final process, or leave the internal flow, before it had been investigated and released. This is exemplified by the following quote, discussing how formulation can proceed despite the batch being investigated for deviations:

Quote 14

"So the first process will let you know that they have a deviation, something is wrong, but formulation will continue until the final process, where the batch will be stopped… …Quite a lot is stopped there. We process on risk, and the batch is stopped before packaging. We move it through the flow, and then it just sits there."

- Interviewee I

This behavior was clearly visible in the quantitative data covering Alpha and Beta. The final process for both brands, the coating process, had significantly longer operation lead times for outliers compared to all data, and outliers were to a large extent made up from batches affected by deviations. The deviation protocols for these two brands showed that the average time spent investigating a deviation for Alpha was 46 factor-adjusted days, while it was 37 days for Beta.

For comparison, the factor-adjusted total formulation lead times for the two brands were an average of 32 and 27 days, respectively. This means that no matter where a deviation were to take place in the formulation of Alpha or Beta, the likelihood of that batch being stopped in the coating process, while awaiting results from the deviation investigation, was very high.

For Gamma, the same behavior could not be observed. Since the complete formulation process could not be followed for a single batch, it was harder to tell if and where batches were stopped. However, the second pellet process showed similar characteristics as the coating process for Alpha and Beta. It was also confirmed during one of the interviews that this was where deviated batches detected during the two pellet processes were stopped. One reason that sorting, the final process, did not have the same characteristic with prolonged lead times could be that some batches with deviations were sent to vision sorting with a different batch number.

The interviews gave a number of reasons that can explain the excessive times spent handling deviations. It was shared that finding times to have joint meetings was a challenge, but different interviewees put the blame on different departments and no clear pattern could be detected. Interviewees also stated that some deviations were complex and required more time to investigate, as mentioned in Section 5.3.3. In other cases, the investigation was stalled while awaiting lab results. This was discussed in the following quote:

Quote 15

”[The lab] has a huge impact on our lead times. In many cases we have to delay the release of batches, even those without deviations, because results from the lab are not available. Those delays are caused by the lab.”

- Interviewee II

Other interviewees went into more detail when discussing the delays caused by the lab, and gave possible reasons, as exemplified by Quote 16:

Quote 16

”There might be more lead time variability from Quality Control and Quality Assurance when it comes to releasing batches. And it can be caused by anything from employees, staffing... Even prioritizations. Another brand can have a higher priority.”

- Interviewee IX

The quote brings up how staffing levels affect lead time variability, but also prioritizations, which was the only code word brought up in every interview. By prioritizing a certain brand in a section, other brands sharing resources with the prioritized brand will be negatively affected. An interviewee explained that when one batch is prioritized, three others are delayed. It was also said in interviews that prioritization can be a necessity to fulfill customer demand, and it was discussed that prioritized brands have shorter and more stable lead times. The following quote exemplified that the planning department was aware of this trade-off:

Quote 17

”...I don’t think that we prioritize when it’s not needed. We usually talk about it too, and make sure to keep the entire chain in mind. Do I really gain something from prioritizing this one batch?”

- Interviewee IIX

No significant difference in the formulation lead times between the product variants could be observed in the collected data. Although the operation lead times differed somewhat between the variants, no interviews discussed this. Producing a mixed flow of products, on the other hand, was discussed by most interviewees as a reason for lead time variability, even though it is often contextual in nature. In one interview, it was also discussed how this may lead to more prioritization. If a variant or product that is produced infrequently has a deviation, it is often prioritized as there is no other batch in production that can replace it to meet customer demand. The following quote exemplifies the difficulty of producing a mixed flow:

Quote 18

"Tableting has a dilemma like that at the moment, but the lead times might not reflect it. [Brand X] is prioritized, so they have to change over to a different product, initialize a set-up time."

- Interviewee I

Changing from one brand to another requires additional set-up times, as mentioned in Quote 18, and Wilson (2016) explains that certain processes are associated with significant set-up times. Another aspect of switching between products in the pharmaceutical industry is the regulatory mandated cleaning procedures. When switching between products, a thorough Level 2 cleaning is according to Ghosh and Dey (2010) required. Wilson (2016) describes this process as being done manually, requiring laboratory tests to confirm cleanliness, and being very time consuming. One interviewee brought up manual cleaning procedures, meaning that they are one of the many manual tasks that can lead to deviations. This is in line with Durivage (2016), who argues for automated cleaning procedures, since they are more repeatable. The author also believes that there needs to be proper procedures in place to ensure the robustness and documentation of cleaning. These beliefs rhyme well with Jacobsen and Thorsvik (2014), who argue for SOPs as a way of ensuring repeatability.

On the other hand, the cleaning required between batches of the same product is comparatively fast, and often built into the equipment and performed automatically (Wilson, 2016). This means that when a single product is manufactured, the only time Level 2 cleaning is required is between campaigns (Pacciarelli et al., 2011). This could be one of the reasons to why all interviewees brought up prioritizations as a cause of lead time variability. Having to squeeze a batch of a different brand or product variant into the production flow requires additional set-up times and time consuming, manual cleaning procedures that could in turn lead to more deviations.

In the presentation of the quantitative data, histograms showed the distribution of batches going through a few different processing steps (see Figure 5.8 and Figure 5.9 for Alpha, Figure 5.17 and Figure 5.18 for Beta, and Figure 5.27 and Figure 5.28 for Gamma). It was clear that a vast majority of all batches went through without any delays, while the distributions had significantly longer tails for outliers. This was confirmed in many of the interviews, as exemplified by Quote 19:

Quote 19

"...but we do have more than 90% of the batches going through each process without any issues, the batches we call "First Class Batches". So it really is a small minority that is affected by deviations."

- Interviewee VI

Even though most batches do advance through the processes in a quite dependable amount of time, the outliers make it impossible to plan for minimal buffer levels when designing the production flow. Once again, mandated cleaning procedures magnify the issues that can arise. Quote 20 exemplifies this, by discussing how additional cleaning is required if machines stand still because of empty buffers:

Quote 20

”In theory, the lead time should be short. Theoretically, it would be nice to have one day between each process, but it really has to be one day. Coating, for example, can’t stand around waiting for batches. That would lead to lots of cleaning procedures, doing dishes if the wait exceeds 24 hours. Coating has to have an even influx of batches.”

- Interviewee I

The quote shows that always having access to batches is of the essence for the coating process, and this is true for the other processes as well. One constraint regarding buffer levels was shown to be the lack of physical space, which was brought up my a few interviewees. One interviewee, especially, discussed how ensuring an inflow of material by stocking the preceding buffer was not an option due to the limited space available for that buffer.

Many of the interviewees mentioned that the factory closed down during the summer and Christmas holidays, and this was also visible in the graphs showing the buffers for all three brands (Figure 5.12,Figure 5.21, and Figure 5.29). One interviewee discussed how it was difficult to organize work around the summer closure:

Quote 21

”If our summer vacation lasts for four weeks, and the material has a hold time of two weeks… How do you deal with that? That is something that comes up every single year, “here, solve this problem!”

- Interviewee III

The interviewee problematizes the hold times. As described by the WHO (2015, Annex 4), there are limits dictating the amount of time that material can be held between two processes. In the case of Quote 21, the summer holiday exceeds that specified hold time. As a result of the regulatory demands, buffers that hold material with shorter hold times than the summer closure will have to be emptied during the holidays. This was visible in the graphs, where only an occasional batch was left in a buffer during the summer closure. The way this was handled at AstraZeneca was explained during some interviews. The operators of the different processes stagger their summer vacations so that the first process closes down before the second one, and so on. The final process is the last one to close down, which is done in an effort to finalize the batches that have started the formulation process in early July. Similarly, the operators of the first process are back at work before the others, so that all processes have material on hand when they return from the holiday. In contrast, the Christmas closure is shorter than most hold times, meaning that the buffers do not show the same clear signs of emptying before the winter holidays. However, no new batches enter the buffers during either closure.

Another aspect investigated during the quantitative analysis of the buffers was the adherence to the queueing policy. During the initial interviews it was discovered that FIFO was supposed to be used in the buffers separating the different processes during formulation, but during the second round of interviews it was disclosed that a different policy was in fact used. The

operators were told to always take the batch with the oldest batch ID when there were many batches at hand in a buffer. In the additional quantitative results presented in Section 5.4, adherence to that policy was investigated. It was clear that the policy was not always followed, but for all three brands and for all buffers the adherence was better for that policy than for FIFO. For example, in the buffers for Alpha operators departed from the FIFO principle 20% of the time, while the departure rate was less than 12% when looking at the policy focused on batch number. The calculations performed on adherence to the queueing policies were done with consideration for batches affected by deviations. Prioritized batches are most likely handled differently in buffers as well, but the collected data could not confirm this. Therefore, one can assume that the figures on adherence to the policy would improve even more if also taking prioritizations into account.

How batches are prioritized in buffers will have an effect on lead time variability. FIFO only takes the time spent in the specific buffer into account, while the policy focused on batch ID looks at the total time spent in formulation, since the batch with the oldest batch ID started the entire process first which Jonsson and Mattsson (2009) refer to as earliest start date first. In addition, the authors argue that by using this priority rule the actual production order on the shop floor will be as similar as possible to the production schedule. Because of the different time frames, FIFO will lead to a smoother and less dispersed operation lead time in each buffer, while oldest batch ID will result in a more even total formulation lead time. Thus, the policy actually in place on the shop floor is the one leading to less formulation lead time variability. It is, however, problematic that not all employees have the same information, which could indicate that communication is lacking between the different departments.

A number of interviewees discussed how departments focused on their own organization when in a time crunch. One interviewee explained that when forced to prioritize, the production department tends to focus on their main task, which is producing batches. However, if production does not provide the QC and QA departments with samples and documentation in a timely manner, the formulation lead times will be prolonged, which was brought up during the interviews. As discussed earlier in the analysis, the level of staffing is perceived to be a problem, which forces prioritizations of activities as described in Quote 22:

Quote 22
”It also depends on staffing and priorities. It’s common to prioritize the production of batches over running a machine that just elevates the quality. That machine does not produce any pills.”
- Interviewee VII

According to one interviewee, a lot of competence existed at AstraZeneca, but it was confined to certain individuals and not spread within the department, or throughout the organization as a whole:

Quote 23
”We have certain individuals who are extremely good at it, they have state-of-the-art competence! But that competence is not diffused to others…”
- Interviewee III

Jacobsen and Thorsvik (2014) mean that a department being occupied with only their own function is a sign of silo mentality, which can lead to suboptimization. Quote 23 indicates that information is not shared sufficiently between employees, which Deighton (2016) argues is a

sign of silo mentality. When organizing departments according to function, separate cultures that hinder effective communication, tend to evolve (Jacobsen & Thorsvik, 2014). This may be the case at AstraZeneca. According to both Deighton (2016) and Jacobsen and Thorsvik (2014), silo mentality results in inefficiencies. One interviewee said that until recently, other departments could not see the current status of batches at QC. Another interviewee expressed that only the QA department had access to a certain IT system, resulting in them having to spend time answering questions from other departments. The following quote is also an example of silo mentality resulting in extra, inefficient work:

Quote 24
"It's easy for Production to take lots of samples, and I can understand them wanting to be super confident with their decision before moving on. But as a consequence, it can mean three days of work for an analyst, because the testing procedures are so extensive."
- Interviewee IV

However, being overly cautious might not always be a sign of silo mentality and structural problems. It was evident from many interviews that having experience matters, both in terms of professional experience, but also in terms of dealing with established products. Some interviewees discussed that closing deviations takes less time for an experienced group, where all members of the team have seen similar problems in the past. Another interviewee discussed how the decision process changes with increased experience, as shown in Quote 25:

Quote 25
"When I was new at this position, I played it extremely safe. I was wary of the smallest things. Now, when I'm starting to get more experience, I do believe that it is beneficial to just keep going at times."
- Interviewee VI

That quote shines a light on the fact that inexperienced employees might not always work in efficient ways. Similarly, new products can also be problematic, as no past experience exists regarding the manufacturing processes and deviations that may occur. Quote 26 exemplifies this problem:

Quote 26
"New products, because of them being new... If questions arise, it might be the first time we deal with that specific question and that means that closing a deviation takes more time."
- Interviewee II

The fact that many interviewees believe that older products have less deviations is in accordance with the deviation handling procedures at AstraZeneca. These procedures include improving and updating processes and standards to avoid having the same deviation repeat itself. Products that have been around for a long time have gone through numerous improvements in the past, which should make them less prone to deviations. However, Yu and Kopcha (2017) state that newer products have shown improved quality over the past decades, while legacy products have been susceptible to recalls. Even though it is hard to know exactly what the interviewees mean by "old" products, at least one of the investigated brands should be defined as a legacy product.

Similarly to established products being manufactured, a few interviewees mentioned that PET OSD uses older equipment for some brands and processes. One interviewee simply declared that "stuff happens" when using old equipment, while another interviewee discussed equipment failure in broader terms:

Quote 27

"The goal is to produce the right batches 90% of the time. But when tableting had an issue, an equipment failure, we were at 15%. Nothing went right. It might have been easier if there weren't as many product types to deal with."

- Interviewee I

In Quote 27, the interviewee explained how severe the ramifications of equipment failure can be, especially when having a mixed product flow. Another interviewee elaborated on this, discussing how the magnitude of the effects of a failure depends on whether parallel machines are in use at the process in question. When it comes to investments, both in terms of employees and equipment, one interviewee might have put it best when asking rhetorically:

Quote 28

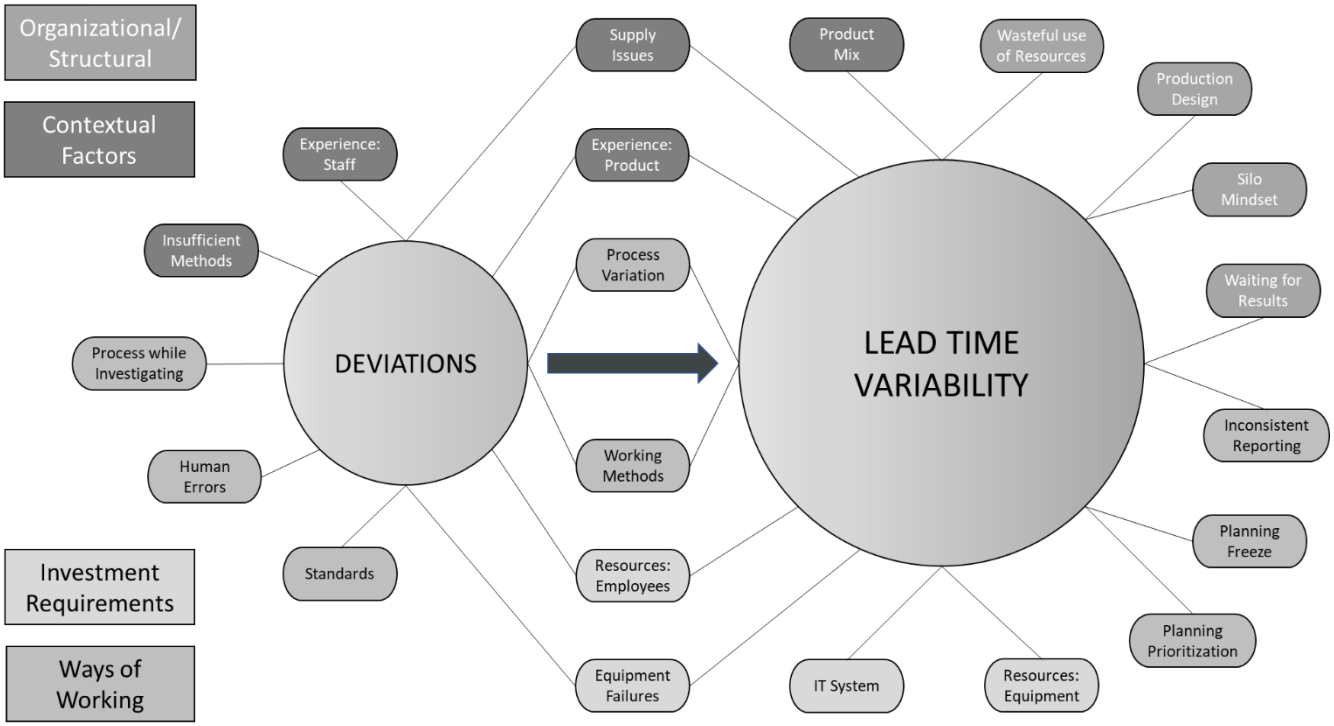
"How much can we ramp up [after a forced stoppage]? Recovering is very challenging… …How much are we willing to spend recouping this loss?"

- Interviewee V

The 21 code words deduced from the interviews gave direct and indirect causes for lead time variability. Indirect causes affected variability by increasing both the number of deviations and the time it took to investigate any deviation. Direct causes were deemed to be the responses that did not lead to more deviations, but that still had negative impacts on lead time variability. There were also some code words that fit both scenarios. This can be seen in Figure 6.3, below.

Figure 6.3

How the Causes Affect Lead Time Variability



6.3 Analysis of the Solutions to Lead Time Variability

From the interviews, it became clear that the proposed improvement ideas addressed the issues brought up as reasons for lead time variability. In many cases, the same code words were used for the two sections, but addressed from a different perspective. For example, the interviews gave that insufficient training could result in lead time variability, but also that more training of operators and improved SOPs could stabilize the situation. Prioritization was mainly brought up as a reason for variability, but for the brand being prioritized it actually resulted in steadier lead times.

A majority of the interviewees discussed more resources for employees as an improvement opportunity, and their statements related to both increased staff levels and the need for training. The following quote illustrates how certifying more employees to take test samples could decrease lead time variability:

Quote 29

"They have said that they will train more people, but also that they will rethink their scheduling. There should always be someone there that is able to take samples, and if that is not possible, that person should be scheduled during the evening or night shifts so that results are available come morning. There should always be samples at QC and documentation at QA when those functions come to work in the morning."

- Interviewee VII

One issue that was brought up as a reason for lead time variability was common occurrence of waiting for results and input from other departments. By identifying where the staff is a bottle neck and investing in training, as the quote above suggests, this waiting time can be reduced which should result in more stable lead times. According to Prina (2017), investing in the training of staff can pay off in the long run. The author describes a study where operators perceived that they were understaffed, but after receiving proper training it turned out that less operators were actually needed. It is possible that by improving the working methods and investing in training, AstraZeneca could decrease the lead time variability without increasing the head count.

Standards are important to create predictability (Jacobsen & Thorsvik, 2014), which is arguably one of the most important factors in decreasing lead time variability. Gallup et al. (2008) argue that standards also increase performance. In Quote 29, the interviewee suggests rethinking the scheduling. By changing the ways of working and then standardizing them, predictability and efficiency should be improved for both QC and QA. When SOPs are followed, it positively impacts the lead time variability, which is discussed in the following quote:

Quote 30

"…the operators work in highly standardized ways, which helps in keeping the lead times short. We know the exact amount of time needed for [each process]."

- Interviewee IIX

As previously mentioned, operator training is an important improvement opportunity, and it relates closely to standards. Gallup et al. (2008) argue that it is important that not only standards exist, but that employees are trained in how to execute them. One interviewee mentioned that the SOPs for operators are too long and detailed, updated too frequently, and are not easy-

enough to follow. Martin and Bell (2011) state that the SOPs should be updated in small increments to make it easier for the operators to learn the new ways of working. Patchong (2012) emphasizes that standards should be created in cooperation with the operators. This is crucial to keep in mind when updating or creating new SOPs.

Many interviewees have given examples of updated standards that have improved production in the past, such as the introduction of batch specific production schedules and the immediate reporting of deviations. Some interviewees have also expressed that there is a need to change the ways of working to a more even workflow. One new standard that will address this is described in Quote 31:

Quote 31

"We are going to start using a system called Kanbanize, which means that we won't run more tests than we have to in a single day… …So we need to reduce the tact on analyses that have a high tact time today, and hopefully use the time we gain on running analyses that currently have a slow tact time."

- Interviewee IV

The quote above is an example of an IT system that enables a change of working routines. Better IT systems were also mentioned in the interviews as an improvement opportunity. Many interviewees gave examples of how IT systems have improved collaboration, but there is still a need for more transparency between departments. Quote 32 describes how one such IT system enables transparency between departments:

Quote 32

"We do have a new module in QlikView called Batch Release Visualization. It's set up so that planners can access the module and see how far along the lab has gotten."

- Interviewee IV

Several interviewees brought up the need for improved cross-functional work. When asked about the reasons for lead time variability, statements were made that indicated the existence of a silo mentality. Cross-functional work was described in interviews as a way to mitigate this mentality, for example by introducing new IT systems, but also through improved communication. Quote 33 illustrates how communication between the production and planning departments allow for better scheduling. Jacobsen and Thorsvik (2014) propose an organization based on business processes and cross functional teams to counteract silo mindset. While the improvement ideas brought up in the interviews were not that radical, the ideas regarding cross-functional work is at least in part in agreement with theory.

Quote 33

"They get the production plan several weeks ahead of time, and give their input and feedback. That way, they can run production in an optimal fashion regarding campaign lengths, cleaning routines, and so on. So there is a constant dialogue happening."

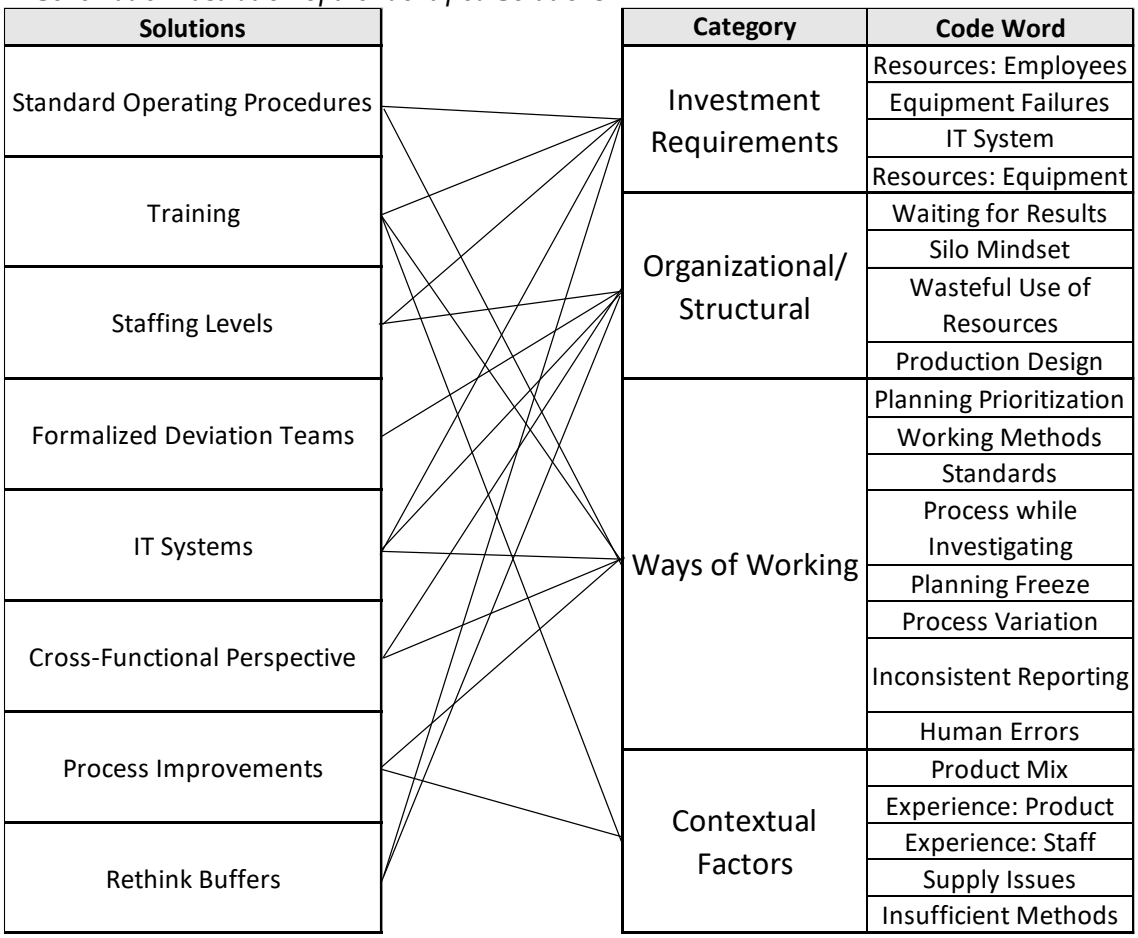
- Interviewee IX

7
DISCUSSION & CONCLUSION

In this section, the findings from the study are discussed. It was found that deviations are the main drivers of formulation lead time variability. Both batches directly affected by deviations and those indirectly influenced by them increase variability. In order to improve the situation, it is crucial to reduce the number of deviations and also to accelerate the investigations thereof. Other factors also affect lead time variability. Some examples include prioritizations, staffing levels, insufficient training opportunities, and uneven product flows. Improvement opportunities to reduce the variability are presented in Figure 7.1, and include improving the standard operating procedures. In the conclusion, the research questions are discussed and answered. Finally, it is recommended that AstraZeneca reduces the number of deviations by reworking their SOPs. The investigation process should be accelerated by formalizing the deviation teams. The company is also recommended to invest in their human capital.

Figure 7.1

A Schematic Illustration of the Identified Solutions



Note. Each solution is connected to the cause category it affects.

7.1 Discussion on the Role of Deviations

The main culprit and driver of formulation lead time variability at AstraZeneca's PET OSD was found to be deviations. During the interviews, the topics of deviations and variability were often intertwined and become synonymous at times. Deviations were described to affect the lead time and its variability in several ways. According to the description of deviation handling at AstraZeneca, batches are stopped when a deviation is detected. A deviation team then decides if the batch can move on in the production flow or if it needs to be stopped while it is being investigated. Letting more batches move on in production was presented as a way to reduce the lead time variability by the interviewees. The average time spent handling a deviation was longer than the average formulation lead time. This means that a deviation is very likely to result in delays for the affected batch, even if it is allowed to move on in the formulation process. As discussed in the analysis, deviations affect more batches than the one which is being investigated. The interviewees provided several examples of this. Batches are held while the extent of the deviation is examined. Deviations were also a common reason for prioritization, according to the interviewees, and this was especially true for product types that were produced infrequently.

In order to decrease the effect of deviations on lead time variability, two main strategies should be employed. The number of deviations need to decrease, and deviation investigations need to be closed faster. The study has shown that by removing all deviations the formulation lead times will decrease. It has also shown that many outliers with extended lead times do not have any deviations, but interviewees explained that they could still have been affected by deviations. The fact that in some instances, the removal of all outliers reduced formulation lead times by more than by removing deviations also show that this is the case. This means that decreasing the number of deviations would reduce the formulation lead times by more than the data showed, since only batches with actual deviations were removed when performing the calculations.

According to Durivage (2016), working systematically with quality management is a requirement in the pharmaceutical industry as specified in the GMP. By definition, deviations occur when the SOPs are not followed (ICH, 2000) and the investigation process results in updated SOPs. This study shows that AstraZeneca's SOPs are in general too long to be read and understood in detail, and also frequently updated. This can lead to a vicious cycle, where deviations lead to updated SOPs, and updated SOPs are hard to learn and follow, leading to more deviations and new updates. In order to decrease the number of deviations at PET OSD, it is vital that the company implements SOPs that are easy-to-follow. It is important that the SOPs are created in collaboration with the operators, who need to fully understand their purpose and contents. The study shows that it is not only important to have good SOPs, the employees also need to be properly trained on them in order to reduce the number of deviations.

The investigation time also needs to decrease in order to reduce formulation lead time variability. It was shown that the deviation teams sometimes lack the information required to initiate the investigation. Ensuring that operators understand the importance of the SOPs and the deviation process will lead to operators providing relevant information, thus speeding up the process. The deviation team was composed of a number of individuals who participate in the investigation besides their other work. This means that the coordination of meetings was challenging and that the members of the team were not able to dedicate their time fully towards the investigation. The deviation team is put together when a deviation is discovered, which

means that, for example, a process engineer can be involved in several deviation teams with different people. This further complicates the coordination process. Instead of "putting out fires" with temporarily connected individuals, AstraZeneca should formalize the deviation teams. This means that the teams should always consist of the same core members handling a number of deviations. By doing this, the complexity of the coordination task is significantly reduced, the meetings should become more efficient, and the team can investigate the deviations in a more structured manner. The deviation investigations should thereby close more quickly.

7.2 Discussion on Other Causes

One of the aspects affecting lead time variability without necessarily being connected to deviations was human capital. Interviewees discussed how staffing levels and some uncertified operators led to delays in certain processes. While employees did not have enough time to spend on handling deviations, they also were unable to spend sufficient amounts of time on their other work tasks. One effect of this was that, for example, process engineers were not able to dedicate enough time to what should be their main job: process improvements. This in turn can have a negative impact on the robustness of processes, and this study has shown that some processes at PET OSD are complicated, problematic, and in need of refinement. Equipment failure was another cause of lead time variability identified by this study, and some of these failures were caused by poorly designed processes. Dedicating more time and resources to process improvement should therefore pay off.

The fact that departments at times were understaffed and forced to prioritize among the work tasks at hand had negative implications for others. When production chose to produce batches rather than taking samples for QC, they made sure to stay on track on internal KPIs while disregarding the other department. Such ways of working can be hard to identify from solely looking at data, since the problem in reality did not lie with the department showing delayed lead times. By doing a thorough review of the staffing levels and needs across the board at PET OSD, many of the causes of lead time variability could be identified and corrected. The fact that departments often had limited insight into the work of other departments was shown to be a cause of lead time variability. Even though cross-functional meetings are taking place, having common IT systems could mitigate the problem, alleviate the need for some of those meetings and free up time for other work. IT systems should also be used on the shop floor to facilitate the batch documentation process.

Another cause of variability connected to investments in employees is the lack of sufficient training, and also inadequate standard operating procedures. A number of interviewees gave examples that indicated that work could have been done in better ways if the employees had received proper training. Gallup et al. (2008) support this, by saying that suitable training leads to improved performance. Some aspects of the staffing levels previously discussed could therefore potentially be solved by expanding the training opportunities at AstraZeneca. It is also important to keep in mind that this study was conducted during the Covid-19 pandemic, which has led to higher rates of sick leave for most companies. Even though the interviewees discussed the subject of staffing in general terms, it is possible that their perspectives were affected by the ongoing situation.

Prioritized batches were frequently discussed as a cause of lead time variability. This study showed that by prioritized brands have steadier formulation lead times than other brands do, but it was also clear that the other brands and batches were negatively impacted by this.

Prioritizations are therefore a solution to lead time variability on the individual brand or batch level, and the cause of variability on the larger scale. One interviewee discussed that the best-case scenario would be to never use prioritizations, but also explained that they are needed at times to meet customer demands. The fact that prioritizations are used as a cure to variability, but at the same time are a major cause of variability make them difficult to analyze.

The production design was another identified cause of variability. Uneven flows, insufficient space for buffers, and high utilization rates were all mentioned by the interviewees. Because of regulations mandating additional cleaning procedures for equipment standing still, it is of the essence to always have material in the buffers. One way of ensuring this is to focus on the buffers and treating them as planned resources. Another aspect is the limited physical space dedicated for buffers at the moment. It might not be feasible to expand the factory, but finding additional storage space could improve adherence to the queueing policy in place. It would also become a necessity if the PET were to ramp up production, as a higher utilization rate requires larger buffers.

7.3 Conclusion

The purpose of this master's thesis was to investigate the lead time variability and its causes at AstraZeneca's OSD Formulation PET in Södertälje. In order to do this, the operation and formulation lead times spanning 24 months from April of 2019 through March of 2021 were investigated in detail and interviews were conducted with relevant stakeholders in order to gain their perspectives on the issue. The purpose was fulfilled by answering the study's four research questions.

1. How are the production systems for the brands in question currently organized at the OSD Formulation PET in Södertälje?

During the initial phase of this study, the formulation process for each brand was mapped out. It was clear that Alpha and Beta had many things in common, both in terms of processes and resources. Their formulation followed the theoretical process of producing oral solid dosages from powdered APIs, even though the terminology and division of processes differed at times. Gamma, on the other hand, was produced by a different section and using an API that needed to be prepared into pellets. Therefore, the formulation steps for Gamma were more numerous. The answers to this research question were used when collecting data for the quantitative part of the study.

2. What do the operation and formulation lead times look like for the different brands?

The study showed that for the majority of batches, the total formulation lead times were relatively stable. Although there was still variability, it was considerably less when excluding the outliers. There was no significant difference in formulation lead time between the product variants for either brand. Moving on to the operation lead times, there was a notable difference between outliers and all data. However, the difference was larger towards the later processes for Alpha and Beta, with the final process having the largest difference. For Gamma, the second pellet preparation process contained the largest difference between outliers and all data. Many

outliers were accompanied by deviation reports, but there was no clear correlation between where the deviation occurred and where the batch was delayed. Therefore, it was not possible to use the collected lead time data to pinpoint problematic operations.

3. What are the causes of lead time variability at AstraZeneca's OSD PET in Södertälje?

During the course of the study, it was clear that deviations were the main reason for lead time variability. This was the main topic of discussion during the qualitative interviews and it could be seen in the quantitative data in the form of deviation reports in combination with operation and formulation lead times. The causes of lead time variability were therefore very closely related to the causes for deviations.

This study shows that there are four main reasons for the variability. *Investment requirements* is an umbrella for discussions related to how the lack of resources can cause lead time variability. This category covers the need for more spending on employees in the form of both training and staffing levels. It also covers the use of old equipment and equipment failures. The *Organizational/Structural* causes relate to how the structural organization of the PET affects lead time variability. For example, there are signs of silo mentality, and many delays are caused by one department awaiting results or responses from another one. The design of the production area is also included in this category, and it relates to the general flow of material and the physical layout of the plant. *Ways of working* encompasses reasons for variability that are caused by how work is done at the PET on a daily basis. For example, the fact that some batches are prioritized, how different departments organize their work flow, and the unsatisfactory standard operating procedures (SOPs). Finally, *Contextual factors* includes causes that are common within the pharmaceutical industry, but can be hard to affect. Examples are the product mix, which often requires additional cleaning procedures, the fact that an inexperienced staff make more mistakes and work less efficiently, and the difference between established and newer products when it comes to deviation rates.

4. What can be done to improve lead time variability at the OSD Formulation PET in Södertälje?

The study also looked into possible solutions for the lead time variability. The themes that developed could in many cases be related to the four causes of variability listed above. It was clear that AstraZeneca could gain from investing more resources into their employees, both in terms of head count and training programs. The study also showed that AstraZeneca should do an oversight of their standard operating procedures, since standardized ways of working lead to more stable lead times. Making sure that the SOPs are created in collaboration with the operators, and ensuring that all work tasks are covered is of the essence. Other ways of working should be looked into as well, and an effort should be made to ensure that all processes and departments have material when needed and that they receive said material in a flow suitable to their process. Related to the flow of material is the design of the production area, where it was clear that some processes would gain from having an enlarged buffer area ahead of their work station. Cross-functional cooperation was shown to help reduce lead time variability, and shared IT systems aided in the collaborative working ways.

7.4 Recommendation

In order to reduce the lead time variability, AstraZeneca is recommended to take measures to limit the number of deviations. This should be done by involving operators and conducting a thorough oversight of the standard operating procedures, to ensure that they are easy to read and follow. Furthermore, the deviation investigations need to be accelerated. By formalizing the deviation teams, predictability and coordination should improve, which would streamline the process. The course of action that would have the biggest impact besides improving the handling of deviations, is investments in human capital. More training opportunities should be extended to all employees, especially when it comes to adherence to the SOPs. The staffing levels should also be evaluated, to ascertain that all employees have time to perform their work tasks to the standards required.

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APPENDIX
A

Sample questions for each brand - first round of interviews:

We would like to record the audio from this interview to ensure that the information is accurately represented. Is this OK with you?

1. We are mapping out the production process from start to finish. Could you please explain all the steps involved?
2. Are these processes dedicated to this brand, or shared with other brands or sections?
    a. How do you prioritize if two different brands are heading into the same process?
3. Are there any planned buffers between processes?
    a. If so, where?
    b. Are there unplanned buffers? If so, where?
4. During what processes do quality controls take place?
    a. Are samples taken to an off-line lab?
    b. How long do the quality controls take?
    c. What happens to the production flow when there are quality controls?
5. Are there any processing steps that can be consolidated into main operations (blending, granulation, tableting, coating)?

B

Sample questions - second round of interviews:

We would like to record the audio from this interview to ensure that your information is accurately represented. Is this OK with you?

1. General Questions
    a. Could you please describe your role at AstraZeneca? Section, etc
    b. Do you believe that there are issues with lead time variability for [Alpha/Beta/Gamma]?
        i. What would you say causes the variability?
        ii. And what effects do they have?
    c. …

2. Related to planning
    a. Can you describe your part of the planning process?
    b. Do you use any time fences?
    c. Does production have autonomy to make changes as needed?
    d. What queueing principle is used in the buffers?
    e. What are the most critical elements in keeping the schedule?
    f. …

3. Quality
    a. How does Q plan between brands and batches?
    b. Do you have enough capacity to handle and analyze samples?
    c. Who decides what tests to run on a batch?
    d. Do you believe that the deviation team has enough knowledge to do their work or do they “play it safe” at times?
    e. Why do some deviation investigation takes so much longer than others?
    f. …

4. Production
    a. Do you believe that those in charge of planning have enough knowledge about your specific processes and all constraints regarding cleaning, etc?
    b. Do you have any flexibility to make changes as needed?
    c. When and how do you register that a batch enters and exits a process?
    d. What do you do when detecting a deviation?
    e. What queueing principle is used in the buffers?
    f. …

5. Process
    a. Lots of questions about deviation investigations
    b. Can you explain why some deviations are connected to batches and some are not?
    c. Are you part of any cross-functional collaborations?
    d. …

C

A complete list of the product variants of Alpha:

	All Data		Outliers	
Product Type	Number of Batches	Rate	Number of Batches	Rate
Type A	173	24.5%	7	19.4%
Type B	159	22.5%	8	22.2%
Type C	95	13.5%	4	11.1%
Type D	91	12.9%	8	22.2%
Type E	70	9.9%	1	2.8%
Type F	33	4.7%	2	5.6%
Type G	24	3.4%	2	5.6%
Type H	19	2.7%	2	5.6%
Type I	12	1.7%	1	0.0%
Type J	12	1.7%	0	2.8%
Type K	5	0.7%	1	2.8%
Type L	3	0.4%	0	0.0%
Type M	3	0.4%	0	0.0%
Type N	2	0.3%	0	0.0%
Type O	2	0.3%	0	0.0%
Type P	1	0.1%	0	0.0%
Type Q	1	0.1%	0	0.0%

D

The code words omitted from Table 5.11 covering reasons for lead time variability:

Exemplifying Quote	Code word	Category
…the planning department couldn't see that there was a batch that was close to being finished. If they had known that, they could have chosen that batch instead and received it the day after. Now, we placed that batch in waiting while starting processing the prioritized batch. They had to wait for 7 days for that batch, because we had to start processing it from the beginning.	IT System (2)	Investment Requirements
We are really bad at identifying exactly what resources that are required, we often exaggerate a bit.	Wasteful use of Resources (3)	Organizational/ Structural
…we try to give them piece of mind during this frozen period…	Planning Freeze (3)	Ways of Working
[The necessary ingredients create a suspension] that gets really thick and hard to handle when it solidifies. Normally, during coating, it's not unusual with stoppages.	Process Variation (3)	
Last week there was a mistake on one batch, and that mistake is a prime example of what can happen. The operators had picked a batch ending with a Y that should have ended with a V.	Human Errors (2)	
…if something were to happen in that final process, the date [in the system] can change. We register that date in our system when we receive the batch, but three days later, the original date might have been changed. We cannot work like that...	Inconsistent Reporting (2)	
And previously, we have had API shortages too, and at those times we have not been able to start as many batches as planned. That requires some rearranging.	Supply Issues (3)	Contextual Factors
We can't discover it until the final analysis on the finished product, because there is no method that can properly	Insufficient Methods (1)	

The code words omitted from Table 5.12 covering solutions to lead time variability:

Exemplifying Quote	Code Word
Pass it onwards either way, dare to process on risk a bit more in order to get rid of the variation!	Process while Investigating (2)
There needs to be a clear plan, and changes should be avoided as much as possible in the short term. A plan should be set, so that production can keep their pace.	Planning Freeze (2)
…but if you want to make really large improvements, you almost have to invest in new equipment and extend the factory.	Resources: Equipment (1)
Having experience from past deviations can help us when investigating established products.	Experience: Product (1)
We do have more stable lead times thanks to being a prioritized brand. We get material in time, and batches are released in time to accommodate the customer.	Planning Prioritization (1)

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